

# **Single Technology Appraisal**

## **Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]**

### **Committee Papers**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## SINGLE TECHNOLOGY APPRAISAL

### **Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]**

#### **Contents:**

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission** from Bayer
- 2. Company summary of information for patients (SIP)** from Bayer
- 3. Clarification questions and company responses**
- 4. Patient group, professional group and NHS organisation submissions** from:
  - a. AMMF – The Cholangiocarcinoma Charity
  - b. Sarcoma UK
  - c. Sarcoma UK appendix of patient and carer statements
- 5. Expert personal perspectives** from:
  - a. Professor Robin Jones – clinical expert, nominated by Bayer
  - b. Dr Olga Slater – clinical expert, nominated by Sarcoma UK
  - c. Shounok Ghosh – patient expert, nominated by Sarcoma UK
  - d. Stephen Bennett – patient expert
- 6. External Assessment Report** prepared by York Technology Assessment Group
- 7. External Assessment Report – factual accuracy check**
- 8. NHS England SACT report**

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours [ID6292]

### Company evidence submission

October 2025

| File name                                                | Version | Contains<br>confidential<br>information | Date      |
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# **1. Decision problem, description of the technology and clinical care pathway**

## **1.1 Decision problem**

The submission covers the technology's full marketing authorisation for this indication. The decision problem that this company submission addresses is summarised in Table 1.

**Table 1. The decision problem**

|                          | <b>Final scope issued by NICE</b>                                                                                                                                                                                                                                                                                                      | <b>Decision problem addressed in the company submission</b>                                                                                                                                                                                                                                                                                     | <b>Rationale if different from the final NICE scope</b>                                                                                                                                                                                                                                            |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population</b>        | For the treatment of adult and paediatric patients with solid tumours who have:<br>- a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and<br>- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and<br>- no satisfactory treatment options | For the treatment of adult and paediatric patients with solid tumours who have:<br>- a tumour with a Neurotrophic Tyrosine Receptor Kinase ( <i>NTRK</i> ) gene fusion, and<br>- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and<br>- no satisfactory treatment options | NA                                                                                                                                                                                                                                                                                                 |
| <b>Intervention</b>      | Larotrectinib                                                                                                                                                                                                                                                                                                                          | Larotrectinib                                                                                                                                                                                                                                                                                                                                   | NA                                                                                                                                                                                                                                                                                                 |
| <b>Comparator(s)</b>     | Established clinical management without larotrectinib                                                                                                                                                                                                                                                                                  | The comparator selected is in line with the final scope issued by NICE                                                                                                                                                                                                                                                                          | NA                                                                                                                                                                                                                                                                                                 |
| <b>Outcomes</b>          | The outcome measures to be considered include:<br><ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rate</li> <li>• duration of response</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>                                | The outcome measures considered include:<br><ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rate</li> <li>• duration of response</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>                                               | NA                                                                                                                                                                                                                                                                                                 |
| <b>Economic analysis</b> | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.                                                                                                                                                                               | Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year. The company's submission adopts a cost-utility approach using partitioned survival analysis and adheres closely to the reference case                                                                                                              | NTRK fusion testing is funded within the NHS through the National Genomic Test Directory and delivered via the Genomic Laboratory Hub network, meaning the cost of testing is already incorporated within the healthcare system. While the infrastructure is in place and testing is performed, in |

|  | Final scope issued by NICE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                     | Rationale if different from the final NICE scope                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p> <p>The availability and cost of biosimilar and generic products should be taken into account.</p> <p>The use of larotrectinib is conditional on the presence of NTRK fusion. The economic modelling should include the costs associated with diagnostic testing for NTRK fusion in people with advanced solid tumours who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.</p> | <p>and previously accepted submission approaches.</p> <p>The time horizon for estimating clinical and cost-effectiveness is set to a lifetime.</p> <p>Costs are considered from an NHS and Personal Social Services (PSS) perspective.</p> <p>Testing costs are not included in the base case analysis but will be explored in sensitivity analyses.</p> | <p>practice, it is often prioritised for rare and paediatric cancers where NTRK fusions are more common. In prevalent tumour types, detection typically occurs incidentally through broader next-generation sequencing (NGS) panels conducted for other molecular drivers.</p> <p>NTRK fusions are not the only biomarkers included in the testing panel, and as such, the cost of the test should not be borne by the company. Furthermore, NTRK fusions are typically rare, meaning that any diagnostic testing conducted will not be exclusively to support the use of larotrectinib.</p> <p>In addition, the expansion of genomic testing is a strategic priority for the NHS in England and ensuring that such testing is publicly funded aligns with national healthcare objectives.</p> |

|                                                                              | Final scope issued by NICE                                                                                                                                   | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Rationale if different from the final NICE scope                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Subgroups to be considered</b>                                            | <p>If evidence allows, subgroup analyses by:</p> <ul style="list-style-type: none"> <li>tumour site</li> <li>previous therapy will be considered.</li> </ul> | No subgroups are considered in the cost-effectiveness analysis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Larotrectinib acts as a histology-independent precision medicine. As such, there are no subgroups considered in the cost-effectiveness analysis. While supportive analyses were conducted to assess consistency across selected subgroups, the study designs and patient numbers do not allow for robust conclusions to be drawn from these analyses. |
| <b>Special considerations including issues related to equity or equality</b> |                                                                                                                                                              | <p>Larotrectinib is an innovative therapy and a 'step change' in the management of NTRK fusion-positive cancers. It is a precision medicine, designed to selectively target NTRK fusion cancer, providing a specific treatment for NTRK fusion-positive solid tumours where previously no treatment was available. Larotrectinib is a histology-independent therapy, offering treatment for both adults and children under a single indication. It is approved by EMA as the first histology-independent drug in the EU.</p> <p>As a rare disease, the data supporting its use come from single-arm basket studies, which are considered best suited to assess the efficacy of targeting genomic alterations that occur at low frequencies across a wide variety of tumour types (1). Indeed, the MHRA agreed that a single-arm study was an appropriate design to support a Marketing Authorisation Application, given the extreme rarity of NTRK fusion cancers.</p> <p>While in the Cancer Drugs Fund (CDF), larotrectinib continued to demonstrate efficacy and safety, mitigating the uncertainty inherent in the clinical trial design and modelling choices from the first submission.</p> <p>The company submission aligns closely to NICE reference case. However, ongoing workstreams aimed at evaluating the suitability of health technology assessments methods for precision medicines indicate that deviations from the reference case are likely to occur. The trial design and the high number of comparators are reflective of</p> |                                                                                                                                                                                                                                                                                                                                                       |

|  | Final scope issued by NICE | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                      | Rationale if different from the final NICE scope |
|--|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
|  |                            | <p>the rarity of the gene fusion and the innovative nature of this product. It is crucial to consider these factors to ensure that patients with rare gene fusions are not disproportionately disadvantaged.</p> <p>Furthermore, it is essential that eligible patients are not denied access to this treatment while HTA methods continue to evolve.</p> |                                                  |



## 1.2 Description of the technology being evaluated

A description of the technology being appraised is provided in Table 2.

**Table 2. Technology being appraised**

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>UK approved name and brand name</b> | Larotrectinib (Vitrakvi)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Mechanism of action</b>             | <p>Larotrectinib is an orally bioavailable, adenosine triphosphate (ATP)-competitive and highly selective tropomyosin receptor kinase (TRK) inhibitor, rationally designed to avoid activity with off-target kinase.</p> <p>The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i> genes, respectively (see Section 1.3).</p> <p>In-frame gene fusion events resulting from chromosomal rearrangements of the human genes <i>NTRK1</i>, <i>NTRK2</i>, and <i>NTRK3</i> lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed, driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell proliferation and survival, leading to TRK fusion cancer.</p> <p>Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.</p> <p>In a broad panel of purified enzyme assays, larotrectinib inhibited <i>TRKA</i>, <i>TRKB</i>, and <i>TRKC</i> with half maximal inhibitory concentration (IC<sub>50</sub>) values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations (2). In <i>in vitro</i> and <i>in vivo</i> tumour models, larotrectinib demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.</p> <p>Results from the two phase 1/2 studies, which also included patients without NTRK gene fusions, showed high objective response rates in patients with tumours harbouring the target, those with a TRK fusion protein (as evidenced by NTRK gene fusions) (3, 4). In contrast, almost no responses were observed in patients without the target, thereby supporting the proposed mechanism of action. Additionally, a relatively favourable safety profile may be interpreted as clinical</p> |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

|                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                         | evidence of a low degree of off-target effects (see section 2.10).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Marketing authorisation/CE mark status</b>                                                           | <ul style="list-style-type: none"> <li>• EU regulatory approval was in 09/2019</li> <li>• UK regulatory approval was in 03/2021</li> <li>• Larotrectinib is already available through the CDF since 2020</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</b> | <p>As monotherapy, it is indicated for the treatment of adult and paediatric patients with solid tumours who have:</p> <ul style="list-style-type: none"> <li>- a tumour with a Neurotrophic Tyrosine Receptor Kinase (<i>NTRK</i>) gene fusion, and</li> <li>- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and</li> <li>- no satisfactory treatment options</li> </ul>                                                                                                                                                            |
| <b>Method of administration and dosage</b>                                                              | <p>Larotrectinib is available as hard capsules (25 mg, 100 mg) to be taken orally, or as an oral solution (20 mg/mL).</p> <ul style="list-style-type: none"> <li>• Adults: The recommended dose is 100 mg larotrectinib twice daily, until disease progression or unacceptable toxicity occurs.</li> <li>• Paediatric population: Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m<sup>2</sup> larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or unacceptable toxicity occurs.</li> </ul> |
| <b>Additional tests or investigations</b>                                                               | The presence of an <i>NTRK</i> gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with larotrectinib. Please refer to section 1.3 on diagnosis.                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>List price and average cost of a course of treatment</b>                                             | <p>The indicative list price is £14,000.00 for the 56*100mg capsule pack, £3,500.00 for the 56*25mg capsule pack and £5,000.00 for the 20mg/ml*100ml bottle of solution (Appendix I).</p> <p>The proposed patient access scheme price is £[REDACTED] for the 56*100mg capsule pack, £[REDACTED] for the 56*25mg capsule pack and [REDACTED] for the 20mg/ml*100ml bottle of solution, after a proposed [REDACTED]% discount (Appendix I).</p>                                                                                                                                                              |
| <b>Patient access scheme (if applicable)</b>                                                            | A submission for a simple discount scheme has been submitted to the Patient Access Scheme Liaison Unit (PASLU).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

## 1.3 Health condition and position of the technology in the treatment pathway

Larotrectinib is licensed for the treatment of adult and paediatric patients with solid tumours who have:

- a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and
- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- no satisfactory treatment options.

### 1.3.1 NTRK fusion cancer

Neurotrophic Tyrosine Kinase (NTRK) gene fusion as a primary oncogenic driver and underlying cause of cancer is known to occur across a diverse and heterogeneous range of solid tumour sites, affecting both adult and paediatric patients.

In the initial submission to NICE, a systematic review identified limited published data on the prognosis of patients with NTRK gene fusion; only six publications in three tumour sites included a comparison with patients without NTRK gene fusion. The presence of an NTRK gene fusion has been associated with a worse prognosis or more aggressive tumours in patients with metastatic colorectal cancer (mCRC), and papillary thyroid carcinoma (PTC) (5, 6). More recently, two real-world retrospective studies utilised databases to understand the difference in overall survival between patients with and without NTRK gene fusion (7, 8). VOYAGER 1 utilises de-identified Flatiron Health Foundation Medicine clinic-genomic database from 2011 to 2018, while VOYAGER 2 is specific to the UK, leveraging the Genomic England 100,000 Genomes Project linked with clinical data from UK databases from 2016 to 2019. Both studies include a large number of tumour sites (e.g., colorectal, lung, sarcoma) that also appear in clinical trials for larotrectinib (see section 2.6). They both report a higher risk of death for patients with NTRK gene fusion compared to patients without NTRK gene fusion, with a hazard ratio (HR) of 1.44 (95% CI [0.61-3.37]) and 1.47 (95% CI [0.39-5.57]), respectively. Although the results are not statistically significant, the close

similarity in findings and further sensitivity analyses suggest an increased risk of death for patients presenting with this gene fusion.

In alignment with the indication for larotrectinib, this overview focuses on 'NTRK fusion-positive cancer' as the disease entity, rather than providing an individual discussion of each of the multiple tumour sites known to harbour NTRK gene fusions and treatable with larotrectinib. This is because the selection of larotrectinib as a treatment will be based solely on the presence of an NTRK gene fusion (the oncogenic driver) rather than the location of the tumour. This approach signifies a paradigm shift and step change in cancer treatment, allowing therapies to be tailored according to causation (i.e., the presence of an NTRK gene fusion [NTRK+; NTRK fusion-positive cancer]) instead of the traditional focus on tumour site (e.g., lung, prostate, thyroid).

Larotrectinib is thus termed a 'tumour-agnostic' or 'histology-independent' therapy. This is consistent with the European Society Medical oncology (ESMO) Tumour-Agnostic Classifier and Screener (ETAC-S) definition, which considers a treatment to be tumour agnostic if each tumour agnostic indication demonstrates an objective response rate in at least one out of five patients (i.e, 20%) in two-third ( $\geq 4$ ) of the investigated tumour sites, with at least five evaluable patients in each tumour type (9).

This will be further highlighted in section 2.6.1. which demonstrates the histology-independent and age-independent efficacy of larotrectinib. This provides a treatment option for both adults and paediatrics with NTRK fusion-positive solid tumours where previously no fusion-specific treatment was available.

#### 1.3.1.1 Epidemiology

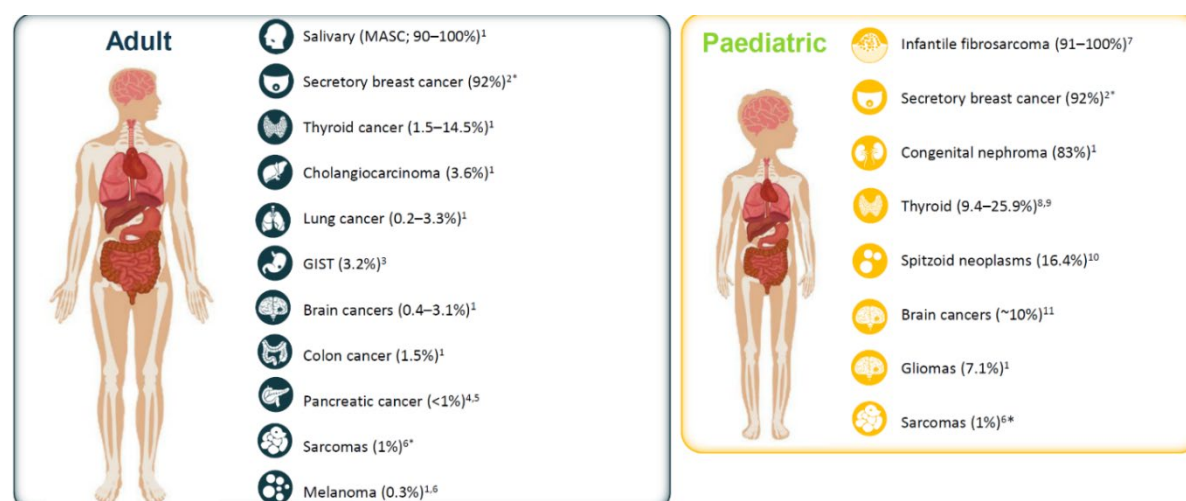
NTRK fusion-positive cancer is considered a rare disease, with a low percentage of solid tumours harbouring an NTRK gene fusion. A paper published by Westphalen *et al.* in 2021 reports that 1.34% of paediatric cancers and 0.28% of adult cancers display an NTRK gene fusion from the FoundationCORE database (10). For the UK specifically, using the National Disease Registration Service (NDRS) database, the average yearly number of cancer cases (estimated between 2017 and 2019) represents a total of 2,459 cases for patients between 0 and 19 years old and 383,016 for adult patients between 20 and 90+ years old (11). Combining these numbers with

the pre-mentioned rates, patients with NTRK fusion positive cancer in the UK would represent approximately 33 cases for paediatric patients and 1,072 for adults, a total of 1,105 cases of NTRK-positive cancer per year if every cancer patient were tested. According to Lin *et al.* 2024, most cancer cases (52.9%) are diagnosed at an advanced stage (12). This suggests that a maximum of 584 patients could be eligible for larotrectinib at an advanced stage, assuming all patients were tested for their genetic mutation. However, since testing is not systematically performed in real-world settings, the actual number of patients treated with larotrectinib is likely to be lower.

The frequency of NTRK gene fusions varies considerably according to tumour histology, occurring rarely (<0.1% to 3%) in common histologies, such as non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), but more frequently (>90%) in several uncommon tumours, such as secretory breast carcinoma and infantile fibrosarcoma (IFS) (see Figure 1).

It is also important to emphasise that there is not a “typical” NTRK fusion-positive patient, the heterogeneous nature of the patient population is inherent in any population that would be constructed by aggregating patients based on their genetic mutation rather than their tumour site.

**Figure 1. Distribution of NTRK gene fusions across tumour histologies**



GIST=gastrointestinal stromal tumour; MASC=mammary analogue secretory carcinoma; NTRK=neurotrophic tyrosine receptor kinase.

\*Frequency in adult vs. paediatric patients not specified.

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

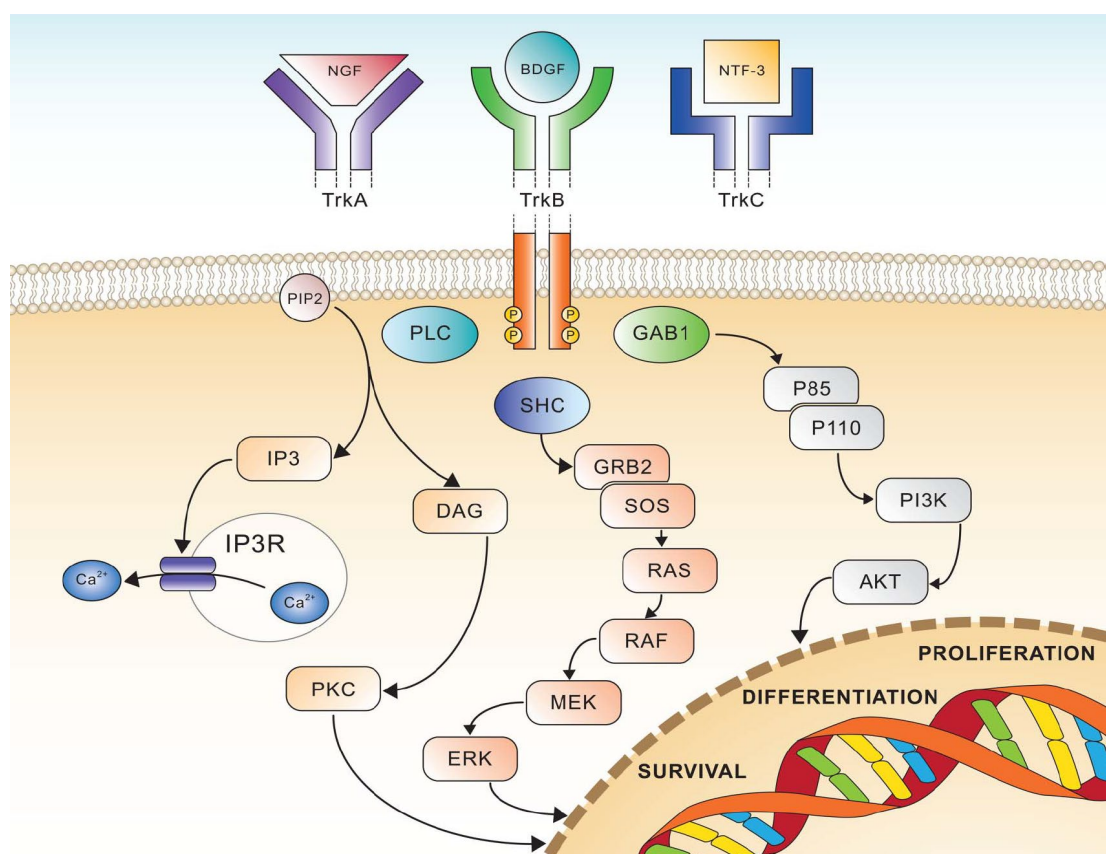
Source: Adapted from Vaishnavi *et al.* 2015 (13), Tognon *et al.* 2002 (14). Brenca *et al.* 2016 (15), Pishvaian *et al.* 2018 (16), Cocco *et al.* 2018 (17), Stransky *et al.* 2014 (5), Bourgeois *et al.* 2000 (18), Ricarte-Filho *et al.* 2013 (19), Prasad *et al.* 2016 (6), Wiesner *et al.* 2014 (20), Wu *et al.* 2014 (21)

### 1.3.1.2 Aetiology

#### 1.3.1.2.1. TRK signalling pathway

Under normal physiologic conditions, the NTRK gene family (*NTRK1*, *NTRK2*, and *NTRK3*) encodes the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, which regulate the proliferation, growth, and survival of neurons through activation of neurotrophins (22-24) (see Figure 2). This process is responsible for normal development and function of the central and peripheral nervous systems (e.g. pain, thermoregulation, proprioception, appetite, and memory).

**Figure 2. TRK signalling pathways**



AKT = v-akt murine thymoma viral oncogene homologue; BDNF = brain-derived growth factor; DAG = diacyl glycerol; ERK = extracellular signal-regulated kinase; GAB1 = GRB2-associated binding protein 1; GRB2 = growth factor receptor-bound protein 2; IP3 = inositol trisphosphate; MEK = mitogen-activated protein kinase; NGF = nerve growth factor; NTF-3 = neurotrophin 3; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2 = phosphatidylinositol 4,5-bisphosphate; PKC = protein kinase C; PLC = phospholipase C; RAF = rapidly accelerated fibrosarcoma kinase; RAS = rat sarcoma kinase; SHC = Src homology 2 domain containing.

Source: Adapted from Amatu *et al.* 2016 (22)

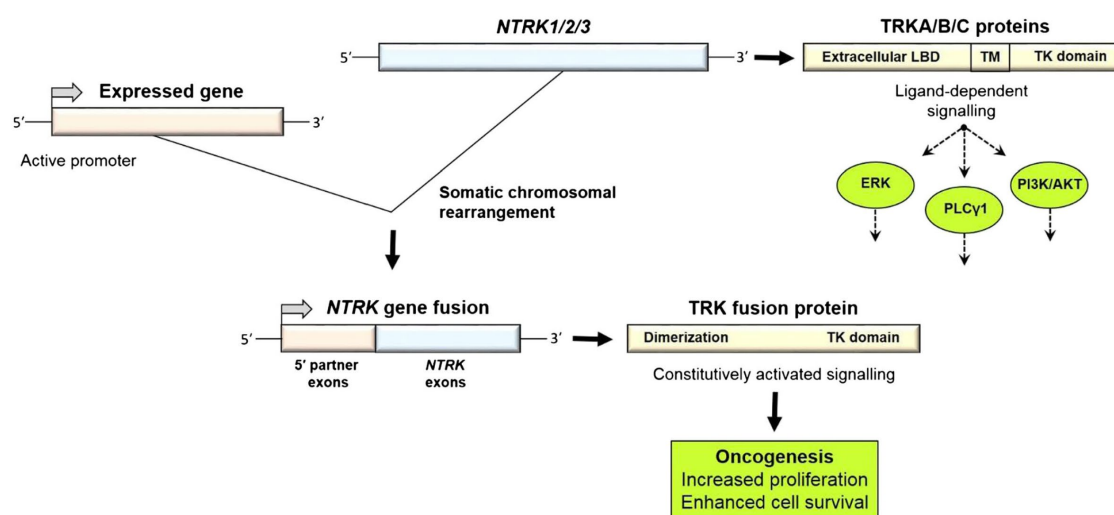
Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours



#### 1.3.1.2.2. *NTRK* gene fusions

*NTRK* fusion-positive tumours arise from a gene rearrangement involving fusion of a portion of the *NTRK1*, *NTRK2* or *NTRK3* gene with an unrelated gene, known as a fusion partner (22). Gene fusions are a well-established class of primary oncogenic drivers. In all reported *NTRK* oncogenic gene fusions, the 3' region of the *NTRK* gene is fused with a 5' region of an unrelated gene, resulting in the expression of a TRK fusion protein (Figure 3). This fusion protein is constitutively active, meaning it can signal even in the absence of its normal ligand. This activity promotes cancer formation by driving unchecked cell proliferation and tumour growth through the TRK signalling pathway.

**Figure 3. *NTRK* gene fusion**



LBD=ligand binding domain; TM=transmembrane; TK=tyrosine kinase  
Source: Kummar and Lassen, 2018 (25)

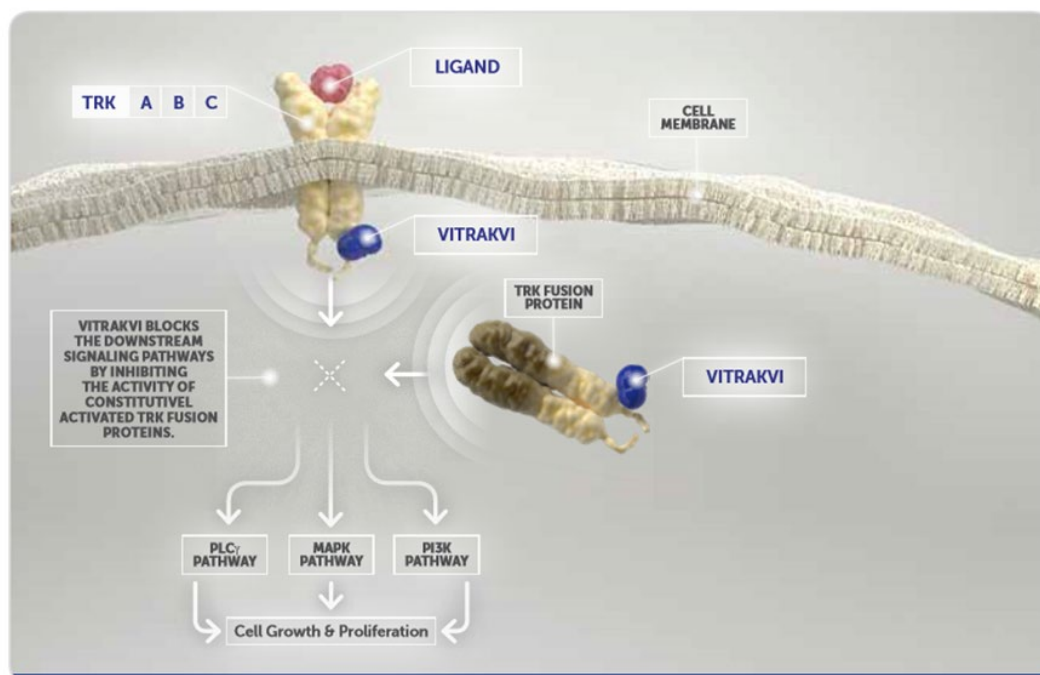
Over 80 different *NTRK* fusion partners have been identified and shown to contribute to the development of *NTRK* fusion cancers across various histologic tumour types (22, 25-28). The fusion partners vary depending on the histological cancer type, with more common cancers typically having a higher number of different fusion partners. In contrast, rarer histologies often have fewer known fusion partners, with some, like mammary analogue secretory carcinoma of the salivary gland, commonly associated with the ETV6-*NTRK3* fusion.

Company evidence submission template for larotrectinib for treating *NTRK* fusion-positive advanced solid tumours

### 1.3.2 Larotrectinib

Larotrectinib is an innovative technology that specifically targets the protein product of the NTRK fusion genes (i.e. TRK fusion proteins), irrespective of the location or histology of the tumour, turning off signalling pathways that usually allow NTRK fusion-positive cancers to grow (Figure 4).

**Figure 4. Mechanism of action – larotrectinib (Vitrakvi®)**



TRK= tyrosine kinase

Source: Adapted from Vitrakvi, Summary of product characteristics (29) and Amatu *et al.* 2016 (22)

The histology-independent, targeted mechanism of action of larotrectinib has been clearly demonstrated through the efficacy observed in diverse tumour types with NTRK gene fusions (25, 30-34). Patients with NTRK gene fusion cancers enrolled in clinical studies for larotrectinib had locally advanced / metastatic cancer that either could not be sufficiently controlled with available therapies, or were likely to result in significant morbidity, such as limb amputation, to achieve control. Many patients had previously received multiple systemic therapies. Treatment of NTRK fusion-positive tumours with larotrectinib exhibited rapid and substantial antitumour activity, with durable disease control that appears to be independent of NTRK isoform, tumour type and patient age (see Appendix C). There was no effect in patients without an NTRK fusion, irrespective

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours



of tumour type. This is not surprising given the mechanism of action of larotrectinib as a potent and selective inhibitor of TRKA, TRKB, and TRKC.

Larotrectinib has demonstrated efficacy across a broad range of tumours, including rare tumours and rare subsets of more common tumours, in both paediatric and adult patients ranging in age from birth to 90 years. Additionally, larotrectinib has a favourable safety profile, with a low incidence of adverse events and limited toxicity (see section 2.11).

This demonstrates the ability to treat patients based on the type of mutation (gene fusion) their tumour contains, regardless of where the cancer originated (9). Targeted therapies are considered a therapeutic advance, particularly in cases where traditional chemotherapy could be of limited benefit. Traditional chemotherapy is often non-specific with respect to molecularly defined targets, generally associated with significant toxicities, and may be unsuitable for certain patient populations, such as very young paediatric patients or elderly or frail adults.

The availability of larotrectinib, a highly selective oral precision medicine, represents a significant therapeutic innovation in the field of precision medicine and targeted therapies. Its introduction aligns with the aspirations of the National Health Service (NHS) Long Term Plan in respect of personalised medicines and genomic-directed therapy.

|                                                                                  |
|----------------------------------------------------------------------------------|
| <b>Larotrectinib was the first histology independent drug approved in the EU</b> |
|----------------------------------------------------------------------------------|

### **1.3.2.1 Management of NTRK fusion-positive cancer**

#### **1.3.2.1.1. *Diagnosis***

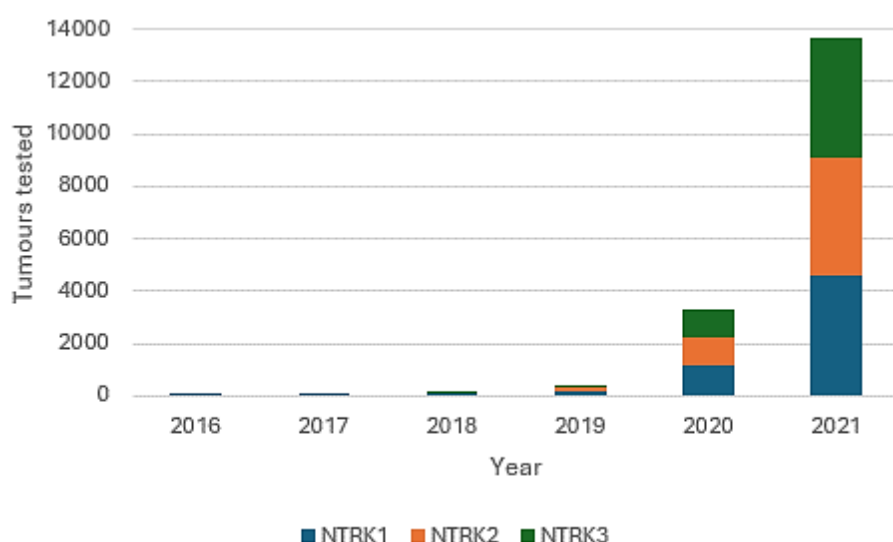
According to ESMO recommendations, multiple standard testing methods are available to identify patients with tumours harbouring NTRK gene fusions (35). Next-generation sequencing (NGS) is a key method that allows for efficient testing, with the capability to detect NTRK gene fusions alongside other genomic targets simultaneously. Other detection methods for NTRK gene fusions include fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), and whole genome sequencing (WGS).

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

In the UK, eligibility for precision medicine using targeted therapies requires patients to be tested for specific oncogenic drivers. For this purpose, diagnostic testing for NTRK gene fusions is routinely available through the NHS, primarily via the National Genomic Test Directory (36). The test is nationally approved and funded, ensuring accessibility for both adult and paediatric patients with solid tumours. It supports the use of precision medicine and promotes equitable access across the country as part of the NHS Genomic Laboratory Hubs (GLHs).

However, discussions with clinicians indicate that the extent to which NTRK gene fusion testing is actively performed in routine clinical practice may vary based on several factors (e.g., geography, clinician awareness, urgency). Testing is generally prioritised for specific tumour types where NTRK fusions are more prevalent (such as salivary gland tumours) or where standard treatments options are limited (e.g., rare cancers, paediatric tumours). An upward trend in NTRK testing in the UK from 2016 to 2021 has been observed, and testing for NTRK1, NTRK2, and NTRK3 has grown steadily over these years (Figure 5).

**Figure 5. Evolution of NTRK testing in the UK from 2016 to 2021**



NTRK: Neurotrophic Tyrosine Receptor Kinase  
Source: NHS Digital. Somatic molecular dashboard (11)

In common tumour types (e.g., lung, breast), broad panel NGS assays may incidentally detect NTRK fusions while testing for more common molecular markers (e.g., KRAS, EGFR) (37). However, it is not uniformly applied across all patients or tumour types and depends on local genomic strategies, the availability of comprehensive genomic profiling, tissue availability, clinical indications, clinician awareness, and the urgency of clinical decisions (as rapid decisions in late-stage disease may preclude full testing). This variability is primarily due to the rarity of NTRK fusions in common cancers. Consequently, oncologists may not prioritise NTRK testing unless standard treatment options have been considered and found inadequate, such as when common driver mutations are absent or when the tumour exhibits unusual histology.

Testing capabilities exist within the NHS infrastructure and are expanding in line with the NHS Genomic Medicine Service, which aims to "make genomics commonplace within the NHS". In 2024, the NHS Genomic Medicine Service delivered 810,000 genomic tests, reflecting an 8% increase since 2023 (38). Despite these encouraging figures, systematic routine testing for all patients with advanced solid tumours is not currently standard practice, and testing decisions are influenced by histology, clinical context, and access to tests.

It is clear from the NHS Long Term Plan and the NHS "Improving Outcomes Through Personalised Medicine" that the intention to implement WGS for all cancers is driven by a broad ambition to improve health outcomes, expand the ability of centres in England to participate in research, and establish England as the first country to have a national NHS Genomic Medicine Service.

#### *1.3.2.1.2. Healthcare pathway*

Following its exit from the Cancer Drugs Fund (CDF), larotrectinib is expected to become an integral option in the treatment pathway for patients with NTRK fusion-positive locally advanced or metastatic solid tumours, allowing for flexibility in physician-led decision-making regarding its placement in the treatment sequence.

Recognising the heterogeneity of tumour types, prior therapies, and individual patient circumstances, the initiation of larotrectinib should remain at the discretion of the

treating clinician, informed by tumour biology, available standard of care options, patient fitness, preferences and treatments severity profiles. This approach aligns with the “no satisfactory treatment option” provision in the product label, which allows for clinician judgement rather than adhering to a fixed treatment line. Such flexibility is consistent with the principles of precision oncology and individualised patient care. Furthermore, introducing larotrectinib as a reimbursable targeted therapy supports the UK GIRFT objectives by promoting equitable access, reducing unwarranted variation, and ensuring the efficient, evidence-based adoption of innovative treatments across the NHS.

Currently, there are no tumour-agnostic standard treatments specifically established for NTRK fusion-positive solid tumours within routine NHS clinical practice, apart from targeted therapies recommended under managed access agreements through the Cancer Drugs Fund (TA630 and TA644). In the absence of such targeted therapies, NTRK fusion-positive patients are typically managed according to standard treatments for their tumour histology and stage, which may include chemotherapy, radiotherapy, immunotherapy, or histology-specific targeted agents. Treatment decisions are currently guided by recommendations for the specific tumour site, regardless of NTRK status.

Treatment recommendations vary by tumour site. More common tumour types, such as NSCLC, CRC, melanoma and pancreatic cancer, have guideline recommendations for multiple lines of therapy, including chemotherapy, targeted therapy, and/or immunotherapy. In contrast, less common tumour types, such as those originating from the appendix, salivary gland, and secretory breast carcinoma, have limited or no treatment guidelines or recommendations due to a scarcity of evidence supporting systemic therapy. These rarer tumours are primarily treated with chemotherapy and/or surgery, or patients may be enrolled in clinical trials. The differences in treatment options drive clinicians to perform testing on patients at different times in the treatment pathway, which will further influence when a targeted TRK inhibitor can benefit the patient.

Since the FDA and EMA approval of larotrectinib, the treatment has been rapidly incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for various solid tumours in the United States (US), as well as the guidelines of the ESMO and European Association of Neuro-Oncology (EANO). To understand the extent of the recommendations, we will focus on European guidelines when available in Table 3. If no European guideline is available, the NCCN guidelines (American) will be referenced.

Importantly, all guidelines that mention NTRK gene fusions recommend treatment with TRK inhibitors in general, or larotrectinib/entrectinib specifically, as part of patient management, as shown below. By providing access to larotrectinib, UK healthcare professionals would be enabled to follow international guidelines.

In summary, the introduction of larotrectinib not only enhances treatment options but also aims to improve the treatment's tolerability and overall outcomes. The incorporation of larotrectinib into routine practice aligns with the principles of precision oncology, ensuring that patients with NTRK fusion-positive tumours receive tailored and effective treatment.

**Table 3. European recommendations for NTRK testing and targeted therapies**

| Guideline                                                                    | NTRK fusion testing recommendation                                                                                                                                                                                                                                                      | Therapy Guidance                                                                                                                                                                                                                                                                                                                                                                                                                    | Date/ ref                                                             |
|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Salivary gland cancer - ESMO                                                 | IHC and molecular testing should be used as supplementary tools when appropriate.                                                                                                                                                                                                       | In patients with secretory carcinoma and NTRK gene fusion, treatment with a TRK inhibitor (larotrectinib or entrectinib) is recommended [III, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: 3; ESCAT score I-C].                                                                                                                                                                                                   | Van Herpen <i>et al.</i> 2022 (39)                                    |
| Thyroid cancer - ESMO                                                        | If a systemic therapy for advanced/metastatic differentiated thyroid cancer is planned, a genetic test targeting actionable cancer mutations should be considered to individualise therapy. Next-generation sequencing (NGS) analysis is the preferred approach, if available [III, C]. | Larotrectinib is an option for the treatment of adults and paediatric patients with metastatic NTRK fusion-positive solid tumours, not amenable to surgery, that have no satisfactory treatment options [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C]                                                                                                                                                                           | Filetti <i>et al.</i> 2022 (40)                                       |
| Soft tissue and visceral sarcomas (excluding GIST) - ESMO                    | Pathological diagnosis should be made by a sarcoma expert pathologist according to the 2020 WHO classification [IV, A].                                                                                                                                                                 | NTRK inhibitors are standard treatment of those rare patients with locally-advanced or metastatic NTRK rearranged sarcomas; larotrectinib [III, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3]; entrectinib [III, A; ESMO MCBS v1.1 score: 3]. This treatment can also be considered in the preoperative setting, when a cytoreduction can improve morbidity and function. | Gronchi <i>et al.</i> 2021 (41)                                       |
| Gastrointestinal stromal tumours (including soft tissue sarcoma GIST) - ESMO | Centralised pathological diagnosis is more strongly recommended for GISTs without typical molecular alterations. In rare cases, a BRAF mutation or an NTRK gene rearrangement may be found, which may have therapeutic implications.                                                    | Patients with GIST with NTRK rearrangement are known to be sensitive to treatment with neurotrophic tyrosine receptor kinase (NTRK) inhibitors such as larotrectinib [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C] and entrectinib [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].                                                                                                                                       | Casali <i>et al.</i> 2021 (42)                                        |
| Lung cancer - ESMO                                                           | Testing for NTRK rearrangements should be carried out [II, A]. Screening for NTRK rearrangements may use IHC or NGS, with appropriate testing follow-up to validate a positive result [II, A].                                                                                          | Larotrectinib and entrectinib are recommended for patients with NSCLC and an NTRK gene fusion and who have no satisfactory treatment options [III, A; ESMO MCBS v1.1 score: 3; ESCAT: I-C]. In the ESMO 2025 living guidelines, TRK inhibitors are recommended as first-line treatment in stage IV metastatic NSCLC when the molecular test (NTRK) is positive.                                                                     | Hendriks <i>et al.</i> 2023 (43) and Hendriks <i>et al.</i> 2025 (44) |

| Guideline                 | NTRK fusion testing recommendation                                                                                                                                                                                                                                                                                         | Therapy Guidance                                                                                                                                                                                                                                                                                                                                                                                                                             | Date/ ref                                                                                              |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Colorectal cancer - ESMO  | NTRK fusions are extremely uncommon in mCRC with an incidence of <0.5%; however, testing is recommended when feasible.                                                                                                                                                                                                     | In the rare event that an NTRK fusion is detected by IHC and/or comprehensive genomic analysis, treatment with larotrectinib or entrectinib is recommended [III, A].                                                                                                                                                                                                                                                                         | Cervantes <i>et al.</i> 2023 (45)                                                                      |
| Melanoma - ESMO           | Testing can be offered for NRAS and c-KIT mutations; testing for NTRK alterations is recommended in the absence of BRAF or RAS mutations.                                                                                                                                                                                  | No recommendation                                                                                                                                                                                                                                                                                                                                                                                                                            | Amaral <i>et al.</i> 2024 (46)                                                                         |
| Breast cancer - ESMO      | Genomic profiling and further diagnostic tests [e.g., on tumour tissue or circulating tumour DNA (ctDNA)] should only be carried out as part of routine clinical practice if the result will change the treatment approach, as guided by the ESCAT scale, or if the patient can access appropriate clinical trials [V, B]. | In MBC, standard therapies are personalised based on biomarkers, as described in the respective sections. In addition, there are now several tissue and site-agnostic approvals. For example, both larotrectinib [ESMO-MCBS v1.1 score: 3; ESCAT score: I-C] and entrectinib [ESMO MCBS v1.1 score: 3; ESCAT score: I-C] are approved for patients with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. | Gennari <i>et al.</i> 2021 (47)                                                                        |
| Pancreatic cancer - ESMO  | For patients with metastatic PC and KRAS-wt tumours, microsatellite instability (MSI) status, NTRK fusion status and other rare fusions should be assessed [III, B]. If multigene sequencing is not carried out, MSI and NTRK fusions can be detected using standard methods [IV, B].                                      | In patients with an NTRK fusion, larotrectinib or entrectinib is recommended [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].                                                                                                                                                                                                                                                                                                            | Conroy <i>et al.</i> 2023 (48)                                                                         |
| Cholangiocarcinoma - ESMO | A core biopsy should be obtained for diagnostic pathology and molecular profiling before any nonsurgical treatment [III, A].                                                                                                                                                                                               | NTRK inhibitors are recommended in patients with NTRK fusions who have progressed on or are intolerant to prior treatment [III, A; ESCAT score: I-C].                                                                                                                                                                                                                                                                                        | Vogel <i>et al.</i> 2023 (49)                                                                          |
| Glioma – EANO & NCCN      | NTRK fusions can be detected in histologically diagnosed glioneuronal tumours, and cancer multi-gene panel tests should be widely and frequently performed.                                                                                                                                                                | In patients with a recurrent NTRK fusion positive CNS tumour and with standard of care therapies exhausted, treatment with an approved NTRK inhibitor is recommended, with a strong preference for treatment in a clinical study or as part of a registry.                                                                                                                                                                                   | Capper <i>et al.</i> 2023 (50), Mirallas <i>et al.</i> 2023 (51) and Funakoshi <i>et al.</i> 2021 (52) |

EANO: European Association of Neuro-Oncology; ESCAT: ESMO Scale for Clinical Actionability of molecular Targets; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; NTRK: Neurotrophic Tyrosine Receptor Kinase; WHO: World Health Organisation; wt: wild type.

There is no specific recommendation for bone sarcoma, appendiceal tumours or IFS.

In line with the marketing authorisation, patients eligible for larotrectinib will be those with locally advanced or metastatic disease, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. This represents a small yet diverse group, ranging from infants to adults with multiple tumour sites and histologies, all sharing a high unmet medical need.

#### *1.3.2.1.3. Personalised 'precision' medicine*

Evidence has shown that the use of targeted therapy paired with a specific oncogenic driver leads to better outcomes for patients compared to a “one-size-fits-all” treatment approach with standard of care therapies (53-56). Landmark examples include the introduction of imatinib for chronic myeloid leukaemia (CML), which transformed a once-fatal disease into one with near-normal life expectancy, and EGFR inhibitors in NSCLC, which significantly improve progression-free survival in biomarker-selected populations compared with chemotherapy (57, 58). Similarly, HER2-targeted therapies in breast cancer have led to unprecedented improvements in survival and durable disease control (59).

Targeted therapies also tend to offer more favourable toxicity profiles than conventional chemotherapy, allowing patients to maintain daily activities, return to work, and experience improved quality of life (QoL) (60, 61). This has also been explored with NTRK-positive patients and their caregivers, leading to the same conclusion (Section 2.15). Beyond the clinical benefits, health economic evaluations demonstrate that precision oncology can reduce the overall cost burden by avoiding ineffective treatments, minimising adverse event-related hospitalisations and optimising the use of healthcare resources (54-56, 60, 62).

Recently, the Genome UK 2022–2025 Implementation Plan for England has outlined NHS ambitions to embed genomics into routine care, with initiatives such as the £26 million Cancer 2.0 programme, which combines AI, genomic sequencing and digital imaging to enhance cancer diagnosis and treatment (63). The plan also expands access to genomic testing through the National Genomic Test Directory, pilots innovative technologies via NHS transformation projects, and introduces diagnostic



discovery pathways for rare diseases, enabling faster and more precise diagnoses that support truly personalised care.

Looking ahead, the continued integration of comprehensive genomic profiling into routine practice is expected to further refine patient selection, enhance outcomes, and support a more sustainable healthcare model. This is further supported by a recent systematic review, which reported that comprehensive genomic profiling-guided treatments improved overall survival (OS) and progression-free survival (PFS), particularly when results were evaluated in multidisciplinary molecular tumour boards (64).

Commissioning larotrectinib for routine use aligns with the NHS's aim to implement personalised medicine, ensuring that patients with NTRK fusion-positive tumours receive targeted therapies based on their unique genetic profiles. This targeted approach not only enhances treatment outcomes but also optimises healthcare resources by reducing the reliance on toxic and low-efficacy treatments. By supporting the use of larotrectinib, NICE can contribute to the NHS's goals of improving patient care and addressing the significant unmet medical need in this population.

## **1.4 Equality considerations**

As highlighted in section 1.3, larotrectinib represents a new paradigm in cancer treatment by targeting the oncogenic driver rather than the tumour location. The histology-independent nature of larotrectinib, the rarity of NTRK gene fusion cancers, combined with the natural heterogeneity of the patient population presents unorthodox challenges to the traditional technology assessment process. Restricting access to TRK inhibitors would raise significant equality concerns within the UK healthcare system. However, overcoming these challenges is crucial to ensure that patients with rare oncogenic drivers, such as those with NTRK fusions, have access to effective therapies like larotrectinib. By doing so, the NHS can ensure that all eligible patients benefit from this targeted treatment, ultimately improving health outcomes and advancing the field of precision medicine.

While NTRK testing is essential for ensuring the appropriate use of larotrectinib, current implementations across the UK vary considerably, potentially limiting access to this targeted therapy. This variation in genomic services is highlighted in the Sarcoma UK report published in 2024 (65). The report highlights three main health inequalities identified by hospitals and healthcare specialists in the UK that can be generalised for patients with NTRK fusion-positive solid tumours across the country:

- Regional disparities, particularly inequalities between patients treated in smaller hospitals versus those treated in urban hospitals.
- Conscious and unconscious biases made by some healthcare professionals may lead to the exclusion of patients from Black and ethnic minority backgrounds from testing opportunities.
- Certain ethnic groups may face exclusion due to language barriers, limiting their access to vital testing and treatment.

*Of note, patients with sarcomas (including bone sarcoma and soft tissue sarcoma) account for almost 1/4 of patients enrolled in larotrectinib's clinical trials and the CDF (cut-off July 2024) (see section 2).*

Additionally, if larotrectinib is not continually funded, access to TRK inhibitors would likely depend on patients' ability to self-fund or seek private healthcare, which is not feasible for everyone. This situation would introduce socio-economic inequalities within the system. Patients with TRK fusion-positive solid tumours in the UK would be denied the same opportunities for targeted treatment as their counterparts in Europe, where access to treatment, as per label, is widespread (e.g., German approval, Danish approval) (66, 67). Finally, there is a risk that patients with rare conditions are systematically disadvantaged in HTA processes. The rarity of these biomarkers often limits the availability of robust clinical and economic evidence, particularly in the absence of randomised controlled trials (68). Additionally, there is a significant heterogeneity in the patient population eligible for larotrectinib which complicates comparability between studies, as different studies are likely to have quite different case mixes of patients. This could lead to structural inequalities in access to innovative treatments for ultra-rare patient populations.

Given these considerations, it is imperative that larotrectinib is routinely commissioned by NICE to ensure access for all patients with NTRK fusion-positive tumours. By doing so, the NHS would uphold its commitment to personalised medicine and ensure that patients have the opportunity to benefit from this targeted therapy. Ensuring access to larotrectinib not only aligns with best practices in cancer care but also promotes fairness within the healthcare system, allowing all patients, regardless of their background or geographic location, to receive the most appropriate treatment for their condition.

## 2. Clinical effectiveness

### Summary of clinical effectiveness and safety of larotrectinib

TRK fusion cancers highlight a critical unmet need in cancer care, demanding targeted and transformative solutions (5, 28). Larotrectinib, a first in class, highly selective TRK inhibitor, is indicated for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours with an NTRK gene fusion.

This company submission provides updated evidence from the three larotrectinib studies that were used as pivotal evidence in the original NICE submission. The updated pooled analyses have longer follow-up, a larger sample size with broader representation of tumour types, and more mature survival data. All clinical trials began enrolling nearly a decade ago (study 20288 in 2014, and studies 20289 and 20290 in 2015), allowing patients to be followed up for an extended period of time to establish larotrectinib's long-term clinical effectiveness and safety. The latest data cut-off (extended primary analysis set 9 **[ePAS9]** and supplementary analysis set 3 **[SAS3]**, **20<sup>th</sup> July 2024**) presented in this section confirms the long-term clinical effectiveness, safety and tolerability of larotrectinib in NTRK fusion-positive solid tumours. This comprehensive analysis addresses previous uncertainties and provides robust evidence supporting the transformative benefits of larotrectinib.

### Clinical effectiveness

Clinical effectiveness was consistent across key subgroups such as age, tumour type, and number of prior systemic therapy received. In addition, the results are remarkably consistent across the datasets with increasing recruitment (with increased number and diversity of tumour types) and longer follow-up. This clinical benefit of larotrectinib was observed across all tumour types included, with the exception of ■ rare tumour types represented by only ■ patient each, therefore not calculable.

For patients with non-CNS tumours (**ePAS9**), response to larotrectinib was rapid and durable, with a median time to response of 1.84 months and a median duration of response of 43.3\_months. Survival data demonstrated the durability of efficacy, with a

median PFS of 28.0 months. Although median OS was not estimable (NE), patients treated with larotrectinib had a █% probability of being alive at 72 months.

In patients with NTRK fusion-positive primary CNS tumours (**SAS3**), an overall response rate (ORR) was observed in █% of patients (n=█), while the Disease Control rate (DCR) was observed at 16 and 24 weeks in █% (n=█) and █% (n=█) of patients, respectively. The median PFS was █ months, and although the median OS was NE, patients treated with larotrectinib had a █% probability of being alive at 72 months.

A post hoc growth modulation index (GMI) analysis used patients as their own control by comparing PFS while on larotrectinib to time to progression or treatment failure on the most recent prior therapy. It showed that █ (█) of patients had a GMI exceeding the threshold of meaningful clinical activity (i.e.,  $GMI \geq 1.33$ ), suggesting an improved disease response over prior therapy received.

Extended follow-up data also showed a rapid and sustained improvement in health-related quality of life (HRQoL) compared to baseline (based on ePAS6). For most patients, scores █ indicating a meaningful improvement in their QoL.

The analysis of outcomes clearly demonstrates larotrectinib's ability to achieve high response rate, rapid time to response and the subsequent durability of most responses. These results are particularly noteworthy, given that most patients in the pooled analyses had metastatic disease and were heavily pre-treated.

### Safety

Larotrectinib is well tolerated in patients with NTRK fusion-positive solid tumours. The latest data cut-off showed a very low rate of grade 3 and 4 treatment-emergent adverse event (TEAE), with no fatal TEAE attributed to larotrectinib. TEAEs that led to permanent discontinuation of larotrectinib occurred in █ (█%) patients, with only █ (█%) assessed to be related to the drug.

The safety profile of larotrectinib is characterised by manageable and reversible adverse events (AEs) that can be monitored, and it is comparable across adult and paediatric patients, as well as across tumour types.

#### Comparative effectiveness and real-world evidence

A series of comparative effectiveness analyses were conducted to provide supportive data on the clinical effectiveness of larotrectinib. Four indirect treatment comparisons of larotrectinib versus real-world non-TRK inhibitor standard of care (SOC) in both adult and paediatric patients with NTRK fusion-positive solid tumours consistently demonstrated statistically significant survival benefits and a longer duration of treatment with larotrectinib compared to real-world SOC. This addresses the uncertainty regarding the comparative effectiveness of larotrectinib highlighted in the original submission.

In addition, both company and publicly sponsored real-world studies demonstrated the generalisability of the larotrectinib trial populations to the real-world clinical setting, including that of the NHS. Specifically, data from the Systemic Anti-Cancer Therapy (SACT) showed that ORR was consistent with that of the larotrectinib trials, reinforcing robust efficacy of larotrectinib within a short timeframe of 10 weeks. The treatment with larotrectinib results in long survival times for a diverse and large proportion of patients, having no other satisfactory treatment options. The findings are also supportive of the proposed positioning of larotrectinib, addressing the key uncertainties mentioned in the original submission.

#### Conclusion

In summary, the results from the pooled analysis of extended follow-up data and improved survival demonstrate larotrectinib's long-term clinical effectiveness, safety and tolerability across a broad population, showcasing robust tumour-agnostic and age-agnostic antitumour activity against NTRK fusion-positive solid tumours. These findings confirm those presented in the original submission. The latest data cut-off presented in this company submission is the most comprehensive dataset for patients with TRK fusion cancer, representing a large diversity of tumour types with NTRK gene

fusions. The evidence base is further strengthened by a series of comparative effectiveness analyses and real-world studies, which demonstrate larotrectinib's clinical benefit versus real-world SOC, as well as supporting the external validity and generalisability of the trial populations to that of the NHS.

## **2.1 Identification and selection of relevant studies**

A systematic literature review (SLR) was conducted for the original submission on 11<sup>th</sup> March 2019 and updated on 6<sup>th</sup> May 2025 to identify studies investigating the efficacy and safety of larotrectinib and treatments recommended by NICE for patients with NTRK fusion-positive solid tumours.

The original SLR included a wider search to identify any evidence for a recognised comparator treatment in the same population, as well as information specifically on prognosis and natural history in patients with NTRK fusion-positive solid tumours and in patients with tumour sites/ locations known to harbour NTRK gene fusions. The updated literature search specifically targeted studies enrolling patients with NTRK fusion-positive solid tumours. A tumour site-specific search was not performed due to the limited availability of data on NTRK fusion status across individual tumour types. Including a wider population than NTRK fusion-positive patients would introduce heterogeneity that misaligns with the decision problem addressed in the company submission. This broader scope would dilute the relevance of the evidence base, making it difficult to draw conclusions specific to the treatment of NTRK fusion-positive solid tumours. Further, studies identified from the wider search conducted in the original SLR had very limited information on the NTRK status of patients, and hence they do not accurately reflect the target population of the assessment scope, leading to uncertainty. Therefore, the updated SLR focused on identifying relevant clinical studies of treatments for NTRK fusion-positive solid tumours.

In the SLR update, a total of 1,070 publications were screened, of which 69 full-text publications were reviewed. After excluding publications that did not meet the eligibility criteria, 16 publications were ultimately included in the SLR update. In addition, four relevant publications were identified through hand searches, resulting in a total of 20 publications included in the SLR update. The evidence comprised of five studies on

larotrectinib (no other treatments in NTRK fusion-positive solid tumours are recommended by NICE under routine commissioning), represented across 29 publications included from both the original and updated SLR. Full details of the SLR, including the search strategy, study selection process and results, are presented in Appendix B.

## **2.2 List of relevant clinical effectiveness evidence**

The SLR identified five unique studies investigating larotrectinib that are considered relevant to the decision problem specified in the NICE scope. Of these, three pivotal interventional clinical studies (Study 20288 [formerly LOXO-TRK-14001], Study 20289 [formerly LOXO-TRK-15002, NAVIGATE], and Study 20290 [formerly LOXO-TRK-15003, SCOUT]), form the core evidence base for this company submission and are the primary focus of the clinical effectiveness evaluation. In addition to the pivotal studies:

- One study evaluated larotrectinib in newly diagnosed IFS and other paediatric patients with NTRK fusion-positive solid tumours (69). This study is discussed in section 2.12, which describes the role of larotrectinib in the first-line (1L) setting.
- One study included patients with NTRK gene overexpression, of whom only two patients had confirmed NTRK fusion-positive solid tumours (70). Due to the limited data available for these two patients, the findings are summarised in Appendix B.

The updated analyses with extended follow-up for the three pivotal studies are presented in Table 4.



**Table 4. Clinical effectiveness evidence of larotrectinib**

| Study                                         | Study 20288 (Phase 1)                                                                                                                                                                                                                                        | Study 20289 (Phase 2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Study 20290 (Phase 1 / 2)                                                                                                                                                                                                                                                                                                                                                                                                                                         | Pooled analyses of studies 20288 and/or 20289 and/or 20290                                                                                                                                                                                                                                       |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Latest publications (since TA630 (71))</b> | Hong, 2019 (72)                                                                                                                                                                                                                                              | Qi, 2025 <sup>a</sup> (73)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Blattmann, 2025 (74)                                                                                                                                                                                                                                                                                                                                                                                                                                              | Brose, 2025 (75)<br>Xu, 2025 (76)<br>Casanova, 2025 (77)<br>Hong, 2025 (78)<br>Kummar, 2023 (79)<br>Waguespack, 2022 (80)<br>Hong, 2020 (81)<br>Mascarenhas, 2025 (82)<br>Perreault, 2024 (83)<br>Orbach, 2024 (84)<br>Kummar, 2021 (85)<br>Tan, 2025 (86)<br>Garcia, 2025 (87)<br>Le, 2024 (88) |
| <b>Study design</b>                           | <ul style="list-style-type: none"> <li>Phase 1, open-label, multicentre, 3+3 dose escalation with expansion phase in patients with NTRK gene fusions only</li> <li>Per protocol version 5.0, all patients must have had a proven NTRK gene fusion</li> </ul> | <ul style="list-style-type: none"> <li>Protocol versions 1–8: Phase 2, open-label, multicentre, basket study</li> <li>From protocol version 9.0 (08 OCT 2019), onwards the recruitment of the basket study stopped, and a new prospective cohort was introduced, to increase the number of patients across more common tumour types where NTRK gene fusions are rare</li> <li>In protocol version 11.0 (21 JUN 2021), a new exploratory objective to assess bone health was added</li> <li>In protocol version 12.0, a new cohort for bone health assessment was introduced</li> </ul> | <ul style="list-style-type: none"> <li>Phase 1: <ul style="list-style-type: none"> <li>Open-label study with a dose escalation and a dose expansion portion</li> </ul> </li> <li>Phase 2: <ul style="list-style-type: none"> <li>Single-arm, open-label study in IFS, other extracranial solid tumours, and primary CNS tumours</li> <li>In protocol version 14.0 (23 FEB 2022), a subcohort for new bone health assessment was introduced</li> </ul> </li> </ul> | See individual studies                                                                                                                                                                                                                                                                           |
| <b>Population</b>                             | <ul style="list-style-type: none"> <li>Adults (≥18yrs) patients with</li> </ul>                                                                                                                                                                              | <ul style="list-style-type: none"> <li>Adults and adolescents</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>Paediatric patients (birth to</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Pooled analysis includes</li> </ul>                                                                                                                                                                                                                       |

| Study                                                                     | Study 20288 (Phase 1)                                                                                                                                                                                                                                                                              | Study 20289 (Phase 2)                                                                                                                                                                                                                                                                                                           | Study 20290 (Phase 1 / 2)                                                                                                                                                                                                                                                                                                                                                                       | Pooled analyses of studies 20288 and/or 20289 and/or 20290                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                           | <p>locally advanced or metastatic, solid tumours refractory to standard therapies, n=75</p> <ul style="list-style-type: none"> <li>NTRK fusion-positive solid tumours: n=13 (8 in the dose escalation phase and 5 in the dose expansion phase)</li> <li>No documented NTRK fusion: n=62</li> </ul> | <p>(≥12yrs) with advanced or metastatic NTRK fusion-positive solid tumour, n=215</p> <ul style="list-style-type: none"> <li>A local amendment in South Korea allowed patients over 5 years of age to be enrolled from protocol version 6.4</li> <li>From protocol version 9.0 onwards, patients were at least 18 yrs</li> </ul> | <p>≤21yrs) with locally advanced or metastatic solid tumour or primary CNS tumours, n=154 (NTRK fusion-positive tumours: n=146)</p> <ul style="list-style-type: none"> <li>Phase 1 portion (dose expansion: n=17; dose escalation: n=24), included patients with or without NTRK gene fusions whereas the Phase 2 portion (n=113), was restricted to patients with NTRK gene fusions</li> </ul> | <p>patients from ePAS9 and SAS3; all patients had documented NTRK gene fusion</p> <ul style="list-style-type: none"> <li>The ePAS9 comprises n=304 patients: PAS (n=55) plus 249 patients who subsequently started study treatment by 19 JAN 2024 and fulfilled the definition of PAS</li> <li>SAS3: n=60 paediatric and adult patients with primary CNS tumours</li> </ul> |
| <b>Intervention(s)</b>                                                    | Larotrectinib administered on continuous 28-day schedule<br>Dose escalation: 50mg o.d. – 200mg b.d.<br>Expansion phase: 100mg b.d.                                                                                                                                                                 | Larotrectinib 100mg b.d. in continuous 28-day cycles                                                                                                                                                                                                                                                                            | Larotrectinib dosing was based on adult equivalent (50mg-150mg b.d.), then 100 mg/m <sup>2</sup> b.d. (with a maximum of 100mg b.d.) in continuous 28-day cycles                                                                                                                                                                                                                                | Larotrectinib (100mg or 150mg orally b.d.)                                                                                                                                                                                                                                                                                                                                  |
| <b>Comparator(s)</b>                                                      | N/A                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Indicate if study supports application for marketing authorisation</b> | Yes, the efficacy and safety evidence for larotrectinib were based on results from these studies, primarily as pooled analyses.                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                 | Yes.<br>FDA: PAS: n=55 (enrolled patients with sufficient duration of follow-up)<br>EU: ePAS: n=73 (enrolled patients with sufficient duration of follow-up)                                                                                                                                                                                                                |
| <b>Indicate if study used in the economic model</b>                       | Yes, data from a pooled analysis of NTRK fusion-positive patients from these trials have been used in the economic model.                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                 | Yes. Largest / most comprehensive dataset providing clinical and safety evidence for larotrectinib in NTRK fusion-positive solid tumours.                                                                                                                                                                                                                                   |
| <b>Rationale if study not used in model</b>                               | N/A                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Reported outcomes specified in the decision</b>                        | <ul style="list-style-type: none"> <li>Primary: safety</li> <li>Secondary endpoints: ORR<sup>b</sup></li> </ul>                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>Primary: ORR<sup>c</sup> (CR+PR)</li> <li>Secondary: BOR, DoR, PFS,</li> </ul>                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>Primary: <ul style="list-style-type: none"> <li>Phase 1: safety</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Primary: <b>ORR by IRC assessment.</b></li> </ul>                                                                                                                                                                                                                                                                                    |

| Study                                                          | Study 20288 (Phase 1) | Study 20289 (Phase 2)                               | Study 20290 (Phase 1 / 2)                                                                                                                                                                                                                                         | Pooled analyses of studies 20288 and/or 20289 and/or 20290                                                                      |
|----------------------------------------------------------------|-----------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| <b>problem</b> (outcomes in <b>bold</b> are used in the model) | (CR+PR), DoR          | OS, DCR, TRR, safety<br>• Exploratory: <b>HRQoL</b> | <ul style="list-style-type: none"> <li>○ Phase 2: ORR<sup>c</sup></li> <li>• Secondary: <ul style="list-style-type: none"> <li>○ Phase 1: ORR, DoR, BOR, DCR, <b>HRQoL</b>, safety</li> <li>○ Phase 2: DoR, BOR, DCR, OS, PFS, TRR, safety</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Secondary: ORR (investigator assessment), DoR, <b>PFS, OS, DCR, safety</b>.</li> </ul> |
| <b>All other reported outcomes</b>                             | Pharmacokinetics, MTD | Concordance between NTRK profiling, bone health     | Pharmacokinetics, MTD, DLT, bone health, concordance between NTRK profiling, postoperative staging                                                                                                                                                                | Time to response / best response, time on treatment                                                                             |

AE=adverse event; b.d.=twice daily; BOR=best overall response; CBR=clinical benefit rate; CNS=central nervous system; CR=complete response; DCR=disease control rate; DLT=dose-limiting toxicity; DoR=duration of response; ePAS=extended Primary analysis set; FDA=Food and Drug Administration; GI=gastrointestinal; GIST=gastrointestinal stromal tumour; HR-QoL=health-related quality of life; IFS=infantile fibrosarcoma; IRC=independent review committee; MASC=mammary analogue secretory carcinoma; MTD = maximum tolerated dose; N/A=not applicable; o.d.=once daily; ORR=overall response rate; OR=objective response; PAS=primary analysis set; PR=partial response; PFS=progression-free survival; RANO=Response Assessment in Neuro-oncology; RECIST=Response Evaluation Criteria in Solid Tumours; SAS=Supplemental Analysis Set (patients with primary CNS tumours); SD=stable disease; TRR=tumour regression rate; TRK=tyrosine receptor kinase; yrs=years

<sup>a</sup> The Qi (2025) study included only patients with gastrointestinal cancer (N=44), drawn from the 20289 study.

<sup>b</sup> By both IRC and Investigator assessment.

<sup>c</sup> By Investigator assessment in the interim CSRs until 20 JUL 2023 data cut-off and by IRC assessment thereafter and in the final CSR (and Investigator assessment secondary for studies 20289 and 20290).

Source: Table 1-2, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

## 2.3 Summary of methodology of the relevant clinical effectiveness evidence

This company submission provides updated evidence of the three larotrectinib studies that were used for regulatory approvals and as pivotal evidence in the original NICE submission (described below and presented in more detail in Appendix N). The updated pooled analysis has a longer follow-up, a larger sample size with broader representation of tumour types and more mature survival data. All clinical trials began enrolling nearly a decade ago (study 20288 in 2014 and studies 20289 and 20290 in 2015), allowing patients to be followed up for an extended period of time to establish larotrectinib's long-term clinical effectiveness and safety.

In addition, comparative evidence demonstrating larotrectinib's effectiveness against treatments for NTRK fusion-positive solid tumours used in clinical practice, where no TRK inhibitor is routinely available (section 2.10), and evidence supporting the clinical effectiveness and safety of larotrectinib in real-world clinical practice (see methodology in Appendix N and results in section 2.6) have become available since the original submission. Notably, results from the study by Laetsch *et al.* (section 2.12) further supports larotrectinib's efficacy and safety in the 1L paediatric population, reinforcing its proposed positioning in the treatment of NTRK fusion-positive solid tumours.

### Pooled analysis

The primary endpoint for the pooled efficacy analysis was overall response rate (ORR) by Independent Review Committee (IRC) assessments, based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, for non-CNS solid tumours. Secondary endpoints included duration of response (DoR), PFS and safety (89, 90). Details of the rationale, study design and methodology were published along with results from the pooled analysis early data cut-off July 2017 (91).

*Unless otherwise specified, the results and analyses of all efficacy and safety outcomes in this submission are presented for events occurring up to the most recent pooled analysis dated 20<sup>th</sup> July 2024.* The pooled analysis of efficacy is presented as two datasets – ePAS9 and SAS3. ePAS9 or 'Extended Primary Analysis set 9', reflects

an updated version of ePAS2, used in the original submission, and includes data from additional patients recruited since the data cut-off in July 2018. SAS3 or 'Supplementary analysis set 3', consists of 60 paediatric and adult patients with primary CNS tumours who otherwise met the PAS eligibility criteria (Appendix N) and were enrolled before the data cut-off. Patients with primary CNS tumours are excluded from the PAS because:

- Disease Control rate (DCR) may better define treatment efficacy in patients with CNS tumours than ORR (92) and could therefore be a more appropriate efficacy endpoint, since:
  - Changes in enhanced area upon CT or MRI have limitations and cannot be equated with changes in tumour size or tumour growth/activity of gliomas. Enhancement primarily indicates a disrupted blood–brain barrier and can be influenced by many factors such as radiologic technique, corticosteroid dose, inflammation, and seizure activity (92).
  - Surgery and radiation treatments can lead to varying amount of oedema, inflammation, and scarring, which can impact the radiological assessment in patients with primary CNS tumours.
- Patients with primary CNS tumours were evaluated by the IRC using the RANO criteria, whereas other solid tumours were evaluated by the IRC using RECIST v1.1. By investigator, primary CNS tumours were assessed by either RECIST v1.1 or RANO, while non-CNS tumours were assessed by RECIST v1.1. The RANO criteria has more detailed requirements to identify PR in CNS tumours in comparison to RECIST. The RECIST criteria mainly rely on changes in the longest diameter of the target lesion to define the response category, while the RANO criteria include other parameters such as clinical stability and reliance on corticosteroids within the definition (89).

### **Study 20288 [formerly LOXO-TRK-14001]: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumours (NCT02122913)**

Study 20288 (completed) is a multicentre, phase 1, open-label, dose escalation and dose expansion study in adult patients with advanced solid tumours. The primary objective of the dose escalation portion of the study was to characterise safety in terms

of dose-limiting toxicities (DLT) and maximum tolerated dose (MTD), with the aim of identifying an appropriate dose of larotrectinib for further study. The study is closed, and the results have been fully published, providing information on efficacy up to a data cut-off of February 19<sup>th</sup> 2018 (72). Following dose escalation, a dose expansion phase was initiated only for patients with documented NTRK fusion-positive solid tumours. Based on its tolerability and the durability of response in these patients with NTRK fusion-positive solid tumours, larotrectinib 100 mg twice daily was set as the recommended phase 2 dose. A total of 13 patients from this study contributed to the ePAS9 pooled analysis.

**Study 20289 [formerly LOXO-TRK-15002; NAVIGATE]: A Phase 2 Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Solid Tumours (NCT02576431)**

Study 20289 is an ongoing, international, multicentre, phase 2, open-label basket study in patients 12 years of age or older. The study included patients with recurrent, advanced solid tumours with a documented NTRK gene fusion, including NSCLC, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, primary CNS tumours, and a separate cohort that enrolled patients of all other histologic types or patients without measurable disease. Study 20289 has yet to be published, however evaluable patients are included in the pooled analyses, published at various analysis time points: Drilon 2018 (32) – data cut-off July 2017; American Society of Clinical Oncology (ASCO) abstracts (76, 86, 93) (see Table 4). A total of 191 patients from this study contributed to the ePAS9 and 19 patients to the SAS3 pooled analyses.

**Study 20290 [formerly LOXO-TRK-15003; SCOUT]: A Phase 1/2 Study of the Oral TRK Inhibitor LOXO-101 in Paediatric Patients with Advanced Solid or Primary Central Nervous System Tumours (NCT02637687)**

Study 20290 is an ongoing, international, multicentre, open-label phase 1/2 study in paediatric patients from birth to 21 years with advanced solid or primary CNS tumours. The primary objective of the phase 1 portion of the study was to assess the safety of larotrectinib in paediatric patients, with the aim of identifying an appropriate paediatric

dose for further study. Study 20290 is thus divided into a dose escalation phase, dose expansion (both phase 1), and a phase 2 portion where enrolment is restricted to patients with documented NTRK fusion-positive solid tumours (IFS, other extracranial solid tumours, and primary CNS tumours). The results of the completed phase 1 dose escalation cohort have been fully published (4). The recommended phase 2 dose was defined as 100 mg/m<sup>2</sup> twice daily (maximum 100 mg per dose) for infants, children, and adolescents, regardless of age. From this study, 100 patients contributed to the ePAS9 and 41 patients to the SAS3 pooled analyses.

Available methodological summary and efficacy results by individual study (up to the 20<sup>th</sup> July 2024 data cut-off) are presented in Appendix N. These data also provide ‘proof of concept’ for larotrectinib, in that they demonstrate lack of activity in solid tumours not harbouring an NTRK gene fusion.

### 2.3.1 Efficacy outcome measures

Similar efficacy endpoints were analysed across the studies; however, there was variation as to which endpoints were primary or secondary in each study. Endpoints used in the economic model, as specified in the scope are presented by study in Table 5. IRC assessments served as the principal data source for response, time to response, time to best response, DoR, DCR, and PFS (89).

**Table 5. Efficacy endpoints by study**

|     | Pooled analyses of studies 20288, 20289, 20290 (ePAS9 and SAS3) | Study 20288            | Study 20289          | Study 20290            |                      |
|-----|-----------------------------------------------------------------|------------------------|----------------------|------------------------|----------------------|
|     |                                                                 |                        |                      | Phase 1                | Phase 2              |
| ORR | Primary <sup>a</sup>                                            | Secondary <sup>b</sup> | Primary <sup>c</sup> | Secondary <sup>b</sup> | Primary <sup>c</sup> |
| DoR | Secondary                                                       | Secondary              | Secondary            | Secondary              |                      |
| DCR | Secondary                                                       | -                      | Secondary            | Secondary              |                      |
| PFS | Secondary                                                       | -                      | Secondary            | Secondary              |                      |
| OS  | Secondary                                                       | -                      | Secondary            | -                      | Secondary            |
| QoL | -                                                               | -                      | Exploratory          | Secondary              | Exploratory          |

DCR = disease control rate (also referred to as clinical benefit rate); DoR = duration of response; IRC = Independent Review Committee; NTRK = neurotrophic tyrosine receptor kinase; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life

<sup>a</sup> By IRC assessment

<sup>b</sup> By both IRC and Investigator assessment.

<sup>c</sup> By Investigator assessment in the interim CSRs until 20 July 2023 data cut-off and by IRC assessment thereafter and in the final CSR (and Investigator assessment secondary for studies 20289 and 20290).

Source: Table 1-4, Bayer, Data on file. Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

### 2.3.2 Patient baseline characteristics

Patient characteristics for the ePAS9 and SAS3 pooled analyses are summarised in Table 6. The pooled analysis datasets (data cut-off 20<sup>th</sup> July 2024) included 304 patients with non-CNS solid tumours (ePAS9) and 60 patients with primary CNS tumours (SAS3), all with an NTRK gene fusion.

For ePAS9 (patients with non-CNS solid tumours), the median age in the pooled analysis was 44.5 years (range 0.0-90.0 years) with [REDACTED] ([REDACTED]%) adults, ≥18 years of age. Most patients were 'white' ([REDACTED]%), and there was a slightly higher proportion of women in the analysis ([REDACTED]%). The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of [REDACTED] ([REDACTED]%). Almost all non-CNS patients ([REDACTED]%) had received prior cancer therapy (surgery, radiotherapy or systemic therapy). Larotrectinib was the initial systemic therapy for [REDACTED]% of patients where no satisfactory treatment option except mutilating surgery was available. A total of 28 different tumour histologies are represented in the pooled analysis dataset, the most common tumour types being soft tissue sarcoma (STS; n=72), primary CNS cancer (n=[REDACTED]), IFS (n=49), lung cancer (n=32), thyroid cancer (n=31), salivary gland tumour (n=[REDACTED]), and colorectal cancer (n=[REDACTED]) (89). The non-CNS tumours were mainly either [REDACTED] ([REDACTED]%) or [REDACTED] ([REDACTED]%) fusions, consistent with published literature indicating that NTRK1 and NTRK3 are the most prevalent in non-CNS tumours (94).

For patients with primary CNS tumours (SAS3), the median age was [REDACTED] years ([REDACTED] years). Patients were predominantly [REDACTED] years of age ([REDACTED]%), mostly [REDACTED] ([REDACTED]%) and there was a slightly higher proportion of women in the analysis ([REDACTED]%). Most patients had an ECOG PS of [REDACTED] ([REDACTED]%). [REDACTED] primary CNS tumour patients ([REDACTED]%) had received prior cancer therapy (surgery, radiotherapy or systemic therapy) (89). Most of the primary CNS tumours studied harboured an [REDACTED] fusion ([REDACTED]%), which is consistent with published literature demonstrating that NTRK2 is the most prevalent in primary CNS tumours compared to other tumour sites (95).



**Table 6. Baseline demographic and disease characteristics for pooled analysis and individual larotrectinib study populations (data cut-off 20<sup>th</sup> July 2024)**

| Baseline characteristics              | Pooled analysis of patients from Studies 20288, 20289 and 20290 <sup>a</sup> |              |
|---------------------------------------|------------------------------------------------------------------------------|--------------|
|                                       | ePAS9<br>n=304                                                               | SAS3<br>n=60 |
| <b>Age, n (%)</b>                     |                                                                              |              |
| Median age, years (range)             | 44.5 (0.0-90.0)                                                              |              |
| <b>Overall age group, n (%)</b>       |                                                                              |              |
| <1 month                              |                                                                              |              |
| 1 month - <1 yr                       |                                                                              |              |
| 1 - < 2 yr                            |                                                                              |              |
| 2 - < 6 yr                            |                                                                              |              |
| 6 - <12 yr                            |                                                                              |              |
| 12 - <16 yr                           |                                                                              |              |
| 16 - <18 yr                           |                                                                              |              |
| 18 - <45 yr                           |                                                                              |              |
| 45 - <65 yr                           |                                                                              |              |
| 65 - <75 yr                           |                                                                              |              |
| ≥75 yr                                |                                                                              |              |
| <b>Paediatric age group, n (%)</b>    |                                                                              |              |
| Infants/toddlers (birth – <24 months) |                                                                              |              |
| Children (2 – <12 yr)                 |                                                                              |              |
| Adolescents (12 – <18 yr)             |                                                                              |              |
| <b>Sex, n (%)</b>                     |                                                                              |              |
| Male                                  |                                                                              |              |
| Female                                |                                                                              |              |
| <b>Race, n (%)</b>                    |                                                                              |              |
| White                                 |                                                                              |              |
| Asian                                 |                                                                              |              |
| Black or African American             |                                                                              |              |
| American Indian or Alaska Native      |                                                                              |              |
| Native Hawaiian or Pacific Islander   |                                                                              |              |
| Multiple                              |                                                                              |              |
| Other                                 |                                                                              |              |
| Not reported                          |                                                                              |              |
| <b>Ethnicity, n (%)</b>               |                                                                              |              |
| Non-Hispanic/Latino                   |                                                                              |              |
| Hispanic/Latino                       |                                                                              |              |
| Not reported/Unknown                  |                                                                              |              |
| <b>Body weight (kg)</b>               |                                                                              |              |
| n                                     |                                                                              |              |

|                                           | Pooled analysis of patients from Studies 20288, 20289 and 20290 <sup>a</sup> |              |
|-------------------------------------------|------------------------------------------------------------------------------|--------------|
|                                           | ePAS9<br>n=304                                                               | SAS3<br>n=60 |
| <b>Baseline characteristics</b>           |                                                                              |              |
| Median (range)                            |                                                                              |              |
| <b>Height (cm)</b>                        |                                                                              |              |
| n                                         |                                                                              |              |
| Median (range)                            |                                                                              |              |
| <b>Body mass index (kg/m<sup>2</sup>)</b> |                                                                              |              |
| n                                         |                                                                              |              |
| Median (range)                            |                                                                              |              |
| <b>Body surface area (m<sup>2</sup>)</b>  |                                                                              |              |
| n                                         |                                                                              |              |
| Median (range)                            |                                                                              |              |
| <b>Primary tumour type, n (%)</b>         |                                                                              |              |
| STS                                       | 72 (24)                                                                      |              |
| IFS                                       | 49 (16)                                                                      |              |
| Thyroid                                   | 31 (10)                                                                      |              |
| Differentiated                            |                                                                              |              |
| Non-differentiated                        |                                                                              |              |
| Lung                                      | 32 (11)                                                                      |              |
| Salivary gland                            |                                                                              |              |
| Colorectal                                |                                                                              |              |
| Colon                                     |                                                                              |              |
| Rectal                                    |                                                                              |              |
| Breast                                    |                                                                              |              |
| Non-secretory                             |                                                                              |              |
| Secretory                                 |                                                                              |              |
| Melanoma                                  |                                                                              |              |
| Pancreas                                  |                                                                              |              |
| GIST                                      |                                                                              |              |
| Cholangiocarcinoma                        |                                                                              |              |
| Bone sarcoma                              |                                                                              |              |
| Gastric                                   |                                                                              |              |
| Cancer of unknown primary                 |                                                                              |              |
| Cervix                                    |                                                                              |              |
| CMN                                       |                                                                              |              |
| Prostate                                  |                                                                              |              |
| Appendix                                  |                                                                              |              |
| Duodenal                                  |                                                                              |              |
| Oesophageal                               |                                                                              |              |
| External auditory canal                   |                                                                              |              |
| Hepatic                                   |                                                                              |              |

|                                                 | Pooled analysis of patients from Studies 20288, 20289 and 20290 <sup>a</sup> |              |
|-------------------------------------------------|------------------------------------------------------------------------------|--------------|
|                                                 | ePAS9<br>n=304                                                               | SAS3<br>n=60 |
| <b>Baseline characteristics</b>                 |                                                                              |              |
| Lipofibromatosis                                | ██████████                                                                   | ██████████   |
| Testes                                          | ██████████                                                                   | ██████████   |
| Thymus                                          | ██████████                                                                   | ██████████   |
| Urothelial                                      | ██████████                                                                   | ██████████   |
| Uterus                                          | ██████████                                                                   | ██████████   |
| Primary CNS                                     | ██████████                                                                   | ██████████   |
| <b>Time from diagnosis, years</b>               |                                                                              |              |
| Median (range)                                  | ██████████                                                                   | ██████████   |
| <b>Disease status at enrolment n (%)</b>        |                                                                              |              |
| Locally advanced                                | ██████████                                                                   | ██████████   |
| Metastatic                                      | ██████████                                                                   | ██████████   |
| Primary CNS                                     | ██████████                                                                   | ██████████   |
| <b>NTRK gene, n (%)</b>                         |                                                                              |              |
| NTRK1                                           | ██████████                                                                   | ██████████   |
| NTRK2                                           | ██████████                                                                   | ██████████   |
| NTRK3                                           | ██████████                                                                   | ██████████   |
| Inferred NTRK3                                  | ██████████                                                                   | ██████████   |
| <b>Tumour stage at initial diagnosis, n (%)</b> |                                                                              |              |
| 0                                               | ██████████                                                                   | ██████████   |
| I                                               | ██████████                                                                   | ██████████   |
| II                                              | ██████████                                                                   | ██████████   |
| III                                             | ██████████                                                                   | ██████████   |
| IV                                              | ██████████                                                                   | ██████████   |
| Not reported/unknown                            | ██████████                                                                   | ██████████   |
| <b>ECOG PS, n (%)</b>                           |                                                                              |              |
| 0                                               | ██████████                                                                   | ██████████   |
| 1                                               | ██████████                                                                   | ██████████   |
| 2                                               | ██████████                                                                   | ██████████   |
| 3                                               | ██████████                                                                   | ██████████   |
| Not reported                                    | ██████████                                                                   | ██████████   |
| <b>No prior cancer therapy, n (%)</b>           |                                                                              |              |
| <b>Any prior cancer therapy, n (%)</b>          |                                                                              |              |
| Surgery                                         | ██████████                                                                   | ██████████   |
| Radiotherapy                                    | ██████████                                                                   | ██████████   |
| Systemic therapy                                | ██████████                                                                   | ██████████   |
| 0 prior systemic / missing                      | ██████████                                                                   | ██████████   |
| 1-2                                             | ██████████                                                                   | ██████████   |
| ≥3                                              | ██████████                                                                   | ██████████   |
| Median of prior systemic (range)                | ██████████                                                                   | ██████████   |

|                                                        | Pooled analysis of patients from Studies 20288, 20289 and 20290 <sup>a</sup> |              |
|--------------------------------------------------------|------------------------------------------------------------------------------|--------------|
|                                                        | ePAS9<br>n=304                                                               | SAS3<br>n=60 |
| <b>Baseline characteristics</b>                        |                                                                              |              |
| <b>Best response to last systemic treatment, n (%)</b> |                                                                              |              |
| CR                                                     | ████                                                                         | ████         |
| PR                                                     | ████                                                                         | ████         |
| SD                                                     | ████                                                                         | ████         |
| PD                                                     | ████                                                                         | ████         |
| Unevaluable/unknown/not applicable                     | ████                                                                         | ████         |

CMN = congenital mesoblastic nephroma; CNS = central nervous system; CR = complete response; ECOG = Eastern Cooperative Oncology Group; ePAS9 = Extended Primary Analysis Set 9; GIST= gastrointestinal stromal tumour; IFS = infantile fibrosarcoma; n = number; no. = number; NSCLC = non-small cell lung cancer; NTRK = neurotrophic receptor tyrosine kinase; PD = progressive disease; PR = partial response; PS = performance status; SAS3 = Supplemental Analysis Set 3; SD = stable disease; STS = soft tissue sarcoma; yr = year;

<sup>a</sup>ePAS9 and SAS3: efficacy-evaluable patients; demographics for individual studies based on safety analysis sets  
<sup>b</sup>n=303. Patient 20289-702-003 had a missing date of initial diagnosis

Note: due to rounding, percentages may not total to exactly 100%

Source: Tables 3-8, 3-9 and 3-10, Bayer, Data on file. Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

## 2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

### 2.4.1 Analysis sets

Patients were selected according to the eligibility criteria and analyses were performed with pooled data from the three larotrectinib trials (Study 20288, Study 20289, and Study 20290) as described in the original submission and section 2.3 of this company submission (71). The pooled population was representative of the anticipated target population for larotrectinib with respect to the range of patient ages (ePAS9: █████ years, median 44.5 years; SAS3: █████ years, median █████ years) and a broad range of tumour types represented (29 different tumour types - 28 types in ePAS9 and 1 type in SAS3) (89).

The original submission included analyses from primary analysis set (PAS) and ePAS2 with data cut-off 30<sup>th</sup> July 2018 (93 patients included). With an increase in patient numbers across the three individual clinical studies, the pooled analysis dataset was extended and further analysed at different cut-off timepoints, 15<sup>th</sup> July 2019 (ePAS4 – 164 patients), 20<sup>th</sup> July 2020 (ePAS5 – 192 patients), 20<sup>th</sup> July 2021 (ePAS6 – 244 patients), 20<sup>th</sup> July 2022 (ePAS7 – 272 patients), 20<sup>th</sup> July 2023 (ePAS8

– 302 patients) and 20<sup>th</sup> July 2024 (ePAS9 – 304 patients). The SAS population also increased from nine patients in the primary CNS population in the first submission (July 2018 data cut-off) to 60 patients in this submission (July 2024 data cut-off).

The primary population for the analysis of clinical effectiveness of larotrectinib in this company submission comprises ePAS9 (n=304) and SAS3 (n=60) datasets. This includes all evaluable patients with documented NTRK gene fusion, advanced solid tumours (ePAS9) or primary CNS tumours (SAS3) with measurable disease as of the data cut-off 20<sup>th</sup> July 2024 (Table 9) (89).

Three analysis sets were defined for safety – the Overall Safety Analysis Set (OSAS), the NTRK Gene Fusion Cancers Safety Analysis Set (NFCSAS), and the Efficacy-evaluable NTRK Gene Fusion Cancers Safety Analysis Set (ENFCSAS) (Table 7) (90).

**Table 7. Definition of relevant larotrectinib data analysis sets included within the company submission**

| Analysis set                     | Definition                                                                                                                                                                                                | Number of valid patients in treatment group |                |                |                    |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------|----------------|--------------------|
|                                  |                                                                                                                                                                                                           | Study 20288, n                              | Study 20289, n | Study 20290, n | Pooled analysis, n |
| Population for efficacy analysis |                                                                                                                                                                                                           |                                             |                |                |                    |
| ePAS9                            | Patients (≥1 dose larotrectinib) with NTRK fusion cancer using RECIST, version 1.1 at baseline (excluding primary CNS tumours and patients without measurable disease) (as of 20 <sup>th</sup> July 2024) | ■                                           | ■              | ■              | 304                |
| SAS3                             | Patients (≥1 dose larotrectinib) with primary CNS tumours, who otherwise met PAS eligibility criteria and were enrolled before 20 <sup>th</sup> July 2024                                                 | ■                                           | ■              | ■              | 60                 |
| Population for safety analysis   |                                                                                                                                                                                                           |                                             |                |                |                    |
| Overall Safety Analysis Set      | All paediatric and adult patients (≥1 dose larotrectinib) with/ without NTRK fusions (as of 20 <sup>th</sup> July 2024)                                                                                   | ■                                           | ■              | ■              | ■                  |
| NTRK Gene Fusion                 | All paediatric and adult patients (≥1 dose larotrectinib) with documented NTRK                                                                                                                            | ■                                           | ■              | ■              | ■                  |

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| Analysis set                                                           | Definition                                                                                                                      | Number of valid patients in treatment group |                |                |                    |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------|----------------|--------------------|
|                                                                        |                                                                                                                                 | Study 20288, n                              | Study 20289, n | Study 20290, n | Pooled analysis, n |
| <b>Cancers Safety Analysis Set</b>                                     | fusions cancer (as of 20 <sup>th</sup> July 2024)                                                                               |                                             |                |                |                    |
| <b>Efficacy-evaluable NTRK Gene Fusion Cancers Safety Analysis Set</b> | All patients included for ePAS9 who provide the primary analysis set for efficacy evaluation (as of 20 <sup>th</sup> July 2024) | ■                                           | ■              | ■              | ■                  |

CNS= central nervous system; ePAS= extended primary analysis set; n= number; NTRK= neurotrophic tyrosine receptor kinase.

Sources: Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89) and Larotrectinib (BAY 2757566) Summary of clinical safety 2024 (90)

## 2.4.2 Overview of statistical analyses

An overview of the statistical analysis for the endpoints of the pooled analysis is presented in Table 8. Data management for handling of missing data and censoring was done as described in original submission (71).

**Table 8. Summary of statistical analyses for the pooled analysis from Study 20288, Study 20289 and Study 20290**

| Trial number (acronym)                                                           | Hypothesis objective                                                                                                                                                                                     | Statistical analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Sample size, power calculation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pooled analyses of patients from Study 20288, Study 20289 and Study 20290</b> | <p>Under the planned primary analysis of effectiveness, a true ORR of <math>\geq 50\%</math> is hypothesised when larotrectinib is administered to patients with NTRK fusion-positive solid tumours.</p> | <p><b>Statistical analyses were performed using SAS® version 9.2 or later.</b></p> <p><b>Primary endpoint:</b></p> <ul style="list-style-type: none"> <li>- Performed according to the ITT principle</li> <li>- Using data cut-off of 20<sup>th</sup> July 2024</li> </ul> <p>The primary endpoint was ORR determined by an independent review committee (IRC). Response rates were summarised descriptively by number and percentage. The agreement rate between IRC and Investigator assessments of response was tabulated. The best overall response was summarised descriptively by number and percentage. Point estimates were accompanied by a two-sided 95% exact binomial CI using the Clopper-Pearson method.</p> <p><b>Supportive analyses of primary endpoint:</b></p> <ul style="list-style-type: none"> <li>- ORR was calculated based on local investigator assessment of response and agreement rate between IRC and Investigator response assessment calculated.</li> <li>- Change in tumour burden was calculated for each patient as the percentage change from baseline in the sum of diameters of target tumour lesions at each time point. The best tumour burden change was summarised descriptively, by calculating the median and interquartile range across patients, and presenting as a waterfall plot. Spider plots displayed change in tumour burden over time for each patient. Swimmer plots showed occurrence of clinical outcomes of interest over time (e.g. Time to response (TTR), DoR, disease progression, treatment discontinuation, death).</li> </ul> <p><b>Secondary endpoints:</b></p> <ul style="list-style-type: none"> <li>- The Kaplan-Meier method was used to evaluate duration of response (DoR), PFS and OS, with the two-sided 95% CI about the median calculated using Greenwood's formula.</li> <li>- Analysis of disease control rate was based on the methods described for ORR.</li> </ul> <p>IRC assessments served as the principal data source for TTR, time to best response (TTBR), DoR, DCR and PFS. Supplemental analyses based on local investigator assessments were provided.</p> | <p>A sample size of 55 patients was estimated to provide 80% power to achieve a lower boundary of the 2-sided 95% exact binomial CI about the estimated ORR exceeding 30%.</p> <p>Ruling out a lower limit of 30% for ORR was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in genetically-defined patient populations who have progressed on prior therapies. Under the primary analysis, the lower limit of the 95% CI would exceed 30% when the estimated ORR was 46% or greater (Clopper-Pearson method).</p> |

| Trial number (acronym) | Hypothesis objective | Statistical analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Sample size, power calculation |
|------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
|                        |                      | <p>TTR and TTBR (calculated for responders only) were summarised descriptively by calculating the median, interquartile range, and minimum and maximum values. The number and percentage of patients by the milestone time points were tabulated. Kaplan-Meier curves were used to graphically present the time to response/time to best response distribution over time.</p> <p><b>Safety analysis:</b></p> <p>AEs were coded using MedDRA. AEs were summarised based on the number and percentage of patients with any AE overall, by MedDRA System Organ Class and preferred term (PT) and in exposure-adjusted tables. TEAEs and treatment-emergent SAEs were also reported. All deaths, AEs leading to discontinuation were monitored. Clinical laboratory evaluations (haematology and serum chemistries) were summarised in a descriptive manner by calculating the mean, standard deviation, median, and range.</p> <p>Vital signs and body weight were measured, and ECGs were performed in each study at screening and at periodic time points following the initiation of larotrectinib and described in a descriptive manner.</p> <p>ECOG performance status was graded depending on patient's age and tumour type.</p> <p>Some categories of AE were designated to be of special interest (ALT/AST elevation, neutropenia, neurologic reactions, withdrawal syndrome and peripheral neuropathy).</p> <p>Incidence of TEAEs were calculated for subgroups and special populations.</p> <p><b>Exploratory analysis:</b></p> <p>The exploratory analysis of PRO data was performed in two phases.</p> <p><b>First phase:</b> Summary statistics (i.e., number of patients with data, mean, standard deviation, median, interquartile range, range) were provided for continuous variables, and number and frequencies were provided for categorical variables.</p> <p>For each PRO instrument, all PRO domain scores, including the total score, were summarised by scheduled visits. Summaries were presented for continuous variables if there were at least two patients with PRO scores at a scheduled visit.</p> |                                |



| Trial number<br>(acronym) | Hypothesis<br>objective | Statistical analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Sample size, power<br>calculation |
|---------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
|                           |                         | <p>For time to event variables, we presented total number of patients, number of patients with event, and, if estimable, 25<sup>th</sup> percentile and median of time to event with 95% CI, minimum, and maximum.</p> <p>PRO scores at baseline or during treatment were presented for each patient through waterfall and swimmer plots. Average scores were presented through bar charts.</p> <p><b>Second phase:</b> Longitudinal data models were constructed to assess whether the BOR rate was accompanied by impairment of EORTC QLQ-C30 physical functioning and EQ-5D-5L mobility and to assess relationship among baseline symptom scores, disease severity, tumour type, and change in EORTC QLQ-C30 fatigue score over time.</p> <p>The variables ECOG baseline score, stage of disease, number of prior systemic regimens, and tumour diagnosis were tested for model inclusion using a forward selection process with P value less than or equal 0.1.</p> <p>The covariance matrix was modelled by random coefficients (i.e., random intercepts and slopes by patient with an unstructured covariance matrix).</p> |                                   |

AE=adverse event; ALT=alanine transaminase; AST=aspartate aminotransferase; BOR=best overall response; CI=confidence interval; DCR=disease control rate; DoR=duration of response; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; EQ-5D-5L=EuroQol 5 dimension 5 level; HR=hazard ratio; IRC=independent review committee; ITT=intention to treat; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcomes; PT=preferred term; SAE=serious adverse event; SAP=statistical analysis plan; SOC=system organ class; TEAE=treatment-emergent adverse event; TT(B)R=time to (best) response  
Source: Bayer Larotrectinib SAP version 6.0 (96)

#### **2.4.2.1 Patient disposition**

The ePAS9 dataset, presented in this company submission, included extended follow-up of 304 patients (until 20<sup>th</sup> July 2024) compared to 93 patients in ePAS2 presented in the original submission. The SAS3 dataset included 60 patients with primary CNS tumour, as compared to only nine patients in the original submission.

A summary of the disposition for the pooled analysis set and by individual studies is presented in Appendix D.

#### **2.4.2.2 Post hoc analysis**

As described in the original submission, an updated post hoc analysis was conducted using the growth modulation index (GMI) for intra-patient comparison. GMI is an intra-patient comparison that uses patients as their own control by comparing PFS on current therapy (larotrectinib) to time to progression (TTP) or treatment failure on the most recent prior therapy (TTP<sub>-1</sub>); namely the ratio of PFS/TTP. Three sensitivity analyses were conducted to account for the fact that not all patients had a recorded date of disease progression prior to starting larotrectinib. In sensitivity analysis set 1, the progression date was imputed as the date of the first dose of larotrectinib. For sensitivity analysis set 2, the missing progression date on prior therapy was censored for Kaplan-Meier analyses, using the discontinuation date on prior therapy as the censoring date. In sensitivity analysis set 3, only patients from study 20289 who had at least one prior therapy and a reported progression date on therapy were included in this analysis (97).

### **2.5 Critical appraisal of the relevant clinical effectiveness evidence**

The Downs and Black checklist was used to assess the risk of bias of the included single-arm non-randomised studies. This checklist consists of 27 items that address the following methodological components: reporting, external validity, internal validity (bias and confounding), and power. Twenty-six items are rated either as yes (=1) or no/unable to determine (=0), and one item is rated on a 3-point scale (yes = 2, partial = 1, and no = 0). Scores range from 0 to 28 with higher scores indicating a better methodological quality of the study. The following cut points have been suggested to

categorise studies by quality: excellent (26-28), good (20-25), fair (15-19) and poor ( $\leq 14$ ). Notably, out of the 27 questions in the checklist, four are not applicable to single-arm trials. These questions pertain to blinding of treatment and outcome assessment, as well as randomisation to treatment, which are not relevant in the context of single-arm trial designs. Similar approaches have been reported in previously submitted NICE systematic reviews that applied the Downs and Black checklist to non-comparative designs, ensuring meaningful quality grading. As the exclusion of non-applicable items lowers the maximum score, thresholds are recalibrated to maintain proportional interpretation. Therefore, the cut points for good, fair and poor quality were arbitrarily adjusted to 23-16, 11-15 and  $\leq 10$  respectively (98).

In the original and updated SLR, five larotrectinib studies (studies 20288, 20289, 20290, ADVL1823 and Thavaneswaran 2024) were included (4, 69, 70, 72, 91). The quality assessment of these studies showed that the study aims, outcomes, patient characteristics, interventions, and AEs were clearly reported. However, as all five were non-comparative and non-randomised, it was not relevant to include methods to reduce bias or adjust for confounding factors. These are basket trials which are designed to evaluate a single investigational drug across multiple tumour types sharing a common molecular alteration and are typically single-arm in nature (68, 99). Overall, these studies were considered to be of fair quality and details of the quality assessment are provided in Appendix B.

## **2.6 Clinical effectiveness results of the relevant studies**

### **2.6.1 Pooled analyses (ePAS9 and SAS3)**

#### **2.6.1.1 Primary efficacy outcome**

##### **2.6.1.1.1 Overall response rate (ORR) by IRC assessment**

As of 20<sup>th</sup> July 2024, the independently assessed ORR in patients with non-CNS NTRK fusion-positive tumours (ePAS9) was 65% (95% CI: 59, 70), with confirmed response in ■■■ patients out of 304. This included 66 patients (22%) with confirmed complete responses (CR), 20 (7%) with CR by surgery/pathology (pCR) and 112 (37%) of patients with partial response (PR), while stable disease (SD) was achieved

in 56 patients (18%). Patients with primary CNS tumours were analysed separately from the ePAS9 patients (SAS3 dataset; n=60) and had █% (95% CI: █ █) independently assessed ORR. Overall, █ patients showed confirmed response of which █ patients (█%) with CR and █ patients (█%) with PR, while SD was achieved in █ patients (█%) (Table 9) (89).

**Table 9. Summary of overall response rate and disease control rate (ePAS9 and SAS3, data cut-off 20<sup>th</sup> July 2024)**

| Outcome                                                | ePAS9<br>(N=304) | SAS3<br>(N=60) |
|--------------------------------------------------------|------------------|----------------|
| <b>BOR<sup>a</sup>, n (%)</b>                          |                  |                |
| Any CR                                                 | 86 (28)          | █              |
| CR                                                     | 66 (22)          | █              |
| pCR <sup>e</sup>                                       | 20 (7)           | █              |
| PR                                                     | 112 (37)         | █              |
| SD                                                     | 56 (18)          | █              |
| <16 weeks                                              | █                | █              |
| ≥16 weeks                                              | █                | █              |
| <24 weeks                                              | █                | █              |
| ≥24 weeks                                              | █                | █              |
| PD                                                     | 32 (11)          | █              |
| BOR Not evaluable                                      | 16 (5)           | █              |
| BOR undefined                                          | 2 (1)            | █              |
| <b>Overall response<sup>b</sup></b>                    |                  |                |
| Number of patients with OR<br>(confirmed CR/pCR/PR)    | █                | █              |
| ORR, % [95% CI]                                        | 65 [59, 70]      | █              |
| <b>Disease Control rate (DCR) 16 weeks<sup>c</sup></b> |                  |                |
| Number of patients                                     | █                | █              |
| DCR, % [95% CI]                                        | █                | █              |
| <b>Disease Control rate (DCR) 24 weeks<sup>d</sup></b> |                  |                |
| Number of patients                                     | █                | █              |
| DCR, % [95% CI]                                        | █                | █              |

BOR = best overall response; CI = confidence interval; CNS = central nervous system; CR = complete response; DCR = disease control rate; ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; N = total number of patients (100%); n = number of patients in category/with event; OR(R) = overall response (rate); pCR = pathological CR; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumours; SAS3 = Supplemental Analysis Set 3; SD = stable disease

Note: SD is measured from the date of the first dose of larotrectinib.

- None or no data available.

<sup>a</sup> BOR classification based on independent radiologist and independent clinical assessments for patients assessed by RECIST v1.1 (non-CNS patients) and based on independent radiologist assessments, clinical status, and corticosteroid use for patients assessed by RANO (CNS patients).

<sup>b</sup> ORR is the proportion of patients with a BOR of confirmed CR, pCR, or confirmed PR. Responses were confirmed by a repeat assessment performed no less than 28 days after the criteria for response were first met. Patients with unconfirmed CR following PR are considered confirmed responders.

<sup>c</sup> DCR (16 weeks) is the proportion of patients with a BOR of confirmed CR, pCR, confirmed PR, or SD lasting 16 weeks or more following the initiation of larotrectinib. Patients with unconfirmed CR following PR are considered confirmed responders for analysis. Otherwise, patients with unconfirmed CR or PR at 16 weeks or more are considered to have SD for analysis.

<sup>d</sup> DCR (24 weeks) is the proportion of patients with a BOR of confirmed CR, pCR, confirmed PR, or SD lasting 24 weeks or more following the initiation of larotrectinib. Patients with unconfirmed CR following PR are considered confirmed responders for analysis. Otherwise, patients with unconfirmed CR or PR at 24 weeks or more are considered to have SD for analysis.

<sup>e</sup> Patients on larotrectinib therapy who underwent surgical resection with no viable tumour cells and negative margins on postsurgical pathology report were considered a CR by surgery/pathology, and their presurgical best response was reclassified pCR after surgery. Previously referred to as surgical CR in source documents.

<sup>f</sup> Patient 20290-402-158 underwent surgical resection with no viable tumour cells and negative margins on postsurgical pathology evaluation and was assessed as a pCR by Investigator. The patient could not be considered pCR as radiological tumour assessment by IRC was SD.

Source: Table 3-13, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

### 2.6.1.1.2. Longevity of IRC assessed ORR across pooled analysis datasets

In this most recent pooled analysis (ePAS9), larotrectinib continues to consistently show remarkable efficacy, with a marked and durable response in NTRK fusion-positive solid tumours across multiple tumour types regardless of age, histology type, or specific NTRK gene fusion (89).

For the primary efficacy endpoint of ORR, the results have been consistent across the datasets with increasing recruitment and longer follow-up. Starting from PAS (2017) and extending to the most recent ePAS9 (2024) dataset, the ORRs (IRC assessed) were 75% and 65% for these datasets, respectively (Table 10). The consistent ORR reinforces strong and reliable efficacy of larotrectinib across a growing patient population. Furthermore, compared to the data from ePAS2 presented in the original submission, this submission presents compelling results in patients with longer follow-up. The median DoR has remained highly consistent across the pooled analysis sets, emphasising the long-term benefit of larotrectinib (89).

**Table 10. ORR and DoR trends across pooled analysis datasets - IRC assessed (data cut-off 20<sup>th</sup> July 2024)**

| Pooled Analysis Set | N   | ORR (%)                                                                             | CR (%)                                                                              | pCR (%)                                                                             | PR (%)                                                                                | Median DoR <sup>a</sup> , Months                                                      |
|---------------------|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| PAS                 | 55  | 75                                                                                  | 24                                                                                  | 4                                                                                   | 47                                                                                    | 43.3                                                                                  |
| ePAS2               | 93  | 71                                                                                  | 23                                                                                  | 3                                                                                   | 45                                                                                    | 43.3                                                                                  |
| ePAS4               | 164 |  |  |  |  |  |
| ePAS5               | 192 |  |  |  |  |  |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

| Pooled Analysis Set | N   | ORR (%) | CR (%) | pCR (%) | PR (%) | Median DoR <sup>a</sup> , Months |
|---------------------|-----|---------|--------|---------|--------|----------------------------------|
| ePAS6               | 244 | ■       | ■      | ■       | ■      | ■                                |
| ePAS7               | 272 | ■       | ■      | ■       | ■      | ■                                |
| ePAS8               | 302 | ■       | ■      | ■       | ■      | ■                                |
| ePAS9               | 304 | 65      | 22     | 7       | 37     | 43.3                             |

CR= complete response; DoR= duration of response; ePAS= extended primary analysis set; ORR= overall response rate; pCR= pathological complete response; PR= partial response.

<sup>a</sup> The median follow-up for each median DoR as presented were as follows: PAS, 50.4 months; ePAS2, 54.8 months; ePAS4, ■ months; ePAS5, ■ months; ePAS6, ■ months; ePAS7, ■ months; ePAS8, ■ months and ePAS9, 45.1 months.

Source: Bayer. Data on file. 8. Tables, figures and listings for Integrated Summary of Efficacy. (BAY 2757556) Database cut-off 20<sup>th</sup> July 2024 (100)

## 2.6.1.2 Secondary efficacy outcomes

### 2.6.1.2.1. ORR by investigator assessment

The ORR was determined by investigator assessment as a secondary outcome and showed high concordance with IRC assessed ORR (89).

### 2.6.1.2.2. Disease control rate (DCR)

Disease control rate (defined as the proportion of patients with best overall response (BOR) of confirmed CR, pCR, confirmed PR, or SD lasting 16 weeks or more following the initiation of larotrectinib) was ■% (95% CI: ■, ■) for the ePAS9 group (per IRC review). DCR in the primary CNS tumour group (SAS3) was ■% (95% CI: ■, ■) per IRC review (Table 9) (89).

### 2.6.1.2.3. Best changes in the sum of diameters of target lesions

As presented in the waterfall plot (Figure 6), tumour shrinkage of ≥■% occurred (data cut-off 20<sup>th</sup> July 2024) in ■ (■%) patients in ePAS9 with baseline assessments and at least one post-baseline assessment (manually calculated from Figure 6) (89). In addition, tumour regression rate (TRR) was ■% (■/304 patients) for ePAS9 by IRC assessment.

For SAS3, tumour shrinkage of ≥50% occurred in ■ (■%) patients with baseline assessments and at least one postbaseline assessment (manually calculated from Figure 7). TRR for SAS3 patients was ■% (■/125 patients; 95% CI: [■, ■]) (89).

**Figure 6. Waterfall plot of best change in sum of diameters of target lesions by tumour type - IRC assessed (ePAS9, data cut-off 20<sup>th</sup> July 2024)**



ePAS9 = Extended Primary Analysis Set 9; GIST = gastrointestinal stromal tumour; IFS = infantile fibrosarcoma; IRC = Independent Review Committee; n = number of patients in category/with event; RECIST = Response Evaluation Criteria in Solid Tumours

Note: Disease assessments based on IRC using RECIST (version 1.1).

n= [REDACTED]

Source: Fig 3-1, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

**Figure 7. Waterfall plot of best change in sum of diameters of target lesions - IRC assessed (SAS3, data cut-off 20<sup>th</sup> July 2024)**



IRC = Independent Review Committee; n = number of patients in category/with event; RANO = Response Assessment in Neuro-Oncology Criteria; SAS3 = Supplemental Analysis Set 3

Note: Disease assessments based on IRC using RANO products of diameters.

n=■

Source: Fig 3-6, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

#### 2.6.1.2.4. Time to response (TTR)

As of 20<sup>th</sup> July 2024, median time to first response for ■ responding patients in ePAS9, according to IRC assessment, was ■ months (range: ■ ■), whereas best response was observed in ■ (range: ■ ■). Similar median TTR of ■ months (range: ■ ■) was observed in 60 patients in SAS3, whereas best response was observed in ■ (range: ■ ■) (Table 11) (89).



**Table 11. Time to first and best response - IRC assessed (ePAS9 and SAS3, data cut-off 20<sup>th</sup> July 2024)**

|                                                                   | ePAS9<br>N=304              |                            | SAS3<br>N=60                |                            |
|-------------------------------------------------------------------|-----------------------------|----------------------------|-----------------------------|----------------------------|
|                                                                   | First response <sup>a</sup> | Best response <sup>c</sup> | First response <sup>a</sup> | Best response <sup>c</sup> |
| <b>Responding patients (confirmed CR, pCR and PR<sup>b</sup>)</b> | ■                           | ■                          | ■                           | ■                          |
| Median time (months)                                              | ■                           | ■                          | ■                           | ■                          |
| 25 <sup>th</sup> , 75 <sup>th</sup> percentiles                   | ■                           | ■                          | ■                           | ■                          |
| Range                                                             | ■                           | ■                          | ■                           | ■                          |
| <b>Time to response, n (%)</b>                                    |                             |                            |                             |                            |
| ≤ 2 months                                                        | ■                           | ■                          | ■                           | ■                          |
| >2 to 4 months                                                    | ■                           | ■                          | ■                           | ■                          |
| >4 to 6 months                                                    | ■                           | ■                          | ■                           | ■                          |
| >6 to 9 months                                                    | ■                           | ■                          | ■                           | ■                          |
| >9 months                                                         | ■                           | ■                          | ■                           | ■                          |

BOR = best overall response; CNS = central nervous system; CR = complete response; ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; N = total number of patients (100%); n = number of patients in category/with event; pCR = pathological CR; PR = partial response; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumours; SAS3 = Supplemental Analysis Set 3

<sup>a</sup> Time to response is defined as the number of months elapsed between the date of the first dose of larotrectinib and the first documentation of objective response (CR, pCR, or PR, whichever occurred earlier) that was subsequently confirmed. Patients with unconfirmed CR following PR are considered confirmed responders for analysis.

<sup>b</sup> BOR classification based on independent radiologist and independent clinical assessments for patients assessed by RECIST v1.1 (non-CNS patients) and based on independent radiologist assessments, clinical status, and corticosteroid use for patients assessed by RANO (CNS patients).

<sup>c</sup> Time to best response is defined as the number of months elapsed between the date of the first dose of larotrectinib and the first documentation of CR or pCR (if patient's BOR is confirmed CR or pCR) or PR (if patient's BOR is confirmed PR) that was subsequently confirmed. Patients with unconfirmed CR following PR are considered confirmed responders at time of first PR.

Source: Table 3-15, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

As of data cut-off 20<sup>th</sup> July 2024, the duration of study treatment ranged between ■ and ■ months in ePAS9 with ■% (■/304) of patients still receiving ongoing treatment and between ■ and ■ months in SAS3 with ■% (■/60) of patients still on treatment (Appendix N) (89).

#### 2.6.1.2.5. Duration of response (DoR)

At the time of data cut-off (20<sup>th</sup> July 2024), ■ patients (■%) in ePAS9 had achieved a response by IRC assessment, with a median follow-up time of 45.1 months and median DoR of 43.3 months (Table 12). The probability of retaining a response at the

six-month milestone was █% (95% CI: █ █) and even at the 60-month milestone the probability was █% (95% CI: █ █) by Kaplan-Meier estimate (Figure 8) (89).

In SAS3, █ patients (█%) achieved a response by IRC assessment, with median follow-up of █ months and median DoR of █ months (Table 12) (89). The probability of retaining a response at the six-month milestone was █% (95% CI: █ █) and █% (95% CI: █ █) at 60 months (Figure 8).

**Table 12. Duration of response - IRC assessed (ePAS9 and SAS3, data cut-off 20<sup>th</sup> July 2024)**

|                                                                    | ePAS9<br>(N=304) | SAS3<br>(N=60) |
|--------------------------------------------------------------------|------------------|----------------|
| <b>Responding patient (confirmed CR, pCR and PR<sup>a,c</sup>)</b> | █                | █              |
| Progressed or died, n (%)                                          | █                | █              |
| Censored, n (%)                                                    | █                | █              |
| <b>Duration of follow-up, months</b>                               |                  |                |
| Median                                                             | 45.1             | █              |
| 25th, 75th percentiles                                             | █                | █              |
| <b>DoR</b>                                                         |                  |                |
| Median, months <sup>b</sup>                                        | 43.3             | █              |
| [95% CI]                                                           | [33.9, NE]       | █              |
| Range                                                              | █                | █              |
| <b>Rate of DoR, % [95% CI]<sup>b</sup></b>                         |                  |                |
| ≥6 months                                                          | █                | █              |
| ≥12 months                                                         | █                | █              |
| ≥18 months                                                         | █                | █              |
| ≥24 months                                                         | █                | █              |
| ≥36 months                                                         | █                | █              |
| ≥48 months                                                         | 48 [40, 57]      | █              |
| ≥60 months                                                         | █                | █              |
| ≥72 months                                                         | █                | █              |
| ≥84 months                                                         | █                | █              |
| <b>Observed DoR, n (%)</b>                                         |                  |                |
| ≤6 months                                                          | █                | █              |
| >6–12 months                                                       | █                | █              |
| >12–18 months                                                      | █                | █              |
| >18–24 months                                                      | █                | █              |
| >24–36 months                                                      | █                | █              |
| >36–48 months                                                      | █                | █              |
| >48–60 months                                                      | █                | █              |

|               | ePAS9<br>(N=304) | SAS3<br>(N=60) |
|---------------|------------------|----------------|
| >60–72 months | ■                | ■              |
| >72–84 months | ■                | ■              |
| >84 months    | ■                | ■              |

+ denotes censored data; BOR = best overall response; CI = confidence interval; CNS = central nervous system; CR = complete response; DoR = duration of response; ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; N = total number of patients (100%); n = number of patients in category/with event; NE = not estimable; pCR = pathological CR; PR = partial response; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumours; SAS3 = Supplemental Analysis Set 3

- None or no data available.

<sup>a</sup> BOR classification based on independent radiologist and independent clinical assessments for patients assessed by RECIST v1.1 (non-CNS patients) and based on independent radiologist assessments, clinical status, and corticosteroid use for patients assessed by RANO (CNS patients).

<sup>b</sup> Estimated based on Kaplan-Meier method.

<sup>c</sup> Patients with unconfirmed CR following PR are considered confirmed responders for analysis.

Source: Table 3-17, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

**Figure 8. Kaplan-Meier plot of duration of response - IRC assessed (ePAS9 (A) and SAS3 (B), data cut-off 20<sup>th</sup> July 2024)**



CR = complete response; DoR = duration of response; ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; pCR = pathological CR; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours

Notes: Disease assessments were performed by IRC using RECIST version 1.1. DoR is defined as the time from the start date of CR, pCR, or PR (whichever response was recorded first) to the earlier of documented PD or death due to any cause. Vertical tick marks represent the DoR for the 115 censored patients at the data cut-off. Vertical reference lines added yearly until the number of patients at risk is less than 10%.

Source: Fig 3-3, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89) and Fig 8.2.3/18, Bayer. Data on file. 8.Tables, figures and listings for Integrated Summary of Efficacy (100)

#### 2.6.1.2.6. Progression-free survival (PFS)

By IRC assessment, the median PFS was 28.0 months (95% CI: 22.0, 38.2) for patients in ePAS9 (median follow-up ■ months) (see Figure 9). Six-month and 60-month PFS rates were ■% (95% CI: ■ ■) and ■% (95% CI: ■ ■) respectively.

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Median PFS in SAS3 was [REDACTED] months (95% CI: [REDACTED] [REDACTED]), with median follow-up of [REDACTED] months (Figure 9). The six-month and 60-month PFS rates were [REDACTED]% (95% CI: [REDACTED] [REDACTED]) and [REDACTED]% (95% CI: [REDACTED] [REDACTED]), respectively (Table 13) (89).

**Table 13. PFS for larotrectinib - IRC assessed (ePAS9 and SAS3, data cut-off 20<sup>th</sup> July 2024)**

|                                                 | ePAS9<br>(N=304) | SAS3<br>(N=60) |
|-------------------------------------------------|------------------|----------------|
| Progressed or died, n (%) <sup>a</sup>          | [REDACTED]       | [REDACTED]     |
| Censored, n (%)                                 | [REDACTED]       | [REDACTED]     |
| <b>Duration of follow-up, months</b>            |                  |                |
| Median                                          | [REDACTED]       | [REDACTED]     |
| 25 <sup>th</sup> , 75 <sup>th</sup> percentiles | [REDACTED]       | [REDACTED]     |
| <b>Duration of PFS</b>                          |                  |                |
| Median, months <sup>b</sup>                     | [REDACTED]       | [REDACTED]     |
| [95% CI]                                        | [REDACTED]       | [REDACTED]     |
| Range                                           | [REDACTED]       | [REDACTED]     |
| <b>Rate of PFS, %<sup>b</sup> [95% CI]</b>      |                  |                |
| ≥6 months                                       | [REDACTED]       | [REDACTED]     |
| ≥12 months                                      | [REDACTED]       | [REDACTED]     |
| ≥18 months                                      | [REDACTED]       | [REDACTED]     |
| ≥24 months                                      | [REDACTED]       | [REDACTED]     |
| ≥36 months                                      | [REDACTED]       | [REDACTED]     |
| ≥48 months                                      | 39 [32, 46]      | [REDACTED]     |
| ≥60 months                                      | [REDACTED]       | [REDACTED]     |
| ≥72 months                                      | [REDACTED]       | [REDACTED]     |
| ≥84 months                                      | [REDACTED]       | [REDACTED]     |
| <b>Observed PFS, n (%)</b>                      |                  |                |
| ≤6 months                                       | [REDACTED]       | [REDACTED]     |
| >6–12 months                                    | [REDACTED]       | [REDACTED]     |
| >12–18 months                                   | [REDACTED]       | [REDACTED]     |
| >18–24 months                                   | [REDACTED]       | [REDACTED]     |
| >24–36 months                                   | [REDACTED]       | [REDACTED]     |
| >36–48 months                                   | [REDACTED]       | [REDACTED]     |
| >48–60 months                                   | [REDACTED]       | [REDACTED]     |
| >60–72 months                                   | [REDACTED]       | [REDACTED]     |
| >72–84 months                                   | [REDACTED]       | [REDACTED]     |
| >84 months                                      | [REDACTED]       | [REDACTED]     |

+ denotes censored data; CI = confidence interval; CNS = central nervous system; ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; N = total number of patients (100%); n = number of patients in category/with event; NE = not estimable; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumours; SAS3 = Supplemental Analysis Set 3

- None or no data available.

<sup>a</sup> Progression status based on independent radiologist and independent clinical assessments for patients assessed by RECIST v1.1 (non-CNS patients) and based on independent radiologist assessments, clinical status, and corticosteroid use for patients assessed by RANO (CNS patients).

<sup>b</sup> Estimate based on Kaplan-Meier method.

Source: Table 3-18, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

**Figure 9. Kaplan-Meier plot of progression-free survival - IRC assessed (ePAS9 (A) and SAS3 (B), data cut-off 20<sup>th</sup> July 2024)**



ePAS9 = Extended Primary Analysis Set 9; IRC = Independent Review Committee; PD = progressive disease; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

Notes: Disease assessments were performed by IRC using RECIST version 1.1. PFS is defined as the number of months elapsed between the date of the first dose of larotrectinib and the earliest date of documented PD or death (whatever the cause). Vertical tick marks represent the PFS times for the 147 censored patients. Vertical reference lines added yearly until the number of patients at risk is less than 10%.

Source: Fig 3-4, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89) and Fig 8.2.3/23, Bayer. Data on file. 8.Tables, figures and listings for Integrated Summary of Efficacy (100)

#### **2.6.1.2.7. Overall survival (OS)**

At the data cut-off on 20<sup>th</sup> July 2024, with a median follow-up period of [REDACTED] months in the ePAS9 dataset, the median OS was not estimable (NE). At the milestone of 72 months, the probability of being alive was [REDACTED]% (95% CI: [REDACTED] [REDACTED]) (Table 14). Kaplan-Meier plot of OS in ePAS9 is presented in Figure 10 (89).

In the SAS3 dataset (data cut-off 20<sup>th</sup> July 2024), median follow-up period was [REDACTED] months, and the median OS was NE (Table 14). Probability of being alive at 72 months was [REDACTED]% (95% CI: [REDACTED] [REDACTED]).

**Table 14. Overall survival in ePAS9 and SAS3 pooled analysis sets (ePAS9 and SAS3, data cut-off 20<sup>th</sup> July 2024)**

|                                                  | ePAS9<br>(N=304) | SAS3<br>(N=60) |
|--------------------------------------------------|------------------|----------------|
| Censored, n (%)                                  |                  |                |
| Dead, n (%)                                      |                  |                |
| <b>Reason censored, n (%)</b>                    |                  |                |
| Alive                                            |                  |                |
| Study discontinuation                            |                  |                |
| <b>Duration of follow-up, months<sup>a</sup></b> |                  |                |
| Median                                           |                  |                |
| 25th, 75th percentiles                           |                  |                |
| <b>Duration of OS, months<sup>a</sup></b>        |                  |                |
| Median                                           | NE               |                |
| [95% CI]                                         |                  |                |
| Range                                            |                  |                |
| <b>Rate of OS, % [95% CI]<sup>a</sup></b>        |                  |                |
| ≥6 months                                        |                  |                |
| ≥12 months                                       |                  |                |
| ≥18 months                                       |                  |                |
| ≥24 months                                       |                  |                |
| ≥36 months                                       |                  |                |
| ≥48 months                                       | 63 [57, 68]      |                |
| ≥60 months                                       |                  |                |
| ≥72 months                                       |                  |                |
| ≥84 months                                       |                  |                |

+ denotes censored data; CI = confidence interval; ePAS9 = Extended Primary Analysis Set 9; N = total number of patients (100%); n = number of patients in category/with event; NE = not estimable; OS = overall survival; SAS3 = Supplemental Analysis Set 3

<sup>a</sup> Estimate based on Kaplan-Meier method.

Source: Table 3-19, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

**Figure 10. Kaplan-Meier Plot of OS (ePAS9 (A) and SAS3 (B), data cut-off 20<sup>th</sup> July 2024)**



ePAS9 = Extended Primary Analysis Set 9; OS = overall survival

Notes: OS is defined as the number of months elapsed between the date of the first dose of larotrectinib and the date of death (whatever the cause). Patients who were alive or lost to follow-up as of the data cut-off date were right-censored. The censoring date was determined from the date the patient was last known to be alive. Vertical tick marks represent the OS times for 193 censored patients. Vertical reference lines added yearly until the number of patients at risk is less than 10%.

Source: Fig 3-5, Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89) and Fig 8.2.2/34, Bayer. Data on file. 8.Tables, figures and listings for Integrated Summary of Efficacy (100)

### **2.6.1.3 Exploratory endpoints**

Initial health-related quality of life (HRQoL) analysis (presented in the original submission) included only a limited number of patients from two studies – Study 20289 and Study 20290, which collected patient-reported outcomes (PROs). The present analysis used data from ePAS6 (data cut-off 20<sup>th</sup> July 2021), which included [REDACTED] patients ([REDACTED] patients from Study 20289 and Study 20290 and [REDACTED] patients from Study 20288) and was used to update the previous analysis results as presented below (101). The analysis was performed for all patients with available PRO data, therefore [REDACTED] patients from Study 20288 were not included, as no PRO data were collected.

#### **2.6.1.3.1. HRQoL**

HRQoL was analysed in ePAS6 (only utility mapping was performed for ePAS9 which is presented in Section 3.4) using EORTC QLQ-30, EQ-5D, PedsQL and FACES. Details of the patient-reported outcome completion rates are presented in Appendix N. All [REDACTED] patients under treatment at baseline in Study 20289 and Study 20290 were used to assess nature of missing PRO data in ePAS6. The overall analysis population

consisted of █ patients (█ adults, █ infants, and █ children), with at least one PRO assessment during the study (101).

The number of patients with MID improvement (i.e., clinically meaningful improvement) for the EORTC QLQ-C30 (global health score), EQ-5D-5L (VAS), and PedsQL (Total Score) were also analysed (Table 15). Overall, █% of patients (█ of █) had their best post-baseline EORTC QLQ-C30 global health score greater than or equal to their baseline, with most of those, █ patients (█%) meeting the criteria for MID improvement ( $\geq 10$  points); only █% of patients (█ of █) had a MID deterioration ( $\leq -10$  points). A total of 97 patients included in the analysis were evaluable for sustained improvement in global health and █% of patients (█ of █) showed sustained improvement lasting until the end of assessments.

Consistent with EORTC QLQ-C30 global health score, █% of patients (█ of █) had their best post-baseline EQ-5D-5L (VAS) health score greater than or equal to their baseline; of those, █ patients (█%) had a MID improvement. Only █% of patients (█ of █) had a MID deterioration. A total of █ patients included in the analysis were evaluable for sustained improvement, with █% of patients (█ of █) showing sustained improvement lasting until the end of assessments.

In the paediatric population (ages 2 to 18 years), PedsQL was used, and most patients (█ of █) had their best post-baseline total score greater than or equal baseline with █ (█%) patients showing a MID improvement ( $\geq 4.5$  points). Only █ patient had a MID deterioration ( $\leq -4.5$  points) and █% of patients (█ of █) showed sustained improvement lasting until the end of assessments (101). The FACES pain scale (0–10) was analysed as a continuous variable across scheduled visits. At baseline, █ patients had a mean score of █ (SD █) and a median of █, indicating that █ of the patients reported no pain.



Further detailed results for the analysis of EORTC QLQ-C30 and EQ-5D-5L in adults, and PedsQL and FACES in the paediatric population, are presented in Appendix N.

**Table 15. Number of patients with MID improvement (ePAS6, data cut-off 20<sup>th</sup> July 2021)**

| PRO measure                         | Patients with best postbaseline score at or above their baseline score, n (%) | Patients with median postbaseline score at or above their baseline score, n (%) | Patients with best postbaseline score at or above MID Improvement <sup>a</sup> n (%) | Patients evaluable for sustained improvement, n | Patients with sustained improvement lasting until the end of assessments, n (%) |
|-------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|
| EORTC QLQ-C30 (Global Health Score) | ██████                                                                        | ██████                                                                          | ██████                                                                               | █                                               | ██████                                                                          |
| EQ-5D-5L (VAS)                      | ██████                                                                        | ██████                                                                          | ██████                                                                               | █                                               | ██████                                                                          |
| PedsQL (Total Score)                | ██████                                                                        | ██████                                                                          | ██████                                                                               | █                                               | ██████                                                                          |

<sup>a</sup> MID: ≥10 points for EORTC QLQ-C30 and EQ-5D-5L; ≥ 4.5 points for PedsQL.  
EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-5L=European Quality of Life 5-Dimensions 5-Levels Health Questionnaire; MID=minimally important difference; PedsQL-Core=Paediatrics Quality of Life–Core Module; PRO=patient-reported outcome  
Source: Table 21 of exploratory analysis of quality of life based on patient-reported outcome assessments for larotrectinib studies 15002 and 15003 (ePAS6 Data Cut-off) 2022 (101)

#### 2.6.1.4 Post hoc analysis - Intra-patient comparison

As outlined in Section 2.4, a *post hoc* analysis using each patient as his/ her own control was performed to compare the effects of larotrectinib versus the effect of the previous line of treatment the patient had received.

GMI was assessed for patients from ePAS9 (n=304) who had received at least one prior systemic therapy in the metastatic setting (n=██████). More detailed methodology can be found in Appendix P. Using IRC assessed response data, a total of ██████% of patients in the analysis had GMI ≥1.33, defined by Von Hoff as the sign of drug activity (Table 16) (97). High number of patients with GMI ≥1.33 (33% better response than previous therapy), despite the natural development of disease emphasises benefit which patients receive with larotrectinib treatment.

**Table 16. GMI for patients with metastatic disease who received  $\geq 1$  prior systemic therapy - IRC assessed (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

|                     |                     | Adult (n= ) | Paediatric (n= ) | Total (n= ) |
|---------------------|---------------------|-------------|------------------|-------------|
| <b>GMI</b>          | Mean (SD)           |             |                  |             |
|                     | Median (Min, Max)   |             |                  |             |
| <b>GMI category</b> | < 1, n (%)          |             |                  |             |
|                     | 1 to <1.33, n (%)   |             |                  |             |
|                     | $\geq 1.33$ , n (%) |             |                  |             |

GMI=growth modulation index; IRC=independent review committee assessed; SD=standard deviation.

Source: Table 1.1/1, Bayer data on file, BAY2731953 GMI analysis 2024 (97)

Further, sensitivity analysis showed that the percentage of patients who had GMI  $\geq 1.33$  remained relatively consistent with the base case analysis (Table 17) (97).

**Table 17. Results of sensitivity analyses for GMI - IRC assessed (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

| Sensitivity analysis       | Sensitivity analysis 1 <sup>a</sup><br>(N=223) | Sensitivity analysis 2 <sup>b</sup><br>(N=223) | Sensitivity analysis 3 <sup>c</sup><br>(N=99) |
|----------------------------|------------------------------------------------|------------------------------------------------|-----------------------------------------------|
| <b>GMI Category, n (%)</b> |                                                |                                                |                                               |
| < 1                        |                                                |                                                |                                               |
| 1 to <1.33                 |                                                |                                                |                                               |
| $\geq 1.33$                |                                                |                                                |                                               |

GMI=growth modulation index; IRC=independent review committee assessed; NC=not calculated.

<sup>a</sup> All patients who had received at least one prior therapy are included in this analysis. Missing progression date on prior therapy is imputed to the larotrectinib first dose date.

<sup>b</sup> The difference between the main GMI analysis and sensitivity analysis 2 are only the censoring rules. In the main analysis we assumed that all patients progressed on their prior therapy (even if no progression date is provided). In sensitivity analysis 2, patients without progression date on prior therapy were censored. This did not have an impact on the calculation of GMI, but only on the KM curves. As such, the calculation of GMI for sensitivity analysis 2 is the same as that reported in Table 16. The missing progression date on prior therapy was censored for Kaplan-Meier analyses, using the discontinuation date on prior therapy as the censoring date.

<sup>c</sup> Only patients with at least one prior therapy from the NAVIGATE trial who had a progression date on therapy reported were included in this analysis

Source: Table 1.1/5 and Table 1.1/9, Bayer data on file, BAY2731953 GMI analysis 2024 (16)

## 2.7 Subsequent treatments

In this data cut-off (20<sup>th</sup> July 2024), (■■■■) of patients received subsequent treatments. OS was analysed in these patients in ePAS9 who received a subsequent NTRK inhibitor after larotrectinib (n=■■■■/304) (Table 18). Median follow-up period was ■■■■ months and median duration of OS (95% CI) was ■■■■ ■■■■ ■■■■. The probability of being alive at 72 months to be ■■■% ■■■■ ■■■■. A summary of post-larotrectinib NTRK inhibitors (paediatrics and adults) is presented in Table 19 (102). Overall, ■■■■■■■■■■ of patients received NTRK inhibitors post-larotrectinib, and these patients have ■■■■■■■■■■ to those in the main analysis.

**Table 18. Overall survival in patients taking subsequent treatments (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

| Status                                            | ePAS9<br>(N=304) |
|---------------------------------------------------|------------------|
| <b>Vital Status<sup>a</sup>, n (%)</b>            |                  |
| Dead                                              | ■■■■             |
| Censored                                          | ■■■■             |
| <b>Reason Censored, n (%)</b>                     |                  |
| Alive                                             | ■■■■             |
| Study discontinuation                             | ■■■■             |
| Start taking a subsequent NTRK inhibitor          | ■■■■             |
| <b>Duration of OS (months)<sup>b, c</sup></b>     |                  |
| Median (95% CI)                                   | ■■■■ ■■■■        |
| Minimum, Maximum                                  | ■■■■ ■■■■        |
| <b>Duration of Follow-up (months)<sup>b</sup></b> |                  |
| Median                                            | ■■■■             |
| 25 <sup>th</sup> , 75 <sup>th</sup> percentiles   | ■■■■ ■■■■        |
| <b>Rate (%) of OS (95% CI)<sup>b, c</sup></b>     |                  |
| ≥6 months                                         | ■■■■             |
| ≥12 months                                        | ■■■■             |
| ≥18 months                                        | ■■■■             |
| ≥24 months                                        | ■■■■             |
| ≥36 months                                        | ■■■■             |
| ≥48 months                                        | ■■■■             |
| ≥60 months                                        | ■■■■             |
| ≥72 months                                        | ■■■■             |
| ≥84 months                                        | ■■■■             |

Percentages are based on the number of patients in the analysis set.

<sup>a</sup> Status as of the last contact on or before visit cut-off.

<sup>b</sup> Estimate based on Kaplan-Meier method.

<sup>c</sup> 95% confidence interval was calculated using Greenwood's formula.

NE = Not estimable; OS = overall survival; + = Censored observation.

Source: Table 1/1 of Bayer. Data on file. Tables, figures and listing for NICE request, 2025 (102)

**Table 19. Summary of post-treatment NTRK Inhibitors (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

| Name of Post-treatment NTRK Inhibitors | Paediatrics (Age < 18 years)<br>N=99 (100%) | Adults (Age ≥ 18 years)<br>N=205 (100%) | Total<br>N=304 (100%) |
|----------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------|
| Selitrectinib                          | (%)                                         | (%)                                     | (%)                   |
| Other NTRK Inhibitor                   | (%)                                         | (%)                                     | (%)                   |
| Repotrectinib                          | (%)                                         | (%)                                     | (%)                   |
| Entrectinib                            | (%)                                         | (%)                                     | (%)                   |

Patients may be counted in more than one row.

NTRK= neurotrophic receptor tyrosine kinase

Source: Table1/2 of Bayer. Data on file. Tables, figures and listing for NICE request, 2025 (102)

## 2.8 Subgroup analysis

Supportive analyses (point estimate of the ORR [and 95% CI]), based on IRC assessment were performed to assess ORR for consistency across key demographic and clinical subgroups (89). There were no clinically relevant differences and ORR was consistent across all the subgroups analysed. A summary of analyses in both ePAS9 and SAS3 populations by key subgroups including demographic characteristics (age, sex, race, number of prior systemic therapies, NTRK gene fusion, gene fusion partner and ECOG status) are presented in Appendix C.

## 2.9 Meta-analysis

Meta-analysis was not performed. Instead, pooled data from the three larotrectinib trials is presented in this company submission.

## 2.10 Indirect and mixed treatment comparisons

Comparative clinical effectiveness from matching-adjusted indirect comparisons (MAICs) of data from larotrectinib trials versus real-world standard of care (SOC) cohorts described below addresses the uncertainty around the lack of comparative data for larotrectinib versus SOC highlighted in the original submission. These MAICs consistently demonstrate longer survival with larotrectinib compared to real-world non-TRK inhibitor SOC in both adult and paediatric patients with NTRK fusion-positive solid tumours, after adjusting for heterogeneity in patient characteristics between the trial and real-world SOC comparator populations. The comparative data from the MAICs

presented in sections 2.10.1 and 2.10.2 are included in various scenario analyses of the cost-effectiveness model (section 3.11.3).

This section presents:

- Three MAICs (sections 2.10.1.1, 2.10.1.2 and 2.10.1.3) comparing patients treated with larotrectinib from studies 20288, 20289 and 20290 with patients aged  $\geq 18$  years who received non-TRK inhibitor SOC in the real-world setting (75, 103, 104).
- A MAIC (section 2.10.2) comparing patients aged  $\leq 21$  years with locally advanced or metastatic IFS treated with larotrectinib in study 20290 versus an external historical control group treated with a chemotherapy-based regimen (105).

## **2.10.1 MAICs of larotrectinib versus real-world SOC - patients aged $\geq 18$ years**

### **2.10.1.1 Flatiron MAIC**

A MAIC was conducted to compare OS of larotrectinib trials (studies 20288, 20289 and 20290; data cut-off July 2020 [ePAS5]) with that of non-TRK inhibitor SOC (104). Individual patient data (IPD) of adult patients from the larotrectinib trials (studies 20288, 20289 and 20290; data cut-off July 2020 [ePAS5]) and aggregated real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron/Foundation Medicine database were used. The key inclusion criteria for patients in the aggregate real-world data SOC comparator cohort included locally advanced or metastatic diagnosis of NTRK fusion-positive solid tumours from January 2011 to December 2019, no prior treatment with a TRK inhibitor,  $\geq 1$  test by next-generation sequencing (NGS) on tumour tissue and  $\geq 1$  NTRK fusion-positive test result, no visit gap of  $>90$  days after diagnosis, and no prior unlabelled study drug as part of a clinical trial (104).

#### *2.10.1.1.1. Methods*

The IPD from larotrectinib trials were matched to the average baseline characteristics from real-world data in the Flatiron/Foundation Medicine database (a US-wide

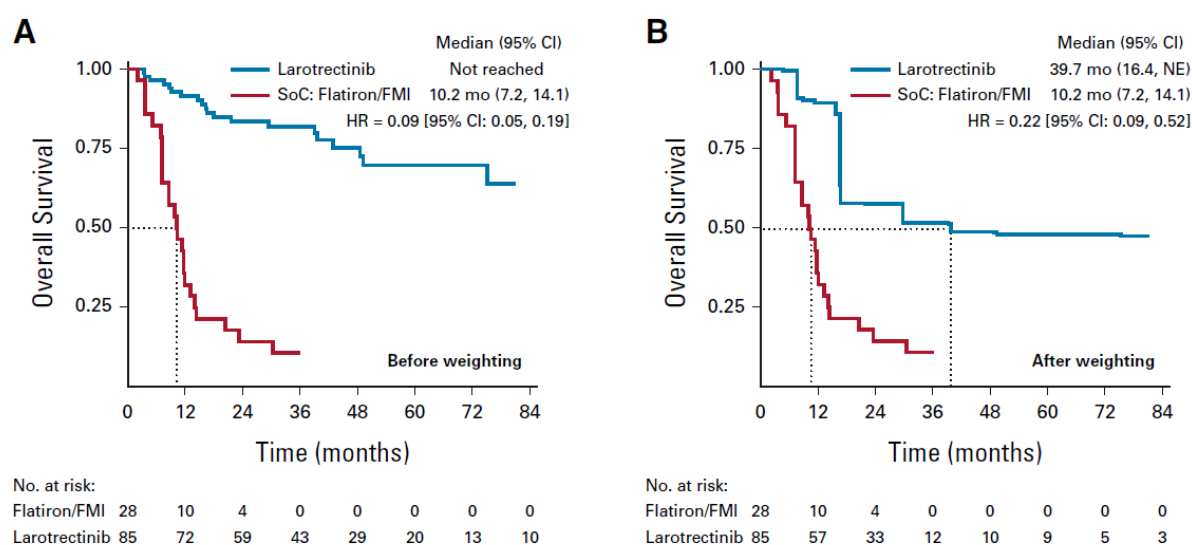
longitudinal database), based on data availability (NTRK gene, age, smoking history, ECOG PS, select tumour types, practice type, number of lines of therapy since diagnosis, stage at diagnosis, and presence of brain metastases) (104). The outcome of interest was OS. For SOC patients with missing data, the number of lines of therapy since diagnosis and ECOG PS variables were imputed such that patients with missing values were assumed to be in the more severe categories (i.e.,  $\geq 3$  lines of therapy; ECOG PS 2-4). These assumptions were made to estimate a conservative HR (104).

#### 2.10.1.1.2. *Results*

A total of 192 patients from the larotrectinib trials were assessed for inclusion, of which 85 met all inclusion criteria (104). Reported baseline characteristics for 28 patients were available for inclusion from aggregate real-world data in the Flatiron/Foundation Medicine database. Matching was performed on the following variables: NTRK1, age, ECOG PS, prior lines of systemic therapy, disease stage, brain metastases, and tumour type (uterine, biliary, stomach, endometrial, cancer of unknown primary, breast, salivary gland, NSCLC, STS, and CRC). Baseline characteristics before and after matching in the primary analysis are presented in Appendix N.

The median OS for NTRK fusion-positive patients in the Flatiron/Foundation Medicine database was 10.2 months (95% CI: 7.2, 14.1). Prior to matching, the median OS for larotrectinib was not reached and after matching, the median OS was 39.7 months. Larotrectinib was associated with a 78% lower risk of death (HR=0.22; 95% CI: 0.09, 0.52;  $p=0.001$ ), which corresponds to a 29.5-month median survival advantage compared with non-TRK inhibitor SOC. The Kaplan-Meier plot of OS before and after weighting is presented in Figure 11 (104).

**Figure 11. Kaplan-Meier curve of OS from time of metastatic/locally advanced diagnosis (A) before and (B) after weighting (Flatiron MAIC)**



FMI= Foundation Medicine Inc; NE= not estimable; OS= overall survival; SOC= standard of care.  
 Source: Bokemeyer *et al.* 2022; Figure 2 (104)

### 2.10.1.2 VICTORIA study

VICTORIA is a comparative effectiveness study of the real-world clinical benefit of TRK fusion-positive cancer patients treated with historical SOC therapies versus patients from the larotrectinib clinical trials (data cut-off July 2022 [ePAS7]) (106).

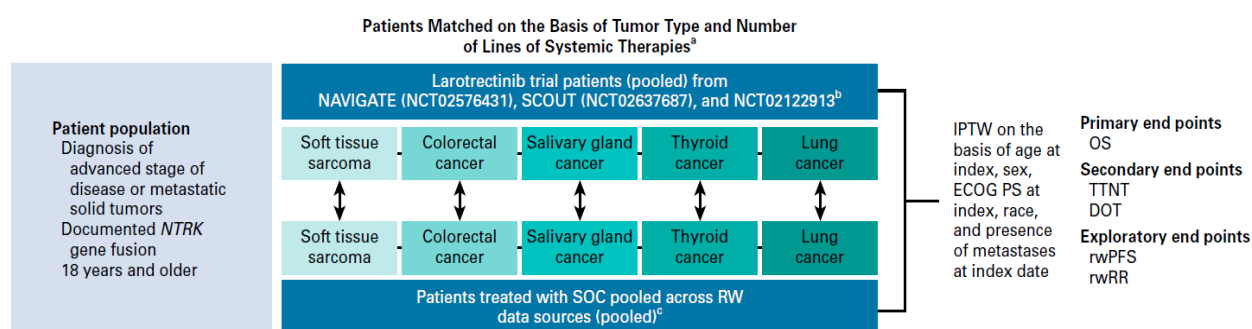
#### 2.10.1.2.1 Methods

The real-world comparator cohort included patients pooled from different data sources, such as American Association for Cancer Research (AACR), Genomics Evidence Neoplasia Information Exchange (GENIE) data (from the US, Canada, France and the Netherlands), Cardinal study data (from the US, Canada, Europe, Australia, China and Japan), Flatiron Health FMI database (US-wide) and global retrospective chart review data (106). This data collection period began January 1, 2013, and ended June 2023. A comparative effectiveness analysis against the larotrectinib trials was conducted in patients with the following five major tumour types of interest: NSCLC, CRC, thyroid cancer, sarcomas, and salivary gland carcinoma, as shown in Figure 12 (106).

The primary outcome was OS, defined as time from index date (i.e., initiation of larotrectinib or SOC/best supportive care [BSC] therapy after matching with tumour

type and larotrectinib treatment line) to the time of death (by any cause) or last observation (106). Secondary outcomes included duration of therapy (DOT) and time to next treatment (TTNT). Exploratory outcomes were PFS (including real-world PFS [rwPFS]) and Response Rate (RR), including real-world RR (rwRR) (106). The primary outcome was OS, defined as time from index date (i.e., initiation of larotrectinib or SOC/BSC therapy after matching with tumour type and larotrectinib treatment line) to the time of death (by any cause) or last observation (106). Secondary outcomes included DOT and TTNT. Exploratory outcomes were PFS (including real-world PFS [rwPFS]) and RR, including real-world RR (rwRR) (106).

**Figure 12. Study design and description of the larotrectinib trial patients and real-world patients (VICTORIA)**



<sup>a</sup>For patients with thyroid cancer, exact matching includes histology (DTC and undifferentiated) and lines of systemic therapies in the advanced/metastatic setting.

<sup>b</sup>July 2022 data cut-off.

<sup>c</sup>Real-world cohort patients who had received larotrectinib/entrectinib/any investigational drug after index therapy will be censored at the date of first dose of the respective drug

DOT= duration of therapy; DTC= differentiated thyroid cancer; ECOG PS= Eastern Cooperative Oncology Group performance status; IPTW= inverse probability of treatment weighting; OS= overall survival; RW= real-world; rwPFS= real-world progression-free survival; rwRR= real-world response rate; SOC= standard of care; TTNT= time to next treatment

Source: Brose *et al.* 2025; Figure 1 (106)

## 2.10.1.2.2. Results

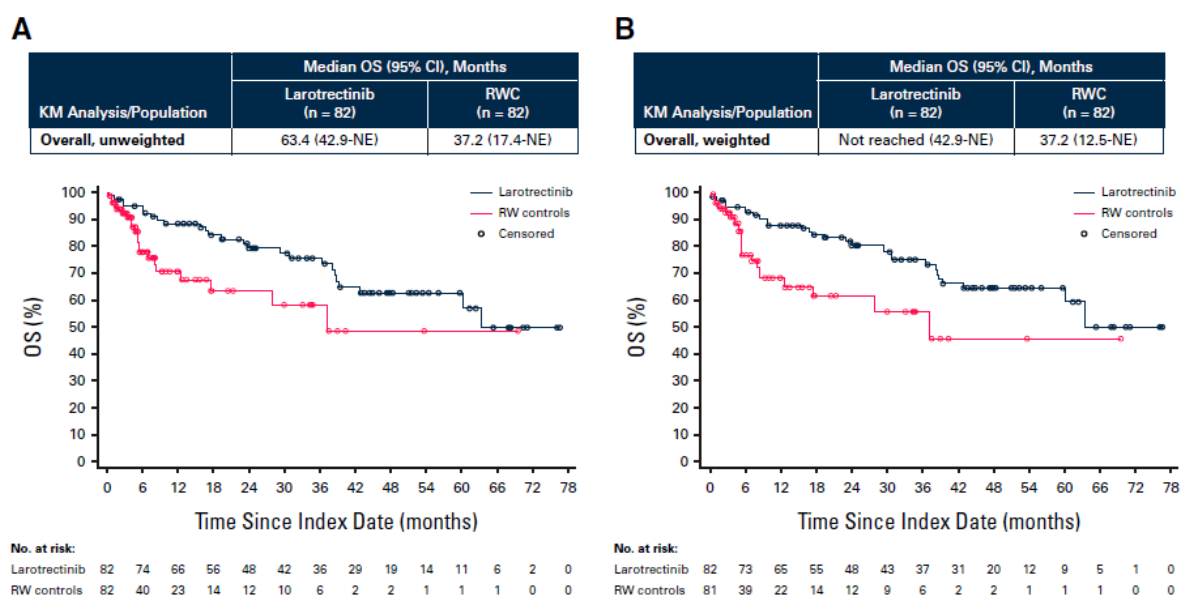
A total of 82 larotrectinib trial patients were matched with 82 real-world patients based on tumour type and number of lines of systemic therapies (patient characteristics before and after matching are presented in Appendix N) (106). There were 28% of patients with STS, 21% with CRC, 18% with NSCLC, 18% with salivary gland carcinoma, and 15% with thyroid cancer. Among these patients, 48%, 24%, 23%, and 5% were treated in first, second, third, and fourth lines of therapy, respectively (106).

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours



In the unweighted sample, median OS was 63.4 months (95% CI: 42.9, NE) for patients treated with larotrectinib and 37.2 months (95% CI: 17.4, NE) in the real-world cohort (Figure 13A) (106). In the weighted sample, median OS was not reached for patients treated with larotrectinib, while it was 37.2 months (95% CI: 12.5, NE) for the real-world cohort (Figure 13B). Patients treated with larotrectinib had a lower risk of death when compared with patients from the real-world cohort in the unweighted samples (HR: 0.47; 95% CI: 0.26, 0.88; p= 0.0176) and weighted samples (HR: 0.44; 95% CI, 0.23, 0.83; p= 0.0109). The comparative effectiveness estimates for the primary and secondary outcomes are presented in Table 20 (106).

**Figure 13. OS in the (A) unweighted and (B) weighted samples (VICTORIA)**



In the real-world cohort, 42 patients were censored because they switched to a TRK inhibitor, investigational drug, or clinical study drug.  
 KM= Kaplan-Meier; NE= not estimable; OS= overall survival; RW= real-world; RWC= real-world cohort; TRK= tropomyosin receptor kinase.  
 Source: Brose *et al.* 2025; Figure 2 (106)

**Table 20. Comparative effectiveness estimates for larotrectinib vs real-world cohort in NTRK fusion solid tumours (VICTORIA)**

| Outcome                     | Larotrectinib (n=82)                    | Real-World Cohort (n=82) |
|-----------------------------|-----------------------------------------|--------------------------|
| Median OS, months (95%CI)   |                                         |                          |
| Unweighted <sup>a</sup>     | 63.4 (42.9, NE)                         | 37.2 (17.4, NE)          |
|                             | HR: 0.47 (95% CI: 0.26, 0.88; p=0.0176) |                          |
| Weighted <sup>b</sup>       | NE (42.9, NE)                           | 37.2 (12.5, NE)          |
|                             | HR: 0.44 (95% CI: 0.23, 0.83; p=0.0109) |                          |
| Median DOT, months (95% CI) |                                         |                          |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

| Outcome                       | Larotrectinib (n=82)          | Real-World Cohort (n=82) |
|-------------------------------|-------------------------------|--------------------------|
| Weighted <sup>c</sup>         | 30.8 (18.2, 47.6)             | 3.4 (2.7, 4.7)           |
|                               | HR: 0.23 (95% CI: 0.15, 0.33) |                          |
| Median TTNT, months (95% CI)  |                               |                          |
| Unweighted                    | 58.1 (53.2, NE)               | 10.0 (6.7, 17.7)         |
|                               | HR: 0.24 (0.14, 0.40)         |                          |
| Weighted                      | NE (53.2, NE)                 | 10.6 (6.1, 17.7)         |
|                               | HR: 0.22 (0.13, 0.38)         |                          |
| rwRR, % (95% CI) <sup>d</sup> |                               |                          |
|                               | 73.8 (62.7, 83.0)             | 53.8 (37.2, 69.9)        |
| Median rwPFS, months (95% CI) |                               |                          |
| Weighted <sup>c</sup>         | 36.8 (25.8, 58.2)             | 5.2 (3.5, 6.8)           |
|                               | HR: 0.29 (95% CI: 0.18, 0.46) |                          |

<sup>a</sup> OS in the FAS (N = 164) was 63.4 (95% CI: 38.7, NE).

<sup>b</sup> OS in the FAS (N = 164) was 63.4 (95% CI: 38.5, NE).

<sup>c</sup> Similar before and after weighting.

<sup>d</sup> Overall response rate was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) during the index or comparative treatment period over patients with non-missing response only.

CI= confidence interval; DOT= duration of therapy; FAS= full analysis set; HR= hazard ratio; NE= not estimable; OS= overall survival; rwPFS= real-world progression-free survival; rwRR= real-world response rate; TTNT= time to next treatment.

Source: Brose *et al.* 2025 (106)

### 2.10.1.3 Hartwig Medical Foundation (HMF) MAIC

Similar to the Flatiron MAIC described above, the aim of this study was to compare OS between larotrectinib and non-TRK inhibitor SOC in patients with NTRK fusion-positive solid tumours (103).

#### 2.10.1.3.1. Methods

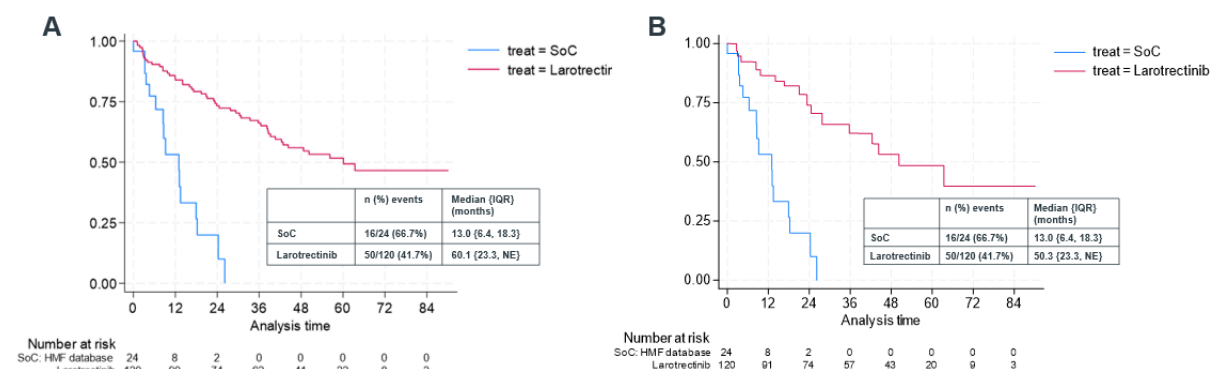
IPD from the three larotrectinib trials (data cut-off July 2023 [ePAS8]) were matched with published aggregated real-world data from 24 patients aged ≥18 years with locally advanced/metastatic NTRK fusion-positive cancer receiving non-TRK inhibitor therapy identified in the Hartwig Medical Foundation (HMF) database (Netherlands) (2012-2020) (103). Matching factors used in this analysis included age group, number of previous lines of therapy, NTRK1 gene fusion, and year of treatment initiation (103).

#### 2.10.1.3.2. Results

A total of 120 larotrectinib patients and 24 non-TRK inhibitor SOC patients were included in the analysis (103). Patient baseline characteristics before and after matching are summarised in Appendix N. In the matching-adjusted analysis,

larotrectinib was associated with an 84% lower risk of death and 37-month median survival advantage (HR: 0.16, 95% CI: 0.07, 0.36;  $p < 0.001$ ) (Figure 14) (103).

**Figure 14. Kaplan-Meier survival estimates of the (A) unadjusted analysis and (B) the matching-adjusted analysis (HMF MAIC)**



MAIC= matching-adjusted indirect comparison; NE= not estimable; SOC= standard of care  
Source: Bokemeyer *et al.* 2024 (103)

## 2.10.2 MAIC of larotrectinib versus real-world SOC - patients aged $\leq 21$ years

### 2.10.2.1 EPI VITRAKVI

In this retrospective, observational, externally controlled study, data from patients aged  $\leq 21$  years with locally advanced or metastatic IFS treated with larotrectinib in study 20290 were compared with those of an external historical control group that represented the historical SOC (i.e., chemotherapy) (105).

#### 2.10.2.1.1. Methods

Data sources for the external historical control group (data of Institut Curie ‘Tag-N-Trak’ and Cooperative Weichteilsarkom Studiengruppe) were selected according to pre-defined selection criteria that included prospective enrolment, prospective and retrospective data collection from 2000 to 2022, and the availability of relevant clinical data. Between-group differences were assessed after balancing the groups using inverse probability of treatment weighting (IPTW) (105). Data for patients treated with larotrectinib were sourced from study 20290 (data cut-off July 2021 [ePAS6]) (105).

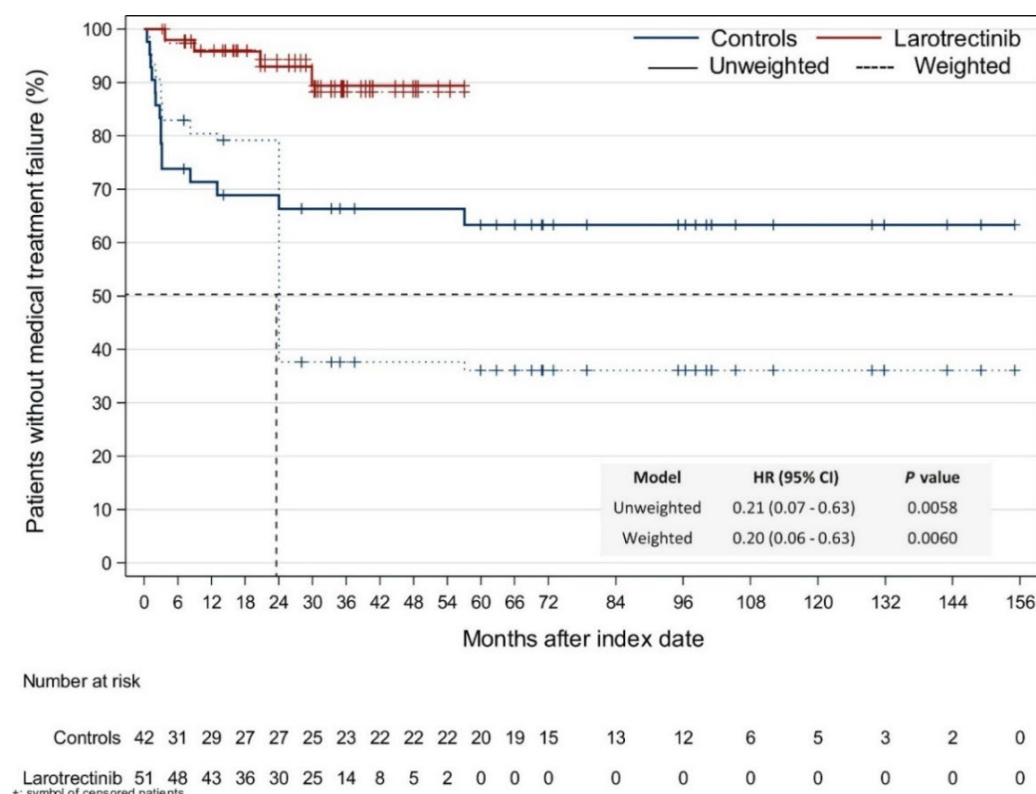
The primary endpoint was time to medical treatment failure (i.e., subsequent systemic therapy, radiotherapy, mutilating surgery, or death due to any cause, whichever came first), while secondary endpoints included subsequent systemic treatment, radiation therapy, mutilating surgery, and OS, along with time to complete surgical resection and incidence of patients with treatment discontinuation due to TEAEs. Exploratory endpoints were PFS, ORR, and DCR (105).

#### *2.10.2.1.2. Results*

A total of 93 patients were compared, 51 in the larotrectinib arm and 42 in the external control arm (105). Patient baseline characteristics are presented in Appendix N.

Larotrectinib significantly prolonged the time to medical treatment failure compared to external historical controls receiving only chemotherapy (105). After therapy, four patients (7.8%) in the larotrectinib group experienced medical treatment failure, compared to 15 patients (35.7%) in the external control group. Larotrectinib was associated with an 80% reduced likelihood of encountering medical treatment failure compared to the external control group (weighted and stratified HR: 0.20, 95% CI: 0.06, 0.63,  $p=0.0060$ ), as shown in the Kaplan-Meier plot (Figure 15). Results from sensitivity analyses of the primary endpoint were similar to those of the main unweighted and weighted analysis, indicating that patients with IFS receiving larotrectinib were less likely to encounter medical treatment failure than patients receiving chemotherapy, regardless of the number of prior lines of therapy. Additionally, patients who received larotrectinib were 86% less likely to receive a new line of systemic treatment than patients who received conventional 1L chemotherapy (weighted and stratified HR: 0.14, 95% CI: 0.03, 0.63,  $p=0.0109$ ) (105).

**Figure 15. Kaplan-Meier plot of time to medical treatment failure according to treatment groups (EPI VITRAKVI)**



Source: Orbach *et al.* 2024; Figure 1 (105)

Median OS was not reached in either treatment arm and no statistically significant difference was observed between the two groups (weighted HR: 0.21, 95% CI: 0.02, 2.84,  $p = 0.2388$ ) (105). The difference in PFS between the two groups was also not statistically significant (weighted log-rank test:  $p = 0.2765$ ; weighted and stratified HR: 0.80, 95% CI: 0.41, 1.58,  $p = 0.5284$ ) (105). However, patients in the larotrectinib group exhibited a better overall response profile, compared to the external control group, with no cases of disease progression reported (Table 21).

**Table 21. Comparative effectiveness estimates for larotrectinib vs external control group in NTRK fusion solid tumours (EPI VITRAKVI)**

| Outcome              | Larotrectinib Group (%) | External Control Group (%) |
|----------------------|-------------------------|----------------------------|
| CR                   | 49.0                    | 35.7                       |
| PR                   | 41.2                    | 40.5                       |
| SD                   | 9.8                     | 4.8                        |
| PD                   | -                       | 9.5                        |
| NE                   | -                       | 9.5                        |
| ORR (95% CI)         | 90.2 (78.6, 96.7)       | 76.2 (60.5, 87.9)          |
| Weighted OR (95% CI) | 1.77 (0.52, 5.97)       |                            |
| p-value              | 0.3596                  |                            |

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| Outcome      | Larotrectinib Group (%) | External Control Group (%) |
|--------------|-------------------------|----------------------------|
| DCR (95% CI) | 100.0 (93.0, 100.0)     | 81.0 (65.9, 91.4)          |
| OR (95% CI)  | NE                      |                            |

CR= complete response; DCR= disease control rate; NE= not estimable; OR= odds ratio; ORR= objective response rate; PD= progressed disease; PR= partial response; SD= stable disease

Sources: Orbach *et al.* 2024 (105)

Notably, no patients in the larotrectinib arm discontinued treatment due to AEs, suggesting a favourable safety and tolerability profile for larotrectinib relative to conventional therapies (105).

### 2.10.3 Uncertainties in the indirect and mixed treatment comparisons

An extensive assessment of uncertainties in the comparative evidence presented above was performed for each study, and the findings are summarised in Table 22. The robustness of the results was confirmed through a rigorous assessment of uncertainties using validated MAIC methodology, which consistently demonstrated a survival advantage for larotrectinib over SOC therapies.

**Table 22. Uncertainties and their assessment in the presented comparative evidence**

| Uncertainty category                | Indirect treatment comparison                                         |                         |                                             |                                                         |
|-------------------------------------|-----------------------------------------------------------------------|-------------------------|---------------------------------------------|---------------------------------------------------------|
|                                     | Flatiron                                                              | HMF                     | VICTORIA                                    | EPI VITRAKVI                                            |
| <b>Excessive matching</b>           | Alternative matching variables tested                                 | NR                      | NR                                          | Use of stabilised IPTW                                  |
| <b>Follow-up duration imbalance</b> | RMST analysis to adjust for longer follow-up in the larotrectinib arm | RMST analysis performed | RMST analysis performed                     | NA (single-arm, retrospective)                          |
| <b>Delayed entry bias</b>           | NR                                                                    | NR                      | Truncation analysis performed               | NR                                                      |
| <b>Propensity score outliers</b>    | NR                                                                    | NR                      | Trimming and exclusion of extreme PS values | NA (no PS modelling)                                    |
| <b>Historical comparator bias</b>   | NA                                                                    | NA                      | NA                                          | Addressed via comparison to historical standard of care |
| <b>Sensitivity analyses summary</b> | RMST, alternative variables for matching                              | RMST                    | RMST, left truncation, PS trimming          | Exact matching and subgroup analyses by treatment lines |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

## 2.11 Adverse reactions

### 2.11.1 Introduction to adverse event data

The safety profile of larotrectinib for the treatment of adult and paediatric patients who have locally advanced or metastatic NTRK fusion-positive solid tumours is based on the analysis of AEs that occurred in the three trials (Study 20288, Study 20289, and Study 20290) as described in the original submission and section 2.3 of this company submission (71).

The results from three studies were integrated to provide a consolidated overview of safety for larotrectinib. For presentation of safety data, the following three datasets have been defined (Table 7) (90):

- Overall Safety Analysis Set, OSAS (N=■)
- NTRK Gene Fusion Cancers Safety Analysis Set, NFCSAS (N=■)
- Efficacy-evaluable NTRK Gene Fusion Cancers Safety Analysis Set, ENFCSAS (N=■)

Data from the NFCSAS is presented in this section, as it is one of the largest datasets available for review and includes a population with documented NTRK gene fusion cancer, therefore, most representative of patients who are likely to receive larotrectinib in clinical practice. The results of the other two safety datasets are presented in Appendix D.

### 2.11.2 Treatment exposure

The median time on study treatment in the NFCSAS was ■ months (range: ■ to ■) (Table 23). Study treatment period includes all patients who were receiving active treatment or, for Study 20290 only, were in a protocol-specified drug hold period (i.e., the wait-and-see period) (90).

**Table 23. Duration of larotrectinib exposure (data cut-off 20<sup>th</sup> July 2024)**

|                                                             | <b><i>NTRK</i> Gene Fusion Analysis Set (N=■)</b> |
|-------------------------------------------------------------|---------------------------------------------------|
| <b>Time on treatment<sup>a</sup>, months</b>                |                                                   |
| Mean (SD)                                                   | ■ (■)                                             |
| Median                                                      | ■                                                 |
| Range                                                       | ■-■                                               |
| <b>Total number of cycles initiated, months<sup>b</sup></b> |                                                   |
| Mean (SD)                                                   | ■ (■)                                             |
| Median                                                      | ■                                                 |
| Range                                                       | ■-■                                               |

Abbreviations: N = total number of patients (100%); NTRK = neurotrophic tyrosine receptor kinase; SD = standard deviation

<sup>a</sup> Includes all patients who were receiving active treatment or, for Study 20290 only, were in a protocol-specified drug hold period (i.e., the wait-and-see period).

<sup>b</sup> Planned cycle length was 28 days.

Source: Table 1-10, Larotrectinib (BAY 2757566) Summary of clinical safety 2024 (90)

### 2.11.3 Summary of adverse events

In the NFCSAS, ■ (■%) patients had at least one treatment-emergent adverse event (TEAE), and ■ (■%) had at least one TEAE considered to be related to larotrectinib. By the maximum severity grade of any TEAE that occurred in each patient, ■% of patients had at least one Grade 3 or 4 TEAE; of these ■ patients (■%) were considered to have TEAEs related to larotrectinib. A total of ■ (■%) patients had at least one SAE, of which ■ (■%) patients had at least one SAE that was considered related to larotrectinib. A total of ■ (■%) patients had at least one TEAE leading to discontinuation from larotrectinib, and ■ (■%) patients had at least one TEAE leading to discontinuation that were considered related to larotrectinib. A total of ■ (■%) patients had a fatal TEAE, but none of the fatal TEAEs were considered related to larotrectinib (Table 24) (90).

**Table 24. Overall summary of adverse events (data cut-off 20<sup>th</sup> July 2024)**

|                          | <b>Incidence, n (%)<br/><i>NTRK</i> Gene Fusion Analysis Set<br/>(N=■)</b> |
|--------------------------|----------------------------------------------------------------------------|
| <b>Any TEAE</b>          |                                                                            |
| All                      | ■ (■)                                                                      |
| Related to larotrectinib | ■ (■)                                                                      |
| <b>Grade 3 or 4 TEAE</b> |                                                                            |
| All                      | ■ (■)                                                                      |



|                                                      | Incidence, n (%)<br>NTRK Gene Fusion Analysis Set<br>(N=██) |
|------------------------------------------------------|-------------------------------------------------------------|
| Related to larotrectinib                             | ██                                                          |
| <b>TEAE leading to larotrectinib discontinuation</b> |                                                             |
| All                                                  | ██                                                          |
| Related to larotrectinib                             | ██                                                          |
| <b>Serious TEAE</b>                                  |                                                             |
| All                                                  | ██                                                          |
| Related to larotrectinib                             | ██                                                          |
| <b>Fatal TEAE</b>                                    |                                                             |
| All <sup>a</sup>                                     | ██                                                          |
| Related to larotrectinib                             | █                                                           |

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = total number of patients (100%); n = number of patients with event/in category; NTRK = neurotrophic tyrosine receptor kinase; PT = Preferred Term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>There were a total of 37 deaths in the NTRK Gene Fusion Analysis Set due to AEs within 30 days of last dose of study treatment. Patients 20289-104-007 and 20289-951-017 had a fatal TEAE recorded 46 and 58 days, respectively after the last dose of study treatment.

Note: TEAEs are defined as AEs that start on or after the first administration of larotrectinib.

Related events are those judged by the Investigator as related to larotrectinib.

Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), grade 4 (life-threatening), grade 5 (fatal). Severity of AEs is maximum grade severity. Grade 3 or 4 may not be the maximum severity of the events for a specific patient.

Source: Table 2-1, Larotrectinib (BAY 2757566) Summary of clinical safety 2024 (90)

The most common TEAEs in the NFCSAS (total patients n=374) were gastrointestinal disorders (n=██), general disorders and administration site conditions (n=██), infections and infestations (n=██), investigations (n=██), nervous system disorders (n=██), respiratory, thoracic and mediastinal disorders (n=██), and metabolism and nutrition disorders (n=██) (Appendix D) (90). Further, TEAEs in ≥10% of patients in the NFCSAS with severity grades (Grades 1 to 4) are also presented in Appendix D, with █ patients with grade 3 and █ patients with grade 4 TEAE (90).

## 2.11.4 Study drug-related TEAEs

A total of █% of patients in the NFCSAS had at least one TEAE (any grade) that was attributed by the investigator to larotrectinib. Those reported in ≥5% of patients in the NFCSAS are presented in Appendix D, the most common (in ≥10% of patients) being increased █ (█%), increased █ (█%), █ (█%), █ (█%), █ (█%) and decreased █ (█%), █ (█%), █ (█%), increased █ (█%), █ (█%), and decreased █ (█%) (90).

In total, █ patients (█%) had a Grade 3 or 4 TEAE that was considered related to larotrectinib; and the most common grade 3 TEAEs included decreased █ (█%), increased █ (█%), increased █ (█%) and increased █ (█%), and grade 4 TEAEs included increased █ (█%) and decreased █ (█%).

### **2.11.5 Adverse events leading to interruption, dose modification or premature discontinuation of larotrectinib**

A total of █ (█%) patients in the NFCSAS had a TEAE leading to either larotrectinib dose modification (dose reduction or different frequency) or interruption. Among █ patients (█%) who experienced TEAEs leading to permanent treatment discontinuation, only █ (█%) were directly related to larotrectinib.

### **2.11.6 Subgroup analyses**

TEAEs were analysed by age group across studies looking at patients aged <18 years (i.e., paediatric patients), those aged ≥18 years (i.e., adult patients), and those aged ≥65 years (i.e., elderly patients). Subgroup analysis was also reported based on sex, race and tumour type, as presented in Appendix D for OSAS. NFCSAS had similar results as observed in OSAS.

The safety profiles are favourable in both the adult and paediatric subgroups, demonstrating the overall tolerability of the treatment across different age groups, despite variations in specific AEs (90).

## **2.12 Larotrectinib use in the first-line (1L) setting**

An analysis published by Hong *et al.* evaluated a subgroup of patients in the ePAS9 dataset who had not received any prior systemic therapies (n=101), showing an impressive ORR of 77% (78). Details of this subgroup analysis can be found in Appendix C.

In addition, a study by Laetsch *et al.* evaluated the efficacy of larotrectinib as a 1L treatment for paediatric patients with newly diagnosed NTRK fusion-positive solid tumours, including IFS (Appendix C) (69). The study enrolled 33 patients between October 2019 and July 2022, with 18 patients diagnosed with IFS (cohort A) and 15

with other NTRK fusion-positive solid tumours (cohort B) (69). The primary endpoint was ORR within six cycles for patients with IFS, while secondary endpoints included event-free survival (EFS) and OS (69). Detailed methodology and additional study design elements are described in Appendix B.

The study demonstrated a high ORR within six cycles: 94% (17/18; 95% CI: 72.5 – 98.6) for IFS and 60% (9/15; 95% CI, 32.3 - 83.7) for other solid tumours (69). The two-year EFS and OS were 82.2% (95% CI: 54.3 - 93.9) and 93.8% (95% CI: 63.2 - 99.1) for IFS, and 80% (95% CI: 50.0 - 93.1) and 93.3% (95% CI: 61.3 - 99.0) for other solid tumours, respectively. Notably, patients who underwent surgical resection of their tumour had prolonged EFS, with only one of 16 such patients experiencing disease progression (69).

Larotrectinib was well tolerated, with only four patients experiencing treatment-related DLT (69). The most common treatment-related adverse event (TRAE) was neutropenia, occurring in six patients. All grade 3 or higher TRAEs were reversible, and no cumulative toxicity was observed over a median of 12 cycles of treatment (range: 4 - 26) (69).

The findings of this study are consistent with the pooled analyses of the larotrectinib clinical trials (89), which reported an ORR of 77% in the treatment-naïve subgroup (78). A study by Garcia *et al.* further supports the early use of larotrectinib, showing that ORR declines with increasing prior therapies, with 100% observed in treatment-naïve patients, and subsequently dropping to 58% after  $\geq 3$  lines of treatment (87).

These results support the proposed positioning of larotrectinib, in that the decision to initiate larotrectinib should remain at the discretion of the treating clinician, guided by the clinical context and aligned with the principles of precision oncology and individualised patient care.

## **2.13 Real-world studies**

Since the original submission, many studies have been conducted to evaluate larotrectinib's effectiveness in NTRK fusion cancers in real-world settings. This

growing body of evidence is particularly valuable given the rarity of the disease, offering a rich understanding of larotrectinib's clinical impact beyond its clinical trials.

### **2.13.1 Prospective non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib (ON-TRK [Global])**

In accordance with the NICE guidance and the CDF Managed Access Agreement (MAA), the company is conducting a global (including patients from several countries of Asia Pacific, Europe and US), non-interventional study (ON-TRK; Study 20324), to prospectively follow patients with locally advanced or metastatic NTRK fusion-positive solid tumours treated with larotrectinib (107). The ON-TRK study provides a comprehensive account of how larotrectinib is being utilised in routine clinical practice worldwide. It offers valuable safety and clinical effectiveness data in a real-world clinical practice setting and serves as a secondary source of evidence complementing the interventional studies 20288, 20289, and 20290 (107).

The results of ON-TRK address the following uncertainties highlighted in the original submission (71):

- Larotrectinib's positioning in the treatment pathway – most patients received larotrectinib in the ■ (■%) or ■ (■) (■%) settings, as presented in Table 25.
- Data on clinical effectiveness and safety in clinical practice – consistent with the pooled analyses of studies 20288, 20289, and 20290, larotrectinib demonstrated effectiveness across several parameters (CR, PR, ORR, DCR, PFS, OS) and exhibited a favourable safety profile, as presented in Table 26 and Table 27.
- Survival after disease progression – survival data from ON-TRK (PFS and OS) provides supporting evidence for long-term survival in clinical practice (Figure 16 to Figure 19).

- Generalisability of the larotrectinib trial populations – several key characteristics of patients in ON-TRK closely mirror those observed in the pooled analyses from studies 20288, 20298, and 20290. Given the consistency in patient profiles and the global nature of the label indication, these similarities support the generalisability of larotrectinib trial findings to real-world clinical settings, including the NHS.

Detailed methodology and results of ON-TRK are presented in Appendix N. The primary endpoint of the study is safety, with an evaluation of the incidence of TEAEs, including their severity, seriousness, outcomes, and causality assessments. Efficacy is a secondary endpoint, which includes ORR, DCR, DoR, TTR, PFS and OS. As of the enrolment closure on 13<sup>th</sup> November 2024, a total of [REDACTED] patients, of whom [REDACTED] were paediatric patients, were enrolled in the study (107). The Safety Analysis Set (SAF; N=[REDACTED]) included all patients who received at least one dose of larotrectinib. The full analysis set (FAS; N=[REDACTED]) was a subset of the SAF, comprising patients who did not violate any major inclusion or exclusion criteria and had at least one post-baseline assessment following treatment. The Sensitivity Analysis Population (N=[REDACTED]) was derived from the FAS, which excluded fifteen patients whose BOR was either missing or not evaluable. Details on patient disposition are provided in Appendix N. The patient baseline characteristics from the interim analysis based on the data cut-off for the FAS and the SAF are presented in Table 25 (107).

Overall, several key characteristics of patients in the FAS and SAF populations are similar to those of the pooled analyses from studies 20288, 20298 and 20290, including median age, proportions of adult and paediatric patients, tumour types, NTRK gene fusion, tumour stage and ECOG performance status (89, 107). Majority of patients in the ON-TRK study received larotrectinib as [REDACTED] or [REDACTED] therapy (89, 107).

**Table 25. Patient baseline characteristics (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**

| Baseline Characteristics | ON-TRK (FAS)<br>N=████ | ON-TRK (SAF)<br>N=████ |              |
|--------------------------|------------------------|------------------------|--------------|
|                          |                        | non-CNS (n=████)       | CNS (n=████) |
| Sex, n (%)               |                        |                        |              |
| Male                     | ████                   | ████                   | ████         |
| Female                   | ████                   | ████                   | ████         |
| Race, n (%)              |                        |                        |              |
| White                    | ████                   | ████                   | ████         |
| Black                    | ████                   | ████                   | ████         |
| Asian                    | ████                   | ████                   | ████         |
| Not reported             | ████                   | ████                   | ████         |
| Country, n (%)           |                        |                        |              |
| Belgium                  | ████                   | ████                   | ████         |
| Canada                   | ████                   | ████                   | ████         |
| Switzerland              | ████                   | ████                   | ████         |
| Germany                  | ████                   | ████                   | ████         |
| Luxemburg                | ████                   | ████                   | █            |
| France                   | ████                   | ████                   | █            |
| South Korea              | ████                   | ████                   | ████         |
| United States            | ████                   | ████                   | ████         |
| Sweden                   | ████                   | ████                   | ████         |
| Italy                    | ████                   | ████                   | ████         |
| China                    | ████                   | ████                   | ████         |
| Finland                  | ████                   | ████                   | █            |
| Spain                    | ████                   | ████                   | █            |
| Austria                  | ████                   | ████                   | █            |
| Argentina                | ████                   | █                      | ████         |
| Ethnicity, n (%)         |                        |                        |              |
| Non-Hispanic/Latino      | ████                   | ████                   | ████         |
| Hispanic/Latino          | ████                   | ████                   | ████         |
| Not reported             | ████                   | ████                   | ████         |
| Missing                  | ████                   | ████                   | █            |
| Age (years)              |                        |                        |              |
| Median (range)           | ████                   | ████                   | ████         |
| Mean (SD)                | ████                   | ████                   | ████         |
| Age category, n (%)      |                        |                        |              |
| < 18 years               | ████                   | ████                   | ████         |
| ≥ 18 years               | ████                   | ████                   | ████         |
| Body weight (kg)         |                        |                        |              |
| n                        | █                      | █                      | █            |
| Median (range)           | ████                   | ████                   | ████         |
| NTRK gene fusion, n (%)  |                        |                        |              |

| Baseline Characteristics                    | ON-TRK (FAS)<br>N= | ON-TRK (SAF)<br>N= |          |
|---------------------------------------------|--------------------|--------------------|----------|
|                                             |                    | non-CNS (n=)       | CNS (n=) |
| NTRK1                                       |                    |                    |          |
| NTRK2                                       |                    |                    |          |
| NTRK3                                       |                    |                    |          |
| NTRK fusion negative                        |                    |                    |          |
| Missing                                     |                    |                    |          |
| <b>Tumour type, n (%)</b>                   |                    |                    |          |
| Gastric                                     |                    |                    |          |
| STS                                         |                    |                    |          |
| CNS                                         |                    |                    |          |
| Lung                                        |                    |                    |          |
| Head and neck                               |                    |                    |          |
| Melanoma                                    |                    |                    |          |
| IFS                                         |                    |                    |          |
| Other                                       |                    |                    |          |
| <b>ECOG PS, n (%)</b>                       |                    |                    |          |
| 0                                           |                    |                    |          |
| 1                                           |                    |                    |          |
| 2                                           |                    |                    |          |
| 3                                           |                    |                    |          |
| 4                                           |                    |                    |          |
| Not done                                    |                    |                    |          |
| Missing                                     |                    |                    |          |
| <b>Tumour stage, n (%)</b>                  |                    |                    |          |
| III A                                       |                    |                    |          |
| III B                                       |                    |                    |          |
| III C                                       |                    |                    |          |
| IV                                          |                    |                    |          |
| IV A                                        |                    |                    |          |
| IV B                                        |                    |                    |          |
| IV C                                        |                    |                    |          |
| Unknown                                     |                    |                    |          |
| Not applicable                              |                    |                    |          |
| Missing                                     |                    |                    |          |
| <b>Status of primary tumour</b>             |                    |                    |          |
| Unresected                                  |                    |                    |          |
| Resected, no residual or recurrent tumour   |                    |                    |          |
| Resected, residual or recurrent tumour      |                    |                    |          |
| Resected, status of residual tumour unknown |                    |                    |          |
| <b>Any metastases</b>                       |                    |                    |          |
| Yes                                         |                    |                    |          |

| Baseline Characteristics                                                   | ON-TRK (FAS)<br>N= | ON-TRK (SAF)<br>N= |          |
|----------------------------------------------------------------------------|--------------------|--------------------|----------|
|                                                                            |                    | non-CNS (n=)       | CNS (n=) |
| No                                                                         |                    |                    |          |
| Missing                                                                    |                    |                    |          |
| <b>Retrospective larotrectinib treatment, n (%)</b>                        |                    |                    |          |
| No                                                                         |                    |                    |          |
| Yes                                                                        |                    |                    |          |
| <b>Duration of documented retrospective larotrectinib treatment (days)</b> |                    |                    |          |
| n                                                                          |                    |                    |          |
| Mean (SD)                                                                  |                    |                    |          |
| Median (range)                                                             |                    |                    |          |
| <b>Prior cancer therapy, n (%)</b>                                         |                    | <b>SAF (N=120)</b> |          |
| Surgery                                                                    |                    |                    |          |
| Radiotherapy                                                               |                    |                    |          |
| RAI therapy                                                                |                    |                    |          |
| <b>Systemic therapy</b>                                                    |                    |                    |          |
| None                                                                       |                    |                    |          |
| 1                                                                          |                    |                    |          |
| 2                                                                          |                    |                    |          |
| 3                                                                          |                    |                    |          |
| >3                                                                         |                    |                    |          |
| Missing                                                                    |                    |                    |          |

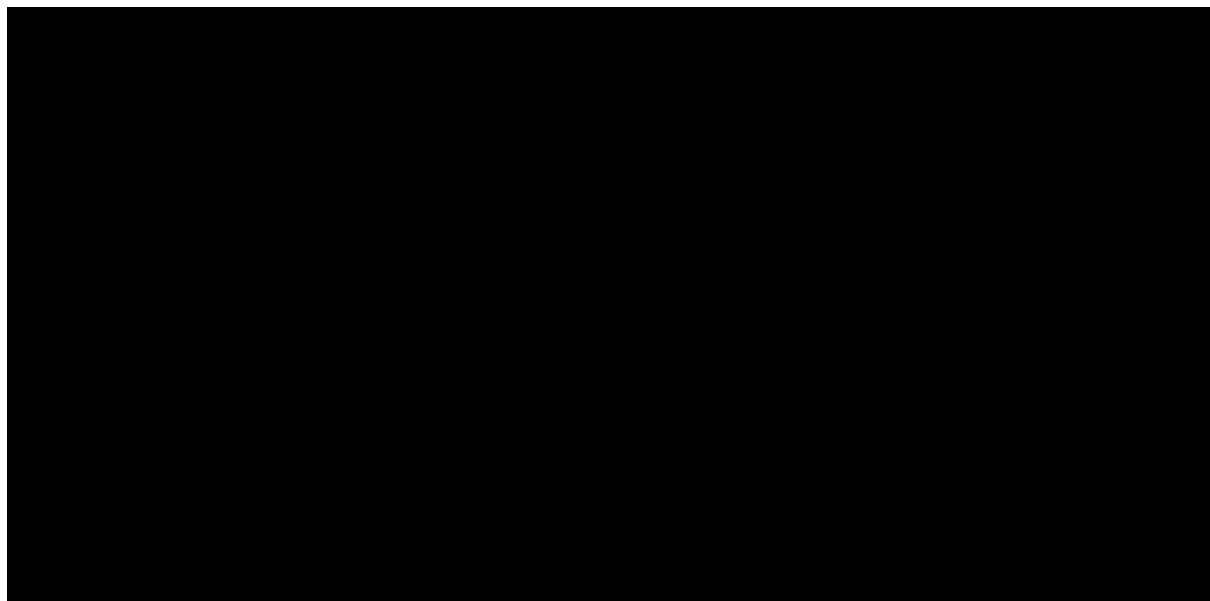
ECOG=Eastern Cooperative Oncology Group; CNS=central nervous system; IFS=infantile fibrosarcoma; NTRK=neurotrophic receptor tyrosine kinase; PS=performance status; RAI=radioactive iodine therapy; SD=standard deviation; STS=soft tissue sarcoma

Source: Bayer, Data on file. ON-TRK Baseline characteristics; Tables 14.2.3.2 and 14.2.4.2 (107)

At the time of data cut-off on 19<sup>th</sup> December 2024, in the FAS (n=), the Kaplan-Meier analysis for patients with non-CNS tumours, the median OS was not reached (95% CI: ), with a total of events reported (Figure 16). For patients with CNS tumours, the Kaplan-Meier analysis showed a median OS of months (95% CI: ), with events reported (Figure 17). The Kaplan-Meier analysis of PFS in the FAS showed a median PFS of months (95% CI: ) and events reported for patients with non-CNS tumours and a median PFS of months (95% CI: ), based on events for patients with CNS tumours (Figure 18 and Figure 19). The PFS curve suggests a meaningful delay in disease progression for a substantial proportion of patients with non-CNS tumours during the first year of follow-up (108).

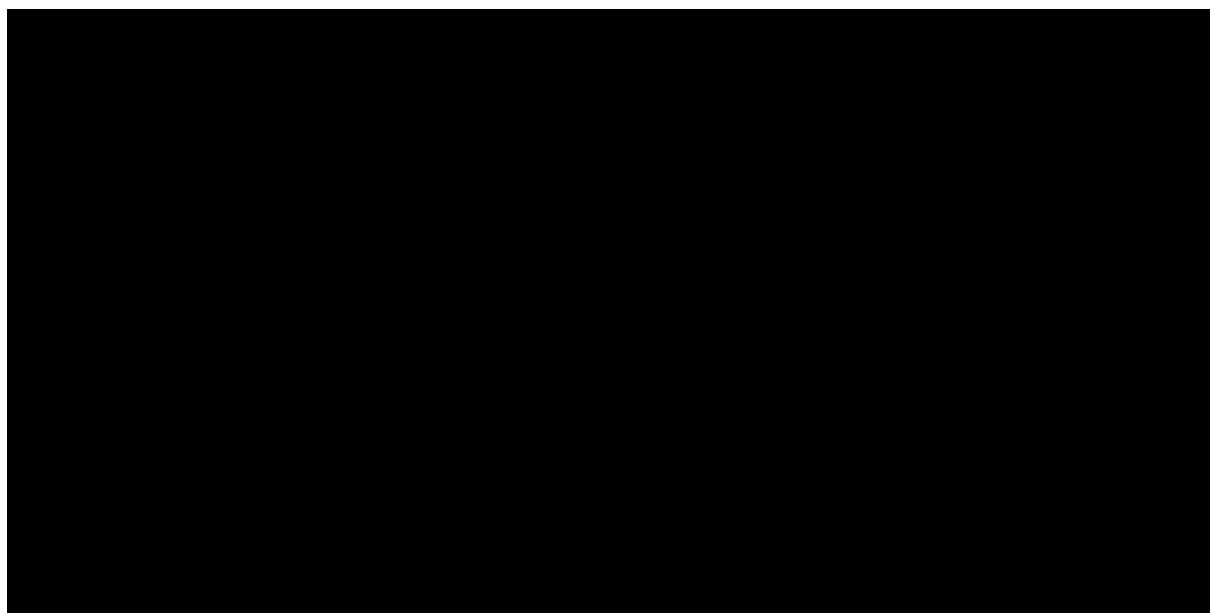


**Figure 16. Kaplan-Meier plot of OS – non-CNS tumours in FAS (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**



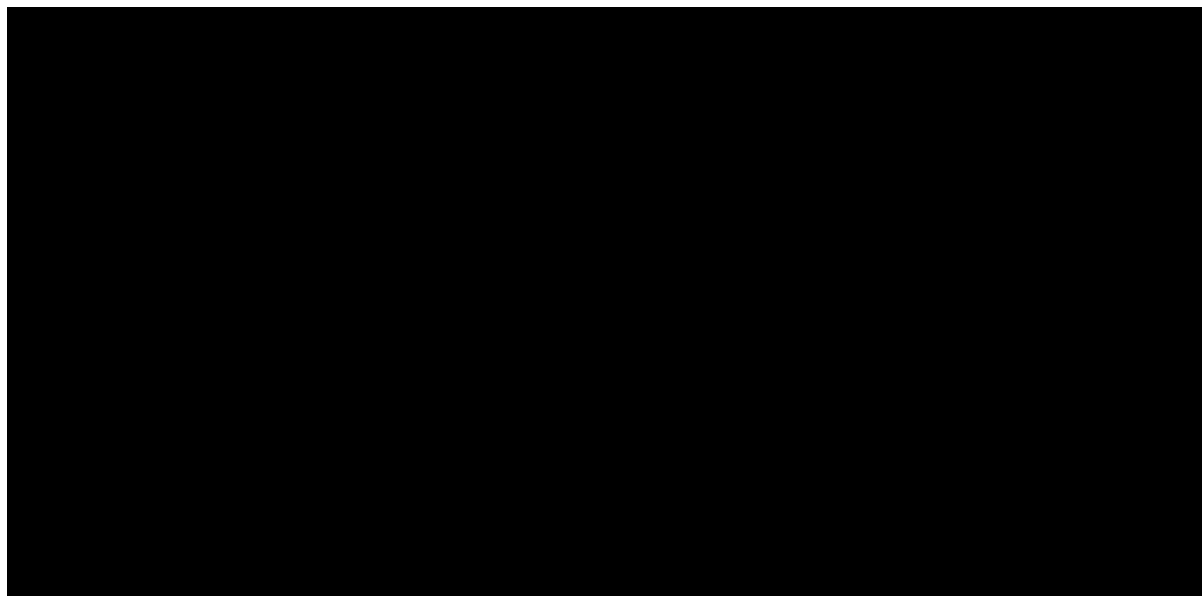
CNS=central nervous system; FAS=full analysis set; OS=overall survival  
Source: Bayer, Data on file. KM curves – ON-TRK, Figure 14.6.1.1 (108)

**Figure 17. Kaplan-Meier plot of OS – CNS tumours in FAS (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**



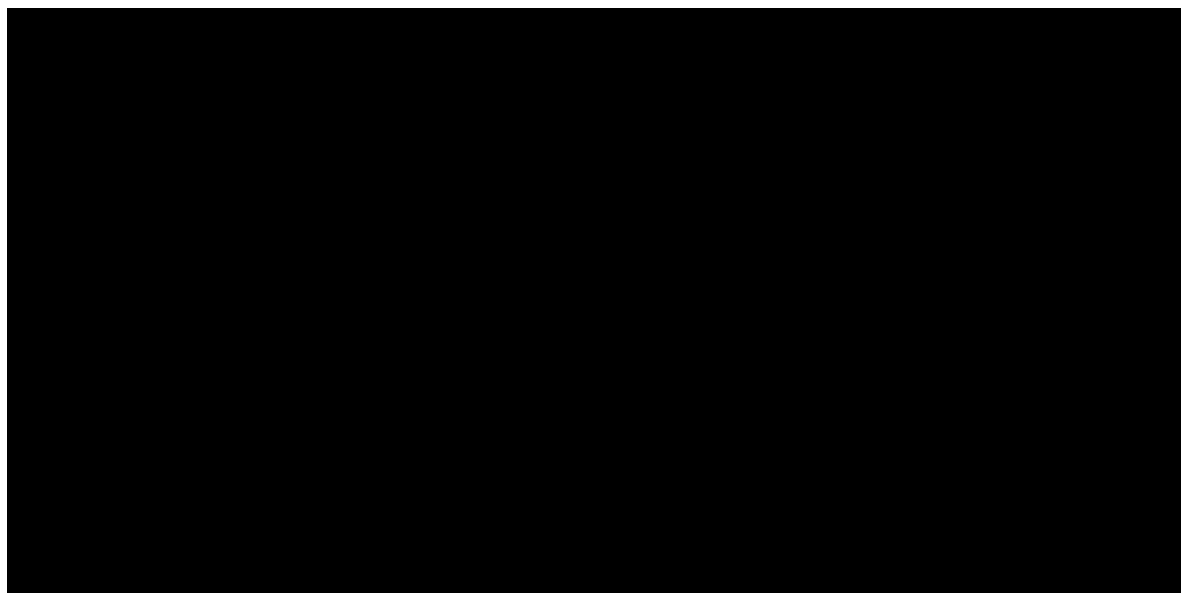
CNS=central nervous system; FAS=full analysis set; OS=overall survival  
Source: Bayer, Data on file. KM curves – ON-TRK, Figure 14.6.1.1 (108)

**Figure 18. Kaplan-Meier plot of PFS – non-CNS tumours in FAS - investigator assessment (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**



CNS=central nervous system; FAS=full analysis set; PFS=progression-free survival  
Source: Bayer, Data on file. KM curves – ON-TRK, Figure 14.6.4.1 (108)

**Figure 19. Kaplan-Meier plot of PFS – CNS tumours in FAS - investigator assessment (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**



CNS=central nervous system; FAS=full analysis set; PFS=progression-free survival  
Source: Bayer, Data on file. KM curves – ON-TRK, Figure 14.6.4.1 (108)

The results of efficacy endpoints, including disease progression, DCR and DoR for the sensitivity analysis of the FAS, based on investigator assessment, are presented in Table 26. Larotrectinib demonstrated an ORR of [REDACTED]% (n=[REDACTED]) in patients with non-

CNS tumours (n=█), with CR in █ patients (█%) and PR in █ patients (█%). SD was achieved in █ patients (█%). The median PFS for the patients with non-CNS tumours was █months (95% CI: █), based on a median follow-up time of █ months (95% CI: █) (107).

For patients with CNS tumours (n=█), larotrectinib achieved an ORR of █% (n=█), with CR observed in █ patients (█%) and PR in █ patients (█%) (107). SD was achieved for almost █ of the patients with CNS tumours (█%). Additionally, larotrectinib showed a median PFS of █ months (95% CI: █), based on a median follow-up of █months (95% CI: █) (107).

**Table 26. Results of the sensitivity analysis of FAS (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**

| Outcome                         | ON-TRK (FAS, sensitivity analysis*) |            |
|---------------------------------|-------------------------------------|------------|
|                                 | Non-CNS<br>n=█                      | CNS<br>n=█ |
| <b>BOR, n (%)</b>               |                                     |            |
| CR                              | █                                   | █          |
| PR                              | █                                   | █          |
| SD                              | █                                   | █          |
| < 16 weeks                      | █                                   | █          |
| >16 and ≤ 24 weeks              | █                                   | █          |
| >24 weeks                       | █                                   | █          |
| PD                              | █                                   | █          |
| <b>ORR, n (%)</b>               | █                                   | █          |
| <b>DCR, n (%)</b>               |                                     |            |
| 16 weeks                        | █                                   | █          |
| 24 weeks                        | █                                   | █          |
| <b>DoR** (N)</b>                |                                     |            |
| Events / censored               | █                                   | █          |
| Median (95% CI)                 | █                                   | █          |
| Follow-up time, months (95% CI) | █                                   | █          |
| <b>PFS**</b>                    |                                     |            |
| Events / censored               | █                                   | █          |
| Median (95% CI)                 | █                                   | █          |
| Follow-up time, months (95% CI) | █                                   | █          |

BOR=best overall response; CI=confidence interval; CNS=central nervous system; CR=complete response; DCR=disease control rate; DoR=duration of response; FAS=full analysis set; NE=not estimable; ORR=objective response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease  
 \*Patients with non-evaluable or missing BOR excluded from sensitivity analysis: BOR missing (N=█), BOR not evaluable (N=█)  
 \*\*Investigator assessment

Source: Bayer, Data on file. 20324 ON-TRK Endorsement of ESMO 2025 Publication (107)

A total of █% of patients in the SAF experienced at least one TEAE, while █% had at least one TRAE during larotrectinib therapy. Among the TEAEs, the most frequent were Grade 2 events (█%), followed by Grade 3 events (█%) and Grade 1 events (█%). These findings indicate that most patients experienced TEAEs of mild to moderate severity.

Similarly, most larotrectinib-related TRAEs were of lower severity, with only a small proportion of patients experiencing grade 3 events or higher. Overall, these results highlight that AEs associated with larotrectinib are predominantly mild or moderate in grade, with serious or life-threatening events being relatively infrequent in this patient cohort.

An overview of the most common grade 3 and 4 TRAEs is presented in Table 27 (107), while grade 1 and 2 TRAEs can be found in Appendix N.

**Table 27. Most common grade 3 and 4 TRAEs by maximum CTCAE grade in SAF (ON-TRK, data cut-off 19<sup>th</sup> Dec 2024)**

| TRAE                                 | TRAEs, n (%)<br>SAF (N=█) |         |
|--------------------------------------|---------------------------|---------|
|                                      | Grade 3                   | Grade 4 |
| Alanine aminotransferase increased   | █                         | █       |
| Aspartate aminotransferase increased | █                         | █       |
| Fatigue                              | █                         | █       |
| Nausea                               | █                         | █       |
| Weight increased                     | █                         | █       |

CTCAE=Common Terminology Criteria for Adverse Events; SAF=Safety analysis set; TRAE=treatment-related adverse event  
Source: Bayer, Data on file. 20324 ON-TRK Endorsement of ESMO 2025 Publication (107)

**2.13.2 Systemic Anti-Cancer Therapy (SACT) real-world data (England)**

**2.13.2.1 Background**

Larotrectinib was recommended for use within the CDF under a MAA for a period of 57 months, from April 2020 to December 2024. Before the managed access period, results from the ongoing clinical trials (studies 20288, 20289, and 20290) were the

primary evidence source to answer uncertainties identified in the original submission (89). The analysis of the SACT dataset, which outlines the collection and analysis of real-world evidence in the UK, now further addresses outstanding clinical uncertainties in accordance with NICE guidance, acting as a secondary source of information.

The SACT dataset provides a comprehensive account of how larotrectinib is being utilised in routine clinical practice across NHS England, thereby enhancing the robustness of the clinical evidence base. Treatment duration, OS and treatment outcomes were assessed for all patients with NTRK fusion-positive advanced solid tumours treated with larotrectinib under the CDF (109).

Between April 21<sup>st</sup>, 2020 and December 31<sup>st</sup>, 2024, 66 CDF applications for larotrectinib were identified in the Blueteq<sup>®</sup> system. Following de-duplication, 62 unique patients were included in the analysis. Of the 62 applications for CDF funding for larotrectinib, one patient died before treatment and one patient was missing from the SACT dataset. Detailed clinical treatment criteria and assessments performed 12 weeks after initiation of larotrectinib are presented in Appendix N.

Completeness of key variables in the SACT dataset was analysed. Completeness was 100% for primary diagnosis, date of birth, gender and treatment dates. It was 98% for site and histology of tumour origin, disease status, NTRK gene, brain metastases, lines of systemic therapy and type of surgical resection. In contrast, completeness was lower for performance status at the start of regimen (47%).

### 2.13.2.2 Patient characteristics

Patient baseline characteristics are presented in Table 28. More than half of the patients were male (57%), and majority of the patient population were adults aged  $\geq 20$  years (63%). Among patients with available performance status, most reported an ECOG PS of 0 or 1 (41%). It is noteworthy that 35% of patients had primary CNS tumour (including “primary brain tumour”, “primary CNS tumour” and “glioma”). Larotrectinib was mostly used as 2L systemic therapy (78% of patients), consistent with the CDF criteria. In terms of NTRK gene fusion types, those captured included NTRK1 (37%), NTRK2 (30%) and NTRK3 (32%) fusions (109).

**Table 28. Patient baseline characteristics (SACT data, 2025)**

| Patient characteristics                | Category                                                                                                                                                                    | N  | %  |
|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|
| Gender                                 | Male                                                                                                                                                                        | 34 | 57 |
|                                        | Female                                                                                                                                                                      | 26 | 43 |
| Age band                               | 0 to 4                                                                                                                                                                      | 8  | 13 |
|                                        | 5 to 9                                                                                                                                                                      | 9  | 15 |
|                                        | 10 to 14                                                                                                                                                                    | 4  | 7  |
|                                        | 15 to 19                                                                                                                                                                    | 1  | 2  |
|                                        | 20 to 24                                                                                                                                                                    | 1  | 2  |
|                                        | 25 to 29                                                                                                                                                                    | 2  | 3  |
|                                        | 30 to 39                                                                                                                                                                    | 6  | 10 |
|                                        | 40 to 49                                                                                                                                                                    | 8  | 13 |
|                                        | 50 to 59                                                                                                                                                                    | 7  | 12 |
|                                        | 60 to 69                                                                                                                                                                    | 8  | 13 |
|                                        | 70 to 79                                                                                                                                                                    | 5  | 8  |
|                                        | 80+                                                                                                                                                                         | 1  | 2  |
| Performance status at start of regimen | 0                                                                                                                                                                           | 11 | 18 |
|                                        | 1                                                                                                                                                                           | 14 | 23 |
|                                        | 2                                                                                                                                                                           | 3  | 5  |
|                                        | 3                                                                                                                                                                           | 0  | 0  |
|                                        | 4                                                                                                                                                                           | 0  | 0  |
|                                        | Missing                                                                                                                                                                     | 32 | 53 |
| Site and histology of tumour origin    | Primary brain tumour                                                                                                                                                        | 15 | 25 |
|                                        | Sarcoma                                                                                                                                                                     | 12 | 20 |
|                                        | Infantile fibrosarcoma                                                                                                                                                      | 4  | 7  |
|                                        | Lung adenocarcinoma                                                                                                                                                         | 4  | 7  |
|                                        | Non-squamous NSCLC                                                                                                                                                          | 4  | 7  |
|                                        | Primary CNS tumour                                                                                                                                                          | 3  | 5  |
|                                        | Thyroid                                                                                                                                                                     | 3  | 5  |
|                                        | Glioma                                                                                                                                                                      | 3  | 5  |
|                                        | Papillary thyroid carcinoma                                                                                                                                                 | 2  | 3  |
|                                        | Lung                                                                                                                                                                        | 2  | 3  |
|                                        | Colorectal adenocarcinoma                                                                                                                                                   | 2  | 3  |
|                                        | Forearm spindle cell sarcoma                                                                                                                                                | 1  | 2  |
|                                        | Head adenocarcinoma                                                                                                                                                         | 1  | 2  |
|                                        | Oesophagus adenocarcinoma                                                                                                                                                   | 1  | 2  |
|                                        | Salivary gland carcinoma                                                                                                                                                    | 1  | 2  |
|                                        | Salivary gland adenocarcinoma                                                                                                                                               | 1  | 2  |
|                                        | Not captured                                                                                                                                                                | 1  | 2  |
| Type of disease                        | Metastatic disease                                                                                                                                                          | 24 | 40 |
|                                        | Locally advanced with systemic therapy                                                                                                                                      | 18 | 30 |
|                                        | Locally advanced with surgical resection resulting in morbidity                                                                                                             | 17 | 28 |
|                                        | Not captured                                                                                                                                                                | 1  | 2  |
| Lines of systemic therapy              | 1 line of systemic therapy                                                                                                                                                  | 47 | 78 |
|                                        | 2 lines of systemic therapy                                                                                                                                                 | 5  | 8  |
|                                        | 3 or more lines of systemic therapy                                                                                                                                         | 6  | 10 |
|                                        | Larotrectinib is being used as first line therapy for locally advanced or metastatic disease as the patient has no satisfactory systemic therapy options as described above | 1  | 2  |
|                                        | Not captured                                                                                                                                                                | 1  | 2  |
|                                        | 1 line of systemic therapy                                                                                                                                                  | 47 | 78 |

| Patient characteristics   | Category                                                                                                                                                                    | N  | %  |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|
| Lines of systemic therapy | 2 lines of systemic therapy                                                                                                                                                 | 5  | 8  |
|                           | 3 or more lines of systemic therapy                                                                                                                                         | 6  | 10 |
|                           | Larotrectinib is being used as first line therapy for locally advanced or metastatic disease as the patient has no satisfactory systemic therapy options as described above | 1  | 2  |
|                           | Not captured                                                                                                                                                                | 1  | 2  |
| NTRK gene                 | NTRK1                                                                                                                                                                       | 22 | 37 |
|                           | NTRK2                                                                                                                                                                       | 18 | 30 |
|                           | NTRK3                                                                                                                                                                       | 19 | 32 |
|                           | Not captured                                                                                                                                                                | 1  | 2  |
| Brain metastases          | The patient does not have brain metastases                                                                                                                                  | 51 | 85 |
|                           | Brain metastases with previous cerebral surgery                                                                                                                             | 6  | 10 |
|                           | Brain metastases and no cerebral surgery                                                                                                                                    | 2  | 3  |
|                           | Not captured                                                                                                                                                                | 1  | 2  |

Note: Figures may not add to 100% due to rounding.

CNS=central nervous system; NSCLC=non-small cell lung cancer; NTRK=neurotrophic tyrosine receptor kinase.

Source: Table 5 and Table 6, SACT report 2025 (109)

### 2.13.2.3 NTRK testing captured in the NDRS molecular dataset

NTRK testing was analysed between 31<sup>st</sup> July 2018 and 31<sup>st</sup> December 2024, and 40,472 unique patients had a record in the NDRS molecular dataset with either a positive, borderline or negative NTRK gene fusion (Table 29).

**Table 29. NTRK test results (SACT data, 2025)**

| Cancer group              | Borderline | Negative | Positive | Total <sup>1,2</sup> |
|---------------------------|------------|----------|----------|----------------------|
| Lung                      | 10         | 18,178   | 110      | 18,298               |
| Lower GI                  | 5          | 4,146    | 26       | 4,177                |
| HPB                       | 1          | 2,110    | 9        | 2,120                |
| Other                     | 5          | 1,973    | 33       | 2,011                |
| Oesophagogastric          | 1          | 1,997    | 10       | 2,008                |
| Gynaecological            | 1          | 1,787    | 14       | 1,802                |
| Brain and CNS             | 7          | 1,528    | 28       | 1,563                |
| Prostate                  | 2          | 1,319    | 2        | 1,323                |
| Soft tissue and bone      | 2          | 1,204    | 28       | 1,234                |
| Skin                      | 2          | 1,094    | 16       | 1,112                |
| Head and neck             | 2          | 849      | 40       | 891                  |
| Endocrine                 | 1          | 760      | 24       | 785                  |
| Breast                    | 1          | 737      | 14       | 752                  |
| Haematology               | -          | 663      | 5        | 668                  |
| Urology excl. prostate    | 1          | 597      | 3        | 601                  |
| Thoracic and mesothelioma | -          | 351      | 1        | 352                  |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

<sup>1</sup>If a patient had more than one diagnosis in the Cancer Registration dataset, the diagnosis date closest to the lab test date was selected. In some cases, the test date was not submitted, or a patient might have more than one tumour registered on the same date, in both cases, patients will be counted multiple times.

<sup>2</sup>Blumetq<sup>®</sup> data was not included in this section.

CNS=central nervous system; NTRK=neurotrophic tyrosine receptor kinase.

Source: Table 8, SACT report 2025 (109)

Of the 404 patients with a positive or borderline result, 251 (62%) had a gene fusion captured in the NDRS molecular dataset (Table 30).

**Table 30. Characterisation of gene fusion (N=404) (SACT data, 2025)**

| Cancer group              | NTRK1      | NTRK2     | NTRK3      | Unknown    | Total      |
|---------------------------|------------|-----------|------------|------------|------------|
| Lung                      | 18         | 3         | 18         | 81         | 120        |
| Head and neck             | 4          | 2         | 22         | 14         | 42         |
| Other                     | 13         | 3         | 17         | 5          | 38         |
| Brain and CNS             | 15         | 12        | 6          | 2          | 35         |
| Lower GI                  | 21         |           | 3          | 7          | 31         |
| Soft tissue and bone      | 13         |           | 8          | 9          | 30         |
| Endocrine                 | 10         |           | 12         | 3          | 25         |
| Skin                      | 11         | 1         | 3          | 3          | 18         |
| Breast                    | 1          | 2         | 8          | 4          | 15         |
| Gynaecological            | 7          |           | 2          | 6          | 15         |
| Oesophagogastric          | 1          |           | 1          | 9          | 11         |
| HPB                       | 4          | 1         | 2          | 3          | 10         |
| Haematology               |            |           | 4          | 1          | 5          |
| Urology excl. prostate    | 1          |           | 2          | 1          | 4          |
| Prostate                  |            | 1         |            | 3          | 4          |
| Thoracic and mesothelioma |            |           |            | 1          | 1          |
| <b>Total</b>              | <b>119</b> | <b>25</b> | <b>108</b> | <b>152</b> | <b>404</b> |

CNS=central nervous system; GI=gastrointestinal; HPB=hepato-pancreato-biliary; NTRK=neurotrophic tyrosine receptor kinase.

Source: Table 9, SACT report 2025 (109)

## 2.13.2.4 Results

### 2.13.2.4.1. ORR

Response was observed in 72% of the patients (CR, 7% and PR, 65%) after 10 weeks from initiation of larotrectinib, with 28% of patients achieving SD (109).

### 2.13.2.4.2. Time-to-treatment discontinuation (TTD)

The median follow-up time in SACT was 13.3 months. By the end of the follow-up period (31<sup>st</sup> December 2024), 32 patients had ended treatment (including patients who died on treatment, patients who died not on treatment and those who stopped



treatment), and 28 patients were still receiving treatment. Median treatment duration was 26.9 months [95% CI: 14.4, 45.4].

Treatment duration at 6, 12, 18, 24, 36, and 48 months was calculated and showed that patients still receiving treatment at 6 months was 79% [95% CI: 70%, 90%] and 26% [95% CI: 15%, 48%] at 48 months (Table 31) (109).

**Table 31. Treatment duration at 6, 12, 18, 24, 36, and 48-month intervals (SACT data, 2025)**

| Time period | Treatment duration (%) |                                 |                                 |
|-------------|------------------------|---------------------------------|---------------------------------|
|             | (%)                    | Lower Confidence Interval (LCI) | Upper Confidence Interval (UCI) |
| 6 months    | 79%                    | 70%                             | 90%                             |
| 12 months   | 67%                    | 56%                             | 81%                             |
| 18 months   | 59%                    | 47%                             | 74%                             |
| 24 months   | 53%                    | 41%                             | 70%                             |
| 36 months   | 39%                    | 26%                             | 57%                             |
| 48 months   | 26%                    | 15%                             | 48%                             |

LCI=lower confidence interval; UCI=upper confidence interval.

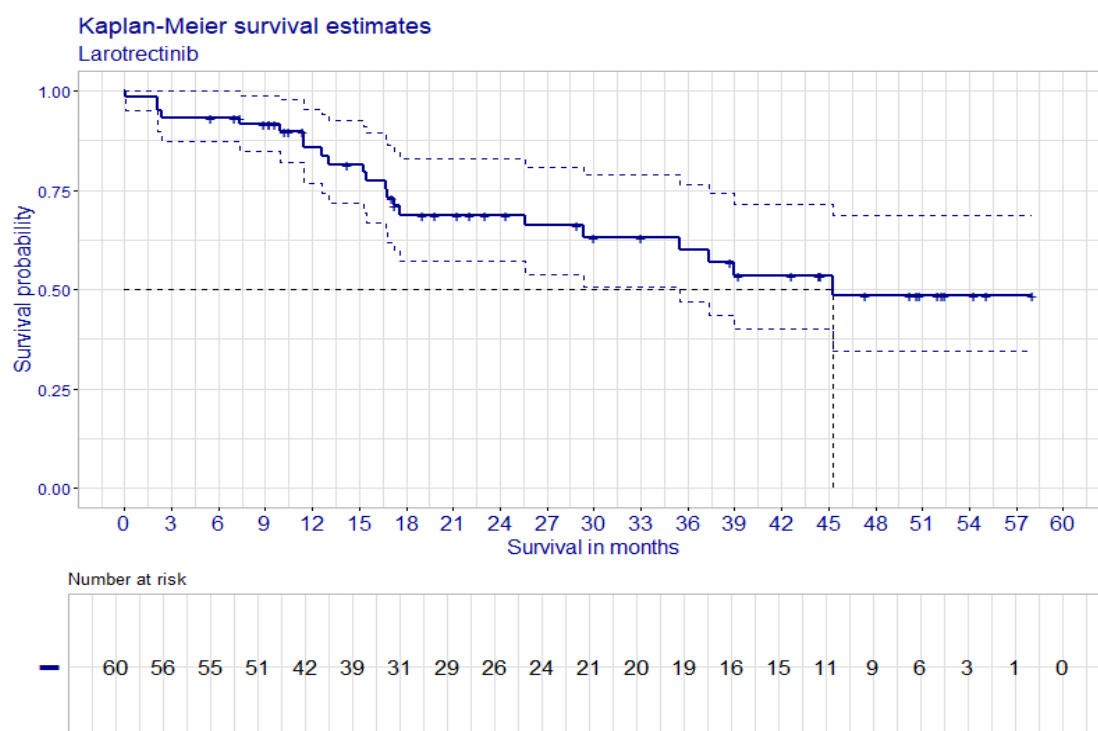
Source: Table 14, SACT report 2025 (109)

#### 2.13.2.4.3. OS

The median follow-up time was 19.4 months and the median OS was 45.2 months, confidence intervals could not be produced as there was an insufficient number of events at the time of analysis (Figure 20).

OS at 6, 12, 18, 24, 36, and 48 months was calculated and showed that the OS at 6 months was 93% [95% CI: 87%, 100%] and 49% [95% CI: 34%, 69%] at 48 months (Table 32) (109).

**Figure 20. Kaplan-Meier survival plot for OS (SACT data, 2025)**



OS = overall survival

Source: Figure 4, SACT report 2025 (109)

**Table 32. OS at 6, 12, 18, 24, 36 and 48-month intervals (SACT data, 2025)**

| Time period | OS (%) |                                 |                                 |
|-------------|--------|---------------------------------|---------------------------------|
|             | (%)    | Lower Confidence Interval (LCI) | Upper Confidence Interval (UCI) |
| 6 months    | 93%    | 87%                             | 100%                            |
| 12 months   | 86%    | 77%                             | 95%                             |
| 18 months   | 69%    | 57%                             | 83%                             |
| 24 months   | 69%    | 57%                             | 83%                             |
| 36 months   | 60%    | 47%                             | 77%                             |
| 48 months   | 49%    | 34%                             | 69%                             |

LCI = lower confidence interval; OS = overall survival; UCI = upper confidence interval.

Source: Table 18, SACT report 2025 (109)

Further results from the analysis are presented in Appendix N.

The results of the SACT analysis address the following uncertainties highlighted in the original submission (71):

- Generalisability of the larotrectinib trial populations to the NHS patient population – when comparing the SACT dataset with the pooled analyses from studies 20288, 20289 and 20290, several outcomes are broadly similar:
  - The proportion of adult and paediatric patients, captured tumour types and NTRK gene fusion in the SACT dataset are consistent with those of the larotrectinib trials. However, it is important to note that some of the key characteristics in the SACT dataset have substantial missing data (e.g., performance status), which could limit comparability to the larotrectinib trial populations.
  - Time to response was short, with response rates similar to those observed in the larotrectinib trials (ORR of 72% (31/43) in the SACT report vs. 65% in the clinical trials). The response rate observed within a relatively short timeframe of 10 weeks (2.3 months) post-initiation indicates robust treatment efficacy.
  - Survival at 48 months was consistent with the OS results from the pooled analyses of the ePAS9 and SAS3 datasets. Treatment with larotrectinib resulted in long survival times for a large proportion of heterogeneous patient population in the SACT dataset for which no satisfactory treatment options would have otherwise existed.
  - PFS was durable and time on treatment is aligned, especially considering that a large pool of the SACT patient population has primary-CNS cancer.
- Larotrectinib's positioning in the treatment pathway – most patients received larotrectinib as 2L (78.0%) therapy, and the results are supportive of those in the pooled analyses of larotrectinib trials. This also aligns with key eligibility criteria for the use of larotrectinib in the CDF, i.e., to apply by the first cycle of systemic anti-cancer therapy. This reinforces the proposed positioning of larotrectinib in the treatment of NTRK fusion-positive solid tumours where the

decision to initiate larotrectinib should remain at the discretion of the treating clinician, depending on the clinical context.

Overall, the findings from the SACT dataset reinforce the external validity and generalisability of the larotrectinib trial results to the NHS setting (109). It is supportive within the confines set by the heterogeneity of the tumour-agnostic adult and paediatric populations, which is magnified by the small number of treated patients in the CDF (60 patients in the SACT dataset vs. 364 in the larotrectinib trials). Inclusion of patients with CNS tumours supports clinical utility of larotrectinib in managing NTRK fusion-positive tumours across diverse populations.

### **2.13.3 LAROTRACKING and SACHA (France)**

The LAROTRACKING and SACHA studies provide supportive evidence to address uncertainties around the real-world clinical effectiveness and safety of larotrectinib. The results reported in these studies are consistent with the pooled analyses of the larotrectinib trials, demonstrating its efficacy (CR, PR, SD, DCR, PFS, OS) and favourable tolerability in both adult and paediatric patients with NTRK fusion-positive solid tumours.

#### **2.13.3.1 Adult cohort – LAROTRACKING**

LAROTRACKING is a national, open-label, retro-/prospective, non-interventional cohort study that assessed the real-world effectiveness and safety of larotrectinib among French adults with NTRK fusion-positive advanced solid tumours (110). The final analysis was conducted using SAS® v.9.4 software, following the Statistical Analysis Plan approved on 20<sup>th</sup> December 2024 and the Blind Review meeting held on 13 December 2024. The database for the final analysis was extracted on 22 December 2024 (110).

The study included 26 patients (median age 56.6 years [range: 24.2-77.8 years]; 69% female), with the most common tumour types being thyroid (38.5%), lung (15.4%), brain (11.5%), and parotid (11.5%) (110). Most patients (84.6%) had at least one prior treatment before starting larotrectinib. At inclusion, all 26 patients had either locally advanced disease (4 patients) or metastatic disease (22 patients) (110).

The best overall response included CR for four patients (15.4%), PR for 14 patients (53.8%), SD for three patients (11.5%) and PD for five patients (19.2%) (110). The best ORR was CR or PR for 18 patients (69.2%). The median time to response after initiating larotrectinib was 2.5 months (range: 1.1-40.6 months). The DCR was 80.8%, with 21 patients achieving CR, PR or SD. A total of 15 patients (57.7%) died, with disease progression being the most common cause. The median follow-up duration, calculated using the reverse Kaplan-Meier method, was 53.9 months (95% CI: 45.1, 61.1) across the 26 treated patients. At the time of analysis, 15 patients had died. The observed median OS was 38.3 months (95% CI: 12.3, NE), while PFS data showed 21 events had occurred, with a median PFS of 16.3 months (95% CI: 4.0, 34.8) (110).

Only AEs related to larotrectinib and classified as grade  $\geq 2$  were collected. Nine patients (34.6%) reported at least one such AE, with two patients (7.7%) experiencing grade 3 events. One patient (3.8%) experienced a grade 3 AE that led to permanent treatment discontinuation. Dose modifications were required in six patients (23.1%), although notably, no grade 4 or 5 AEs were reported (110).

### 2.13.3.2 Paediatric cohort – SACHAxLaro

The SACHAxLaro study is a French prospective observational cohort designed to evaluate the real-world use of larotrectinib in paediatric and young adult patients with NTRK fusion-positive locally advanced or metastatic solid tumours (111). The study has been open for inclusion since May 2021 and the reported data of patients treated with larotrectinib are up to 31<sup>st</sup> December 2024 (111).

This cohort comprised of █ patients, predominantly male (█%), with a median age of █ years (range: █ years). A large proportion of the patients had STS (█%) or CNS tumours (█%). A total of █ patients (█%) were treatment-naïve at the time of larotrectinib initiation, while █ (█%) had metastatic disease (111).

Efficacy and safety outcomes were promising. Among the █ evaluable patients, █ (█%) achieved a CR, █ (█%) experienced PR, and █ (█%) maintained SD (111). Safety data also supported the use of larotrectinib in this group, with only █ patients (█%) experiencing grade 2 or higher AEs (█), and no Grade 4 or 5 events were reported. Notably, majority of patients (n=█; █%) did

not experience any AEs. Ultimately, █ patients (█%) discontinued treatment, most commonly due to disease progression (█%) or a medical decision following a good therapeutic response in █ patients (█%) (111).

2.14 Case studies

To reflect the growing clinical experience with larotrectinib within NHS England since its availability through the CDF, an updated set of case studies is provided. Collectively, the selection of case studies serve as additional evidence supporting the durable efficacy and safety of larotrectinib across various NTRK fusion-positive solid tumours and age groups (Table 33 to Table 36).

Table 33. Case 1: KCTD16-NTRK2 diffuse infantile spinal high-grade glioma

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>A █-old child was diagnosed with █, with molecular testing confirming an █ gene fusion (112). The patient initially received █ months of intensive chemotherapy, achieving █ as the best response, though treatment was associated with significant side effects.</p> <p>At █ and █ of age, the patient was enrolled in the SCOUT trial and began targeted therapy with larotrectinib. █ (112).</p> <p>Dose reductions were implemented due █, in line with trial protocol. These counts were considered █ and █ (112).</p> <p>The patient is currently █ and █ old and remains on treatment, now in █. The regimen continues to be █ (112).</p> <p>Importantly, the patient has not required spinal radiotherapy, which has helped preserve quality of life and avoid the long-term side effects associated with radiation in a growing child (112).</p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Table 34. Case 2: ETV6-NTRK3 IFS**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>A [REDACTED]-old male infant was diagnosed at birth with [REDACTED] of the left arm, with molecular testing confirming an [REDACTED] gene fusion via RT-PCR (113). The patient began treatment with larotrectinib at 1 mg/kg PO BID, which was increased to 100 mg/m<sup>2</sup> PO BID starting with the second cycle (each cycle is 28 days) (113).</p> <p>Following [REDACTED] cycles, [REDACTED] in the size of the mass was observed. A repeat MRI after [REDACTED] cycles demonstrated [REDACTED] (113). By the end of [REDACTED] cycles, the patient had [REDACTED]. Supportive care included intravenous fluids and furosemide (113).</p> <p>Given the complete response (CR) and excellent functional outcome, surgical intervention (i.e., amputation) was not pursued. The patient remains on larotrectinib therapy with a planned total of [REDACTED] cycles (113).</p> |
| <b>Baseline</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>After 2 cycles</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>After 4 cycles</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

**Table 35. Case 3: ETV6-NTRK3 secretory breast cancer**

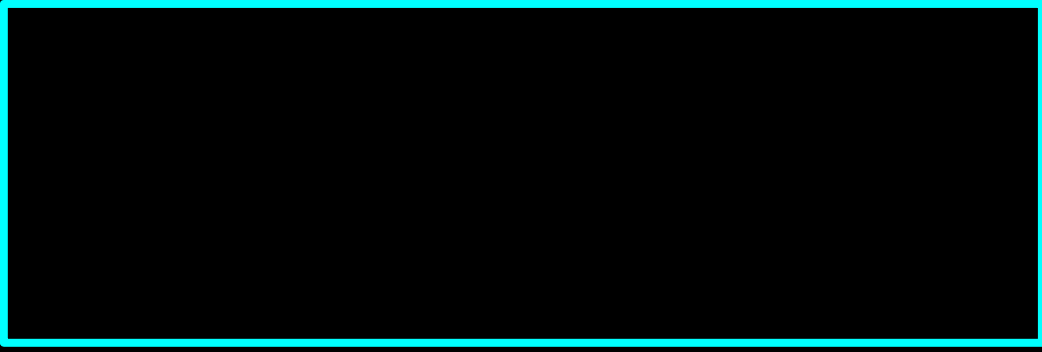
| <p>A █████-old male was diagnosed with █████ at the age of █████. Initial treatment included a mastectomy, followed by palliative radiotherapy to a left second rib metastasis (114). Subsequent PET imaging revealed increased FDG uptake in the rib lesion and a new L1 vertebral lesion, prompting initiation of capecitabine (114).</p> <p>Approximately █████ later, the patient experienced progressive disease (PD) in the bone and possibly the lungs (114). Molecular testing identified an █████ gene fusion via FISH, and the patient was started on larotrectinib (100 mg BID) (114).</p> <p>A partial response (PR) was achieved at █████. However, disease progression occurred at █████, and subsequent analysis revealed the presence of an NTRK3 G623R solvent front mutation, associated with resistance to TRK inhibition (114).</p> |                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2 months after larotrectinib |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                              |

**Table 36. Case 4: TPR-NTRK1 recurrent metastatic colon cancer**

| <p>A █████-old female with █████ initially underwent a right hemicolectomy with segmental small-bowel resection in June 2018 for Stage IIB disease, but deferred adjuvant chemotherapy. Disease progression followed treatment with four cycles of pembrolizumab and two cycles of ipilimumab/nivolumab between June and September 2019 (115).</p> <p>Molecular profiling revealed a █████ gene fusion via next-generation sequencing (NGS), and the tumour was also microsatellite instability-high (MSI-H) with a high tumour mutational burden. In November 2019, the patient began larotrectinib therapy, leading to rapid symptomatic improvement within one week, including reduced pain and weight gain (115).</p> <p>A CT scan at █████ showed a █████ in the largest peritoneal metastasis and interval shrinkage of other lesions (115). Given the █████ clinical, biochemical, and radiographic response, larotrectinib was discontinued, and the patient underwent curative-intent surgical resection in February 2020, █████ (115).</p> <p>The patient opted for observation rather than adjuvant TRK inhibitor therapy. As of the latest follow-up, there is no evidence of disease recurrence at █████ (115).</p> |                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 5 weeks after larotrectinib |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                             |



## **2.15 Caregiver and patient testimonials**

This section presents the experiences of two caregivers of paediatric patients and one patient receiving larotrectinib for the treatment of NTRK fusion-positive solid tumours in the UK (116).

Caregivers reported that after starting larotrectinib, patients experienced a significant improvement in their HRQoL (116). The need for hospital visits was significantly reduced, allowing families to return to more typical routines, such as the patient attending school and participating in family activities, which had previously been disrupted by the disease and its treatment (116).

Prior to initiating larotrectinib, the burden of care was significant. The side effects of chemotherapy and the frequency of medical interventions made caregiving extremely demanding (116). Additionally, the caregivers were overwhelmed by hospital visits and intensive care, leaving them little time to care for their other children. However, after starting treatment with larotrectinib, managing the patient's care became considerably easier, enabling parents to spend quality time with their other children and greatly improving the family's overall quality of life. The stability offered by the treatment, through effective disease management, easy dosing and administration, and a well-tolerated safety profile, allowed at least one caregiver to return to work, and life at home became less dictated by the illness. Larotrectinib's effectiveness in maintaining disease control also alleviated the anxiety associated with the fear of disease progression (116).

Another important aspect was how well the patients tolerated larotrectinib. Unlike previous treatments that often resulted in severe side effects, patients on larotrectinib experienced few or no significant side effects. This improved tolerability made the daily routine of taking the medication easier and contributed further to a sense of normalcy for the whole family. The simplicity of the dosing regimen, including its liquid formulation and twice daily schedule, also made administration more manageable, allowing caregivers to fit doses around school timings and daily routines with minimal disruption (116).

These testimonials illustrate that larotrectinib has been transformative for patients and their families, enabling them to engage more fully in daily life and allowing caregivers

to regain balance and optimism (116). The treatment's predictability and tolerability have provided both practical and emotional relief, allowing families to focus less on illness and more on living their lives together. This renewed stability and hope have had a lasting, positive impact on the entire family dynamic (116).

This third testimonial comes from a UK patient diagnosed with NTRK fusion-positive salivary gland cancer who was treated with larotrectinib. The patient shared profound insights into the impact of their disease on daily life and treatment experiences. Initially, they faced significant challenges, including debilitating symptoms, deteriorating mental health, and financial hardships following their diagnosis of metastasised salivary gland cancer at 32 years old.

However, after transitioning from ineffective chemotherapy to the oral treatment larotrectinib, the patient reported a remarkable turnaround in both physical and mental well-being. They highlighted the ease of the larotrectinib treatment regimen, which provides greater flexibility and autonomy, significantly improving their quality of life.

The patient's renewed sense of hope and optimism is evident; they now feel capable to return to work and engage in social activities, ultimately reclaiming a sense of normalcy and vitality after a tumultuous period (117).

## **2.16 Ongoing studies**

### **2.16.1 Ongoing studies with results expected in the next 12 months**

A hand search of clinical trial registries was conducted as part of the updated SLR. This search identified seven ongoing studies of larotrectinib with results expected in the coming 12 months. Three studies that contributed to the clinical effectiveness and safety evidence of larotrectinib (studies 20289, 20290 and ADVL1823) are still ongoing at the time of this company submission, with study participants being actively followed up. The remaining ongoing studies (Phase 1 and 2) are sponsored by public institutions, indicating broader clinical interest in larotrectinib beyond the pharmaceutical company sponsored research (Table 37).

**Table 37. Ongoing clinical studies of larotrectinib**

| Registry number | Study title                                                                                                                                                                                  | Phase         | Sponsor                             | Population condition                                                                                                                                                                             | Intervention                                                                                                                                                                                                              | Estimated sample size | Status                 | Primary completion date |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------|-------------------------|
| NCT04655404     | A pilot study of larotrectinib for newly diagnosed high-grade glioma with NTRK fusion                                                                                                        | Early Phase 1 | Nationwide Children's Hospital      | Patients $\leq$ 21 years of age that have been newly diagnosed high-grade glioma with TRK fusion                                                                                                 | <ul style="list-style-type: none"> <li>Feasibility Cohort: Larotrectinib with/ without chemotherapy backbone</li> <li>Surgical cohort: Larotrectinib for 3 to 5 days pre-surgery, then 2 cycles of monotherapy</li> </ul> | 15                    | Recruiting             | 1-Dec-2025              |
| NCT05783323     | Larotrectinib to enhance RAI Avidity in differentiated thyroid cancer                                                                                                                        | Phase 2       | Children's Hospital of Philadelphia | Patients aged $\geq$ 12 months and $\leq$ 21 years diagnosed with differentiated thyroid cancer harbouring NTRK fusions                                                                          | <ul style="list-style-type: none"> <li>Larotrectinib monotherapy with 131I therapy</li> </ul>                                                                                                                             | 13                    | Recruiting             | 1-Oct-2026              |
| NCT06390852     | Testing LOXO-101 as potentially targeted treatment in cancers with NTRK genetic changes (MATCH - Subprotocol Z1E)                                                                            | Phase 2       | National Cancer Institute           | Patients with 18 years and older, have a malignancy harbouring an NTRK1, NTRK2 or NTRK3 gene fusion. Patients with advanced or refractory solid tumours, lymphoma or multiple myeloma harbouring | <ul style="list-style-type: none"> <li>Larotrectinib orally twice daily on days 1 to 28 of each cycle</li> </ul>                                                                                                          | 35                    | Active, not recruiting | 31-Dec-2025             |
| NCT03213704     | Larotrectinib in treating patients with relapsed or refractory advanced solid tumours, non-Hodgkin lymphoma, or histiocytic disorders with NTRK fusions (A Paediatric MATCH Treatment Trial) | Phase 2       | National Cancer Institute           | Patients with solid tumours, non-Hodgkin lymphoma, or histiocytic disorders harbouring NTRK fusions that have advanced and are either relapsed or refractory to prior treatment                  | <ul style="list-style-type: none"> <li>Larotrectinib sulphate orally or via nasogastric or gastric tube twice per day on days 1-28 of each cycle</li> </ul>                                                               | 9                     | Active, not recruiting | 30-Sep-2024             |

NTRK = neurotrophic receptor tyrosine kinase

## **2.17 Interpretation of clinical effectiveness and safety evidence**

### **2.17.1 Principal findings from the clinical evidence**

The clinical effectiveness and safety results presented in this company submission have thoroughly addressed uncertainties highlighted in the original submission (71). The latest data cut-off with extended follow-up (i.e., ePAS9 and SAS3) included a substantially larger sample size, broader tumour type representation, a greater number of patients with primary CNS tumours and more mature survival data compared with the original submission (71, 89). Importantly, this population represents an area where no targeted treatment currently routinely exists for these patients. The results of the pooled analysis from the extended follow-up data of the three pivotal studies (20288, 20289 and 20290) confirmed the remarkable clinical effectiveness and long-term safety of larotrectinib in treating NTRK fusion-positive solid tumours (89).

It is important to note that there is no “typical” larotrectinib patient. The eligible population is inherently heterogeneous due to multiple factors such as age, prior therapies and tumour types. Consequently, any comparison between datasets carries uncertainty, which can be accentuated by the number of included patients. Despite these differences, comparative analyses with real-world treatments consistently support the robust efficacy and safety of larotrectinib in the treatment of NTRK fusion-positive solid tumours.

For patients with primary CNS tumours, where treatment options are limited and disease management is inherently more complex, clinicians emphasise that both ORR and SD are key indicators of clinical benefit (118). In this context, non-progression is a meaningful outcome, and the high proportion of patients achieving SD further underscores the value of larotrectinib in this population (118).

Despite these compelling findings, challenges remain in translating clinical benefit into equitable access under the current CDF criteria (118). Specifically, the restriction on treatment breaks, which prevents the restarting of larotrectinib after a gap exceeding six

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

weeks, may not accurately reflect the clinical realities of managing patients with rare and complex cancers and this limitation could contribute to clinicians' hesitance to prescribe larotrectinib (118).

Additionally, the subjective interpretation of the phrase “no satisfactory treatment options” within the indication can lead to inconsistent application across treatment centres, potentially resulting in inequities in access. These limitations are particularly concerning given the high unmet need in this patient population, many of whom have exhausted standard therapies or face disfiguring surgical options such as amputation (118).

#### **2.17.1.1 Clinical effectiveness and safety from the pooled analyses of larotrectinib trials**

In the pooled analyses of the ePAS9 and SAS3 populations (data cut-off 20<sup>th</sup> July 2024), the primary endpoint of ORR was 65% in patients with non-CNS tumours and █% in those with primary CNS tumours (89). Among patients with non-CNS tumours, 22% achieved a CR on larotrectinib, while 18% of patients experienced SD. Among those with primary CNS tumour, █% of patients achieved a CR, and SD was reported in █% of patients. Subgroup analyses demonstrated a consistent efficacy profile across key demographic and clinical characteristics, including age, gender, ECOG performance status, prior treatments, and primary cancer diagnosis (89). Larotrectinib showed clinical efficacy across all diverse tumour types included, with the exception of some rare tumour types represented by only one patient each, where data were not sufficiently calculable.

DCR was █% for patients with non-CNS tumours and █% in patients with primary CNS tumours (89). While ORR remains an important measure of antitumour activity, it is essential to recognise that in the context of primary CNS tumours, where radiographic response assessment can be more nuanced, DCR may provide a broader view of clinical benefit, particularly given the high proportion of patients achieving SD (89).

The DoR was █ and █ months in patients with non-CNS tumours and with CNS primary tumours, respectively (89). Most patients responded within █ months of starting larotrectinib, and these responses proved durable, with █% of responding patients with

non-CNS tumours having a response lasting six months or more, while ■% for 12 months or longer. This highlights larotrectinib's ability to achieve rapid, effective and durable responses in NTRK fusion-positive solid tumours. This is particularly noteworthy given that most patients in the pooled analysis had metastatic disease and were heavily pretreated (89). The median PFS was 28.0 months in patients with non-CNS tumours and ■ months for those with primary CNS tumours. Although median OS was NE, the 72-month survival probabilities were ■%, and ■% for the patients with non-CNS tumours and primary CNS tumours, respectively (89).

The post hoc GMI analysis showed that ■% of patients had a GMI exceeding the threshold of meaningful clinical activity (i.e.,  $GMI \geq 1.33$ ), indicating an improved disease response compared to prior therapy received (97).

The sustained tumour shrinkage and improvements in HRQoL further reinforce larotrectinib's important role in the treatment pathway for patients with NTRK fusion-positive solid tumours. The extended follow-up and improved survival estimates provide greater confidence in the long-term benefits of treatment with larotrectinib (89).

In terms of safety, larotrectinib demonstrated a very low rate of grade 3 and 4 TEAEs, with no fatal TEAEs attributed to larotrectinib. TEAEs leading to permanent discontinuation of larotrectinib occurred in only ■% (n=■) of patients, with ■% (n=■) of them related to larotrectinib. The safety profile of larotrectinib is characterised by ■ AEs that can be monitored, and it is comparable across adult and paediatric patients, as well as across different tumour types (90).

Building on these findings, the ePAS9 and SAS3 datasets further reinforce the efficacy and tolerability of larotrectinib, regardless of the number of prior lines of therapy (89). A subgroup of patients from the ePAS9 dataset, who received larotrectinib as the first systemic treatment in the metastatic/ unresectable setting, achieved an impressive ORR of 77% (78). Additionally, the findings from Laetsch *et al.* showed that larotrectinib is an effective and well tolerated 1L treatment option in paediatric patients with newly

diagnosed IFS and other NTRK fusion-positive solid tumours. Response rates were high, with an ORR of 94% for IFS and 60% for other solid tumours (69).

A study by Garcia *et al.* further supports the early use of larotrectinib, showing that ORR declines with increasing prior therapies – 100% in treatment-naïve patients, dropping to 58% after ≥3 lines of treatment (87). As clinicians gain greater familiarity with the efficacy and side effect profile of larotrectinib, there is increasing confidence in its earlier use within the treatment pathway (118).

For adult patients, clinicians are already considering NTRK fusion-specific treatment relatively early in the treatment sequence, and reflects a recognition that, in many cases, alternative treatment options are less satisfactory, and larotrectinib offers a more compelling choice, particularly in the context of unmet medical need and the desire to provide timely access to targeted therapy (118).

#### **2.17.1.2 Comparative effectiveness**

The comparative effectiveness of data from the larotrectinib trials versus real-world non-TRK inhibitor SOC was assessed across four MAICs (three in adults and one in paediatric patients), covering a broad range of real-world datasets. The results from these analyses consistently demonstrate a statistically significant survival benefit for patients treated with larotrectinib versus those receiving real-world SOC, indicating a 78% to 84% lower risk of death and a median survival advantage of 29.5 to 37.0 months (103, 104). Additionally, treatment with larotrectinib was associated with longer OS and prolonged time to event and treatment failure compared to SOC (75, 105).

#### **2.17.1.3 Real-world data**

Complementing the results of the pooled analyses, findings from real-world studies of larotrectinib (ON-TRK, SACT, LAROTRACKING and SACHA) further support its clinical effectiveness and safety in routine clinical practice and provides valuable additional insights on long-term survival (107, 109). In addition, given the consistency in key patient profiles (e.g., age, gender, tumour types, NTRK gene fusion) and the global nature of the

label indication, these similarities support the strong generalisability of larotrectinib trial findings to real-world clinical settings, including that of NHS England.

The outcomes of patients in the SACT dataset are broadly aligned and supportive of those reported in the larotrectinib trials, with similar ORR and OS irrespective of age and non-primary CNS tumour type. The observed response rate demonstrates strong treatment efficacy within a relatively short timeframe of 10 weeks (2.3 months) post-initiation. Broad patient population (including patients with CNS tumours) showing SD and long survival times further supports its clinical utility in managing NTRK fusion-positive tumours for a large proportion of patients for which no other satisfactory treatment existed.

The time on larotrectinib treatment in the real-world setting supports the outcomes of the registrational studies for PFS, even with 30% of patients with primary CNS tumours.

### **2.17.2 Strengths of the clinical evidence base**

A key strength of the evidence base is that larotrectinib continues to demonstrate compelling clinical effectiveness, balanced with an acceptable safety profile, in a population with significant unmet medical needs. Larotrectinib's profile supports physician flexibility in treatment sequencing, allowing for use according to clinician discretion, as supported by real-world evidence that align with the principles of precision oncology and individualised care.

In the evolving landscape of precision oncology, the ESMO Tumour-Agnostic Classifier and Screener (ETAC-S) represents a pivotal advancement in standardising how the tumour-agnostic potential of molecularly guided therapies should be assessed and supports their development (9). This paradigm shift aligns with the ESMO NSCLC guidelines, which recommend early, comprehensive molecular testing at diagnosis to guide optimal 1L treatment and uncover actionable targets (43, 44, 119, 120). Such an approach reinforces the importance of integrating targeted therapies early in the treatment pathway, ensuring that patients receive molecularly guided options tailored to the specific oncogenic drivers of their disease. The importance of early testing has also



been emphasised by clinicians, as current NTRK testing practices vary depending on tumour type, patient age, available resources and clinical circumstances (118).

The pooled analysis represents an extensive clinical investigation, encompassing [REDACTED] patients with NTRK fusion-positive tumours across 121 international sites. Furthermore, assessment of key endpoints (i.e. ORR, TTR, time to best response, DoR, DCR, PFS) in the pooled analysis were performed by a centralised IRC. Larotrectinib was first approved based on data from [REDACTED] different tumour types and [REDACTED] NTRK gene fusion partners. Since then, the number of tumour types included into the clinical studies has [REDACTED], and the number of identified NTRK gene fusion partners has increased to [REDACTED], as reflected in the latest dataset (20<sup>th</sup> July 2024). This is the largest and the most comprehensive dataset for patients with TRK fusion cancer that exists and represents a large diversity of tumour types with NTRK gene fusions. The population included a substantial number of adult and paediatric patients with locally advanced (n=[REDACTED]), metastatic (n=[REDACTED]) or primary CNS tumour (n=[REDACTED]), at different tumour stages and grades at diagnosis. Considering such a diverse patient population, the outcomes presented in the clinical trials are highly meaningful, even if they appear low compared to other solid tumours (89).

The evidence base also provides information on the clinical effectiveness and safety of larotrectinib in both adult and paediatric patients, facilitating a timely approval and use in the paediatric population, which in the past has lagged behind use of new medicines in adults (89). This is particularly important if no suitable or standard treatments are available, or when patients face the alternative of amputation or disfiguring surgery. Notably, larotrectinib is available in both capsule and oral solution formulations, with the latter representing a significant reduction in treatment burden, particularly for infants and young children, for whom administering life-saving cancer therapy via intravenous infusion or less palatable solid forms presents substantial challenges. The ability to take larotrectinib at home twice daily not only eases the strain on patients and caregivers but also reduces pressure on healthcare resources. Additionally, the oral solution allows for

precise dosing adjustments based on the child's weight and clinical condition, supporting optimal therapeutic outcomes.

### **2.17.3 Limitations of the clinical evidence base**

The evidence base for larotrectinib has some limitations that are commonly encountered in rare oncology indications. The studies 20288, 20289 and 20290 are single-arm Phase 1/2 trials, which do not allow direct comparisons with standard treatments. To address this, the company has conducted a series of ITCs. Patients with NTRK fusion-positive solid tumours are a rare patient population, with prevalence often below 1% across many tumour types (121). In addition to their rarity, these fusions occur across a wide range of histologies, each with distinct SOC therapies, making traditional tumour-specific trial designs not feasible owing to insufficient patient enrolment. To navigate these complexities, it was agreed with regulatory authorities that the clinical evidence for larotrectinib would be based on single-arm 'basket' studies, enrolling patients who have the same molecular feature (i.e., NTRK gene fusion) across anatomically and histologically diverse solid tumours. A benefit of this approach was that the 'histology-independent' mode of action of larotrectinib could be tested. Basket trials are considered best suited to assess the efficacy of targeting genomic alterations that occur at low frequencies across a wide variety of tumour types. This approach was further supported by the compelling efficacy observed in the early phase 1 trial, as it raised ethical concerns about randomising patients to placebo or BSC (32).

The primary endpoint in the pooled analysis for larotrectinib efficacy was ORR, which is a surrogate endpoint formally recognised by regulatory authorities, such as the FDA, for use in accelerated approval pathways for innovations intended to treat serious or life-threatening diseases and that generally demonstrate an improvement over available therapy or provide therapy where none exists. Disease response is a real-world tool used daily in the clinic for ongoing assessment of patients, where significant and prolonged reduction of tumour burden can be clinically meaningful. This limitation is mitigated by the more mature survival data available from the latest data cut-off presented in this company submission, which is further supported by real-world evidence. Together, these data

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address the uncertainties regarding the long-term clinical effectiveness and safety of larotrectinib that were highlighted in the original submission. This strengthened evidence base has been incorporated into the cost-effectiveness model, enabling more robust and reliable estimates of larotrectinib's long-term value.

Among the real-world studies presented, only data from SACT included NHS patients, whereas ON-TRK is an international study, and LAROTRACKING and SACHA are French studies. Despite differences in the populations studied, key patient characteristics such as age, tumour types, prior lines of therapy are similar to those who received larotrectinib under the CDF (118). This consistency is likely driven by the same label indication for larotrectinib across geographies, as well as similar testing practices, and thus these studies collectively reflect its use in real-world clinical practice, supporting the generalisability of the larotrectinib trial populations to that of the NHS.

The European Reference Network for Rare Adult Solid Cancers (EURACAN) data was not included in this company submission due to recruitment challenges and delays in the study, with no results available at the time of submission.

#### **2.17.4 Innovation**

Patients with NTRK fusion-positive solid tumours have limited treatment options and poor outcomes following disease progression (122, 123). Larotrectinib is a first in class, highly selective TRK inhibitor that provides rapid, durable, and transformative outcomes for patients with NTRK fusion-positive solid tumours, a rare disease in oncology. Larotrectinib is very well tolerated and has the potential to improve patients' HRQoL. Debilitating surgeries or suboptimal and invasive treatments can be avoided, making larotrectinib a value-based investment that has been shown to transform patients' lives, as reflected in patient testimonials (116). Clinical evidence presented in this company submission have shown that larotrectinib delivers durable, meaningful responses with a manageable safety profile in both adult and paediatric patients with NTRK fusion-positive solid tumours. Its integration into the CDF has already provided many eligible patients with access to this innovative therapy and the clinical benefits it offers. Continued availability beyond the

CDF would ensure that patients with otherwise limited options can benefit from this breakthrough, while also expanding clinician choice and supporting more personalised treatment decisions.

### **2.17.5 Conclusion**

The extended follow-up data from the studies 20288, 20289 and 20290, along with real-world evidence and ITCs, have collectively addressed the uncertainties previously identified in TA630. The new data provides robust evidence of the remarkable long-term survival benefit and sustained progression-free outcomes associated with larotrectinib in patients with NTRK fusion-positive solid tumours. The updated analyses confirm that larotrectinib offers compelling clinical effectiveness, supported by real-world data, while maintaining a favourable and manageable safety profile and supporting patient HRQoL. Given these findings, larotrectinib is now recommended as a tumour- and age-agnostic treatment for NTRK fusion-positive solid tumours in Denmark, which aligns with the broader European regulatory approval (124).

Importantly, clinicians have highlighted real-world challenges with the current CDF criteria, particularly concerning treatment breaks. One clinician shared a case where a patient on larotrectinib achieved near resection and paused treatment for over a year due to remission. Upon relapse, resuming larotrectinib was clinically necessary but administratively challenging due to the CDF restriction on restarting treatment after a break longer than six weeks. The clinician sought exceptional funding from the hospital and applied for compassionate use from the pharmaceutical company. After several stressful weeks, compassionate use was granted, and the child resumed larotrectinib. Ultimately, the patient achieved a CR, underscoring the importance of flexible access pathways (118, 125).

Furthermore, clinicians consistently express that the ability to stop and restart larotrectinib is critical for delivering optimal care. Some clinicians have reported preferring cytotoxic therapies over larotrectinib, not due to concerns about efficacy, but because of the anxiety

and uncertainty surrounding re-access under current CDF criteria. This concern is shared by paediatricians, who face similar stress when managing treatment interruptions (118).

In addition to concerns around treatment breaks, clinicians have highlighted issues with the wording of the CDF criteria. The current phrasing appears to reflect early phase trial protocols rather than clinical practice, particularly the implication that patients must have exhausted all treatment options. While the CDF has clarified that “no satisfactory treatment option” does not require full exhaustion of therapies, this nuance is not consistently applied. Clinicians noted that in some settings, especially remote or resource-limited areas, the criteria are interpreted literally, creating inequities in access. Furthermore, the term “satisfactory” is inherently subjective; availability or funding alone does not equate to clinical appropriateness. Clinicians must be able to assess efficacy and tolerability in the context of individual patient needs, without being constrained by ambiguous or rigid criteria.

Therefore, the permanent commissioning of larotrectinib is both clinically justified and essential for maintaining high-quality care in this setting. It would secure access for patients with limited options while alleviating clinician and patient anxiety, enabling more confident and personalised treatment decisions.

**3. Cost effectiveness**

**Summary of cost-effectiveness analysis**

This cost-effectiveness analysis of larotrectinib, compared with relevant comparators, is based upon the original submission (TA630). Updates were made to incorporate newly available larotrectinib trial and real-world data, estimate comparator outcomes using indirect treatment comparisons and align with larotrectinib’s positioning in real-world practice.

The analysis employed a partitioned survival model (PSM) with three health states (progression-free, progressed and death). It was consistent with the NICE reference case, conducting a cost-utility analysis with a National Health Service (NHS) and Personal

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Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon (80 years) was adopted.

Clinical outcomes (PFS and OS) for larotrectinib were based on the most recent ePAS9 and SAS3 pooled datasets from the single-arm clinical trials (studies 20288, 20290, 20290). In the base case analysis, comparator outcomes were estimated by applying a treatment effect to larotrectinib's PFS and OS, derived from a MAIC between the larotrectinib datasets and real-world evidence. Alternative approaches to estimate larotrectinib and SOC survival data were applied in scenario analyses.

Health state utilities were informed by the larotrectinib trials (studies 20288, 20290, 20290), published sources and previous NICE appraisals, with age-adjusted utility decrements and AE-related disutilities applied. Costs and healthcare resource use captured in the analysis included drug acquisition and administration, monitoring and follow-up, AE management and end-of-life care.

### **Summary of cost-effectiveness results**

In the deterministic base case analysis, larotrectinib was associated with an additional [REDACTED] QALYs and incremental costs of £[REDACTED] compared to SOC, meaning that larotrectinib was cost-effective vs. SOC with an incremental cost-effectiveness ratio (ICER) of £[REDACTED].

Extensive scenario and sensitivity analyses were conducted to explore the impact of key model inputs and assumptions. The results of the scenario analyses were largely consistent to the base case, highlighting the robustness of the results.

Larotrectinib is a life-extending, cost-effective treatment option for patients with NTRK fusion- positive solid tumours, strongly supporting its permanent commissioning after its exit from the CDF and ensuring continued patient access.

### **3.1 Published cost-effectiveness studies**

A SLR was originally conducted on 5<sup>th</sup> May 2019 to identify any cost-effectiveness models or relevant publications (covering healthcare cost and resource use [HCRU] evidence) quantifying the cost-effectiveness of treatment options available for NTRK fusion-positive solid tumours. Additionally, a wider search in the original SLR was conducted in May – August 2018 and updated in January – March 2019 to generate relevant cost-effectiveness (covering HCRU) evidence in tumour locations known to harbour NTRK gene fusions, reflective of those patients investigated so far in the larotrectinib clinical studies (presented in the previous company submission for TA630) (71).

The original SLR was updated on 7<sup>th</sup> May 2025 to identify relevant cost-effectiveness and HCRU evidence associated with treatments for NTRK fusion-positive solid tumours. Details of the original SLR are presented alongside the results of the updated SLR search in Appendix E.

A total of nine unique studies from both original and updated SLRs were identified. Of these, six studies reported cost-effectiveness data (Table 38). One additional study that reported cost-effectiveness data was identified through the review of NICE submissions and was also included.

The identified cost-effectiveness studies included patients with NTRK fusion-positive locally advanced or metastatic solid tumours (126-132). Two studies reported on specific tumour locations, such as breast cancer (131), and unresectable locally advanced or metastatic extracranial solid tumours with brain metastases (126). Across the included studies, larotrectinib (127, 129) and entrectinib (126-128, 130, 132) were the primary interventions evaluated against SOC or conventional chemotherapy regimens. Of these included studies, two were conducted in the Netherlands (127, 129), one each in Canada (126), China (130), UK (132), and US (131). One study reported results across multiple countries, including the UK, Hungary, and the Netherlands (128). The perspectives adopted in these studies were varied, including the healthcare system (126, 130, 132), societal (127, 129), and both healthcare payer and societal (128). One study did not report

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the perspective explicitly (131). The majority of studies reported the use of a partitioned survival model (PSM) (126, 129, 130, 132), while a minority used a microsimulation approach (127, 128). Time horizons were reported in nearly all studies, with most adopting a lifetime horizon and applying discount rates ranging from 3.5% to 5%.

The implications of the literature on the model structure are described in Section 3.2.2.



**Table 38. Summary list of published cost-effectiveness studies**

| Author, Year          | Population                                                                                      | Model summary                                                                                                                                                                                                                                                                                                                                                | Treatments    | Cost and cost benefit outcomes (Cost, LYs, QALYs)                                                             | Cost-effectiveness (ICERs, INMB),                                                                                          |
|-----------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Chen, 2024 (130)      | NTRK fusion-positive locally advanced or metastatic solid tumours                               | <ul style="list-style-type: none"> <li>Model type: Partitioned survival</li> <li>Model health states: In PFS and in progression</li> <li>Time horizon: 20 years</li> <li>Perspective: Healthcare system</li> <li>Country: China</li> <li>CE threshold (¥/QALY): NR</li> </ul>                                                                                | Entrectinib   | <ul style="list-style-type: none"> <li>Mean total cost: ¥ 414,277</li> <li>Total QALYs: 2.72</li> </ul>       | Entrectinib versus SOC:<br><ul style="list-style-type: none"> <li>ICER (¥/QALY): 57,720</li> </ul>                         |
|                       |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                              | SOC           | <ul style="list-style-type: none"> <li>Mean total cost: ¥ 329,465</li> <li>Total QALYs: 1.25</li> </ul>       |                                                                                                                            |
| Dheer, 2024 (131)     | NTRK gene positive breast cancer in adult patients                                              | <ul style="list-style-type: none"> <li>Model type: NR</li> <li>Model health states: NR</li> <li>Time horizon: NR</li> <li>Perspective: NR</li> <li>Country: NR</li> <li>CE threshold (societal) (\$/QALY): 75,000</li> </ul>                                                                                                                                 | Larotrectinib | <ul style="list-style-type: none"> <li>Total cost: \$651,718</li> <li>QALYs: 5.8</li> </ul>                   | Larotrectinib versus entrectinib:<br><ul style="list-style-type: none"> <li>ICER (\$/QALY): 72,499</li> </ul>              |
|                       |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                              | Entrectinib   | <ul style="list-style-type: none"> <li>Total cost: \$397,970</li> <li>QALYs: 2.3</li> </ul>                   |                                                                                                                            |
| Huygens, 2023 (127)   | NTRK fusion-positive patients with locally advanced or metastatic solid tumours                 | <ul style="list-style-type: none"> <li>Model type: Microsimulation</li> <li>Model health states: Alive and on treatment, alive and off treatment and dead</li> <li>Time horizon: 80 years (Lifetime)</li> <li>Perspective: Dutch societal perspective</li> <li>Country: The Netherlands</li> <li>CE threshold (€/QALY): 80,000</li> </ul>                    | Entrectinib   | <ul style="list-style-type: none"> <li>Total cost: €129,240</li> <li>Total effects in QALYs: 2.186</li> </ul> | Entrectinib versus SOC:<br><ul style="list-style-type: none"> <li>ICER, (€/QALY): 38,563</li> <li>INMB: €69,945</li> </ul> |
|                       |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                              | SOC           | <ul style="list-style-type: none"> <li>Total cost: €71,131</li> <li>Total effects in QALYs: 0.679</li> </ul>  |                                                                                                                            |
| Vellekoop, 2023 (128) | Subgroup: NTRK fusion-positive adult patients with locally advanced or metastatic solid tumours | <ul style="list-style-type: none"> <li>Model type: Microsimulation</li> <li>Model health states: Alive and on treatment, alive and off treatment and dead</li> <li>Time horizon: Start of treatment until death</li> <li>Perspective: Healthcare payer</li> <li>Country: UK</li> <li>CE threshold (severity-adjusted) (€/QALY): 36,000 (€ 35,576)</li> </ul> | Entrectinib   | <ul style="list-style-type: none"> <li>Total cost: €67,729</li> <li>Total effects in QALYs: 2.0685</li> </ul> | Entrectinib versus SOC:<br><ul style="list-style-type: none"> <li>ICER (€/QALY): 29,577</li> <li>INMB: €8,405</li> </ul>   |
|                       |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                              | SOC           | <ul style="list-style-type: none"> <li>Total cost: €23,621</li> <li>Total effects in QALYs: 0.7159</li> </ul> |                                                                                                                            |
|                       |                                                                                                 | <ul style="list-style-type: none"> <li>Model type: Microsimulation</li> </ul>                                                                                                                                                                                                                                                                                | Entrectinib   | <ul style="list-style-type: none"> <li>Total cost: €111,480</li> </ul>                                        | Entrectinib versus SOC:                                                                                                    |

Company evidence submission template for larotrectinib for treating NTRK fusion-positive advanced solid tumours

| Author, Year        | Population                                                                                                                                                                                                                             | Model summary                                                                                                                                                                                                                                                                                                                                                          | Treatments                                    | Cost and cost benefit outcomes (Cost, LYs, QALYs)                                                           | Cost-effectiveness (ICERs, INMB),                                                                                                                                                                                                                                               |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     |                                                                                                                                                                                                                                        | <ul style="list-style-type: none"><li>Model health states: Alive and on treatment, alive and off treatment and dead</li><li>Time horizon: Start of treatment until death</li><li>Perspective: Healthcare perspective</li><li>Country: Hungary</li><li>CE threshold (severity-adjusted) (HUF/QALY): 4,921,820 (€ 21,294)</li></ul>                                      |                                               | <ul style="list-style-type: none"><li>Total effects in QALYs: 2.0576</li></ul>                              | <ul style="list-style-type: none"><li>ICER (€/QALY): 70,100</li><li>INMB: €−53,088</li></ul>                                                                                                                                                                                    |
|                     |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        | SOC                                           | <ul style="list-style-type: none"><li>Total cost: €8,661</li><li>Total effects in QALYs: 0.7146</li></ul>   |                                                                                                                                                                                                                                                                                 |
|                     |                                                                                                                                                                                                                                        | <ul style="list-style-type: none"><li>Model type: Microsimulation</li><li>Model health states: Alive and on treatment, alive and off treatment and dead</li><li>Time horizon: Start of treatment until death</li><li>Perspective: Societal perspective</li><li>Country: The Netherlands</li><li>CE threshold (severity-adjusted) (€/QALY): 80,000 (€ 69,666)</li></ul> | Entrectinib                                   | <ul style="list-style-type: none"><li>Total cost: €112,545</li><li>Total effects in QALYs: 2.1862</li></ul> | Entrectinib versus SOC: <ul style="list-style-type: none"><li>ICER (€/QALY): 33,582</li><li>INMB: €54,372</li></ul>                                                                                                                                                             |
|                     |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        | SOC                                           | <ul style="list-style-type: none"><li>Total cost: €60,978</li><li>Total effects in QALYs: 0.7296</li></ul>  |                                                                                                                                                                                                                                                                                 |
| CAD-AMC, 2022 (126) | Adults with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, which have an NTRK gene fusion without a known acquired resistance mutation and with no satisfactory treatment options | <ul style="list-style-type: none"><li>Model type: Partitioned survival model</li><li>Model health states: NR</li><li>Time horizon: Lifetime (10 years)</li><li>Perspective: Canadian publicly funded health care payer</li><li>Country: Canada</li><li>CE threshold (CAD\$/QALY): 50,000</li></ul>                                                                     | Entrectinib                                   | <ul style="list-style-type: none"><li>Total cost, (600 mg daily, 28 days): CAD\$8,007.72</li></ul>          | Entrectinib versus best supportive care: <ul style="list-style-type: none"><li>Pooled analysis of second line therapy ICER (CAD\$/QALY) 1,272,991</li><li>Pooled analysis for comparators the sponsor identified as first-line therapies: ICER (CAD\$/QALY) 2,057,174</li></ul> |
|                     |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        | Best supportive care                          | <ul style="list-style-type: none"><li>Total cost: NR</li></ul>                                              |                                                                                                                                                                                                                                                                                 |
|                     | Subgroup: MASC patients with NTRK fusion                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                        | Entrectinib                                   | <ul style="list-style-type: none"><li>Total cost, (600 mg daily, 28 days):</li></ul>                        | Entrectinib versus sunitinib, gefitinib, cisplatin + gemcitabine: <ul style="list-style-type: none"><li>ICER (CAD\$/QALY) 94,645</li></ul>                                                                                                                                      |
|                     |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        | Sunitinib, gefitinib, cisplatin + gemcitabine | <ul style="list-style-type: none"><li>Total cost: NR</li></ul>                                              |                                                                                                                                                                                                                                                                                 |

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| Author, Year        | Population                                                                                                                                                                                                                                | Model summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Treatments           | Cost and cost benefit outcomes (Cost, LYs, QALYs)                                                                      | Cost-effectiveness (ICERs, INMB),                                        |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Michels, 2022 (129) | Adult and paediatric patients with NTRK fusion-positive solid tumour, which are locally advanced or metastatic                                                                                                                            | <ul style="list-style-type: none"> <li>Model type: Microsimulation</li> <li>Model health states: Alive and on treatment, alive and off treatment and dead</li> <li>Time horizon: Lifetime</li> <li>Perspective: Societal perspective</li> <li>Country: The Netherlands</li> <li>CE threshold (€/QALY): 80,000</li> </ul>                                                                                                                                                                                             | Larotrectinib        | <ul style="list-style-type: none"> <li>Total QALYs: 7.41</li> <li>Total cost: €232,260</li> </ul>                      | Larotrectinib versus SOC:                                                |
|                     |                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | SOC                  | <ul style="list-style-type: none"> <li>Total QALYs: 1.97</li> <li>Total cost: €63,477</li> </ul>                       | <ul style="list-style-type: none"> <li>ICER, (€/QALY): 41,424</li> </ul> |
| NICE (2020) (132)   | Adults and adolescents (≥12 years) with NTRK fusion-positive solid tumours that are locally advanced or metastatic, or where surgery would be severely debilitating, who are NTRK inhibitor-naïve and lack satisfactory treatment options | <ul style="list-style-type: none"> <li>Model type: Partitioned survival</li> <li>Model health states: Progression-free, progressed disease and death</li> <li>Time horizon: NR</li> <li>Cycle length: NR</li> <li>Perspective: Healthcare payer</li> <li>Country: UK</li> <li>Discount rate: 3.5% for cost and effects</li> <li>Currency and cost year: Pounds (£), NR</li> <li>Sensitivity analysis: Univariate sensitivity analysis, DSA, PSA, scenario analyses</li> <li>CE threshold (£/QALY): 30,000</li> </ul> | Entrectinib          | <ul style="list-style-type: none"> <li>Total cost, (600 mg daily):</li> <li>Cost of 200 mg capsule: £ 57.33</li> </ul> | Entrectinib versus best supportive care:                                 |
|                     |                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Best supportive care | <ul style="list-style-type: none"> <li>Cost: NR</li> </ul>                                                             | Deterministic ICER (£/QALY): 49,358                                      |

CAD= Canadian dollar; CE= cost effectiveness; ¥= Chinese Yuan; DSA= deterministic sensitivity analysis; DTC= differentiated thyroid cancer; HUF= Hungary Forint; ICER= incremental cost-effectiveness ratio; €= international Euros; INMB= incremental net monetary benefit; Lys= Life years; MASC= mammary analogue secretory carcinoma, NSCLC= non-small cell lung cancer; NTRK= neurotrophic tropomyosin receptor kinase; NR= not reported; OS= overall survival; PFS= progression-free survival; PSA= probabilistic sensitivity analysis; QALYs= quality-adjusted life years; SOC= standard of care; STS= soft tissue sarcoma; UK= United Kingdom; US= United States

## **3.2 Economic analysis**

### **3.2.1 Patient population**

The patient population considered in the economic model reflects those enrolled in the larotrectinib clinical trials and the Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation, i.e., patients with NTRK fusion cancer that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

The model incorporates data from the ongoing larotrectinib clinical trials, including multiple tumour locations that harbour TRK fusions (outlined below). The data are based on the patients included in the recent ePAS9 and SAS3 datasets, with the following tumour locations representing unique model engines: NSCLC, salivary gland, melanoma, colorectal (including appendix), STS in adults (GIST), STS in adults (non-GIST) (including bone sarcoma patients), STS in paediatrics (including IFS patients), breast, cholangiocarcinoma, CNS/Gliomas, pancreas, thyroid (including both thyroid anaplastic and thyroid follicular/papillary). These tumour types were selected because they were the most frequently observed across the datasets (representing approximately 97% of patients, including proxy tumour locations) and are reflective of NHS clinical practice, as referenced in the SACT data in section 2.13.2.

If no relevant published studies were identified from the clinical SLR or additional evidence generation and RWE MAICs activities that could inform the economic model, or in the case of small sample sizes, the tumour locations were grouped. This occurred in the rarer tumour locations, for example, where published survival data for a pre-treated population was not available. Groupings were validated in an advisory board and are in line with the previous assumptions used in TA630 (118).

### **3.2.2 Model structure**

The economic model is a cohort state transition model with a partitioned survival approach. This technique is commonly used in oncology modelling, as noted in the literature identified in Section 3.1, and is appropriate for capturing progressive, chronic

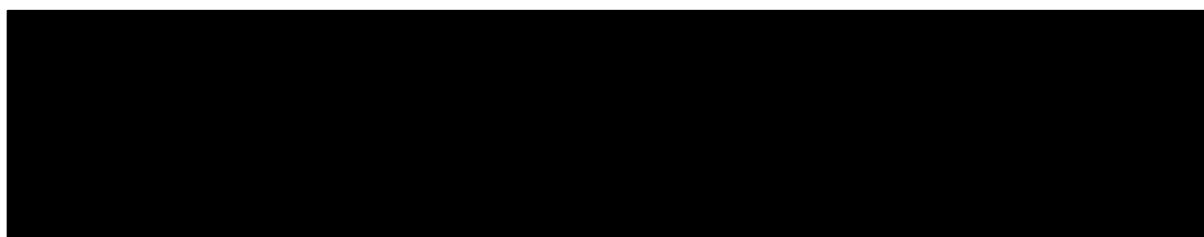
conditions described by clinical outcomes that require an ongoing, time-dependent risk, such as progression and death (133, 134). It was designed in accordance with the requirements of NICE guidance (135), and the International Society for Pharmacoeconomics and Outcomes Research – Society for Medical Decision Making (ISPOR-SMDM) guidelines (136).

Considering this submission is a re-assessment of larotrectinib for this indication, the originally submitted model structure was retained, with adaptations made to account for the updated decision problem and new evidence collected in accordance with the MAA and feedback from the first submission. The additional evidence supports retaining the original PSM approach. A microsimulation was not pursued due to the transparency and assumptions needed to inform such a model, given the limited information available.

Unlike a Markov model, cohort partition models do not require the explicit estimation and use of transition probabilities. Instead, the number of patients in each health state is calculated directly from the treatment and comparator's PFS and OS curves. This allows direct application of the key clinical trials' endpoints. Additional assumptions are only made to estimate the extrapolated portion of the curves. This ensures that the fitted PFS and OS match the clinical trial data and does not require the model to assume a definite relationship between PFS and OS, as would be required in a Markov model to calculate transition probabilities between "progressed" and "dead" health states.

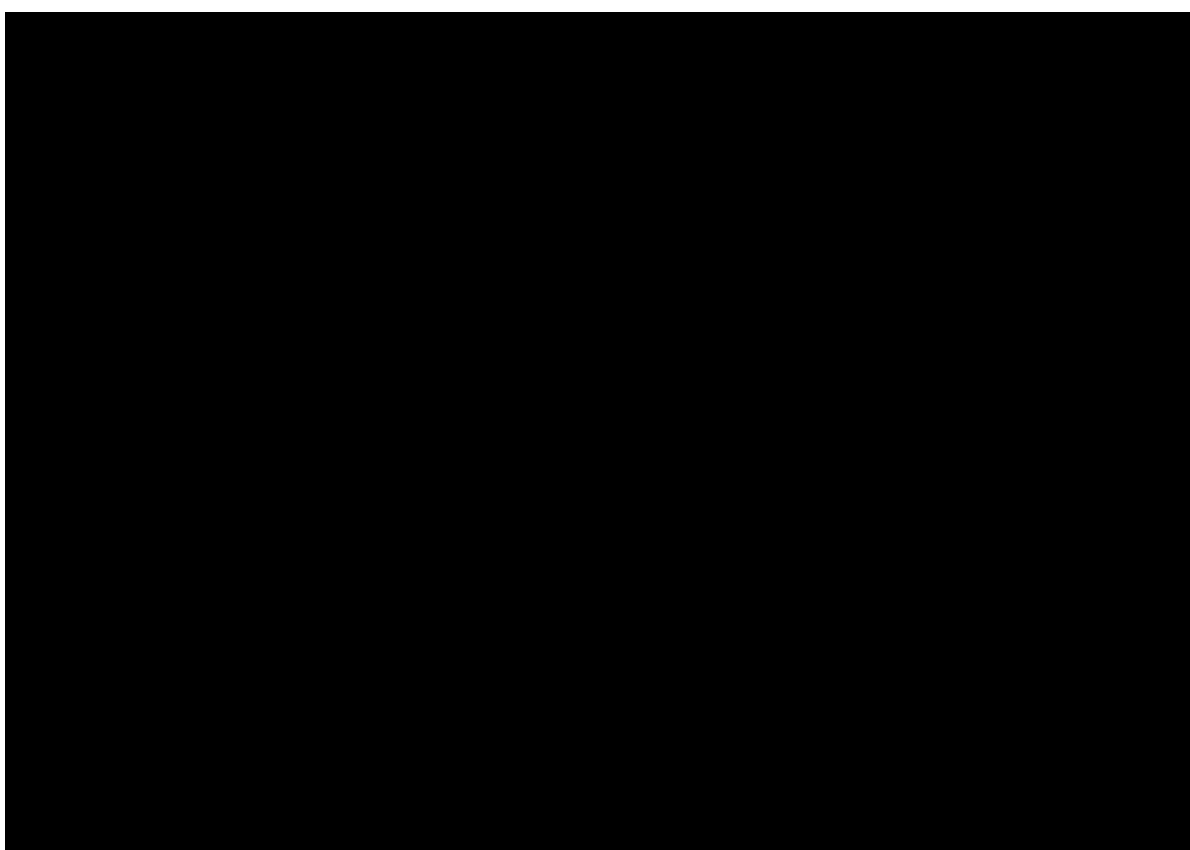
In each cycle of the model, patients are assigned to one of three mutually exclusive health states according to the proportion of patients who are 'progression-free', 'progressed', or 'dead' (Figure 21). In each cycle of the model, patients are assigned to one of three mutually exclusive health states according to the proportion of patients who are 'progression-free', 'progressed', or 'dead' (Figure 21).

**Figure 21. Model schematic**



Both the larotrectinib and comparator arms of the model follow the same health states. However, to account for differences in conventional standard of care across tumour locations in the comparator arm, health states are stratified by tumour locations. This stratification allows tumour-specific costs and utilities to be applied, as there are variations in treatment pathways, prognosis, HRQoL, costs and resource use. Figure 22 outlines the stratification of the model structure. The model was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) 2025.

**Figure 22. Economic model schematic**



CNS = central nervous system; GIST = gastrointestinal stromal tumour; IFS = infantile fibrosarcoma; NSCLC = non-small cell lung cancer; TRK = tyrosine kinase; STS = soft tissue sarcoma

### **3.2.3 Features of the economic analysis**

The model primarily utilises recent data from the larotrectinib clinical trials (studies 20288, 20289 and 20290; data cut-off 20<sup>th</sup> July 2024) to assess the cost-effectiveness of larotrectinib relative to comparators used in the model. Cost-effectiveness is assessed using clinical and cost data from indirect sources (further information is presented in Section 3.3 and Appendix I) following the SLRs, and reviews of previous TAs, RWE and NICE guidance. Data gaps were addressed by additional targeted literature searches and assumptions where appropriate.

#### ***Time horizon***

The economic model adopts a lifetime horizon in the base case, as recommended by NICE for treatments with a survival benefit (135). The time horizon is set to 80 years for the base case. The cohort age varies across tumour locations; therefore, a time horizon was selected which is sufficiently long enough to have less than 1% of patients alive within the model for most tumour locations. Only paediatric patients treated with larotrectinib have a survival rate of less than 10% at the end of the model time horizon. This means that less than 2.3% of the total larotrectinib cohort and less than 1% of the comparator arm are alive at the end of the model time horizon in the base case.

#### ***Cycle length***

The economic model uses a seven-day cycle length. This cycle length was selected to accommodate the evidence sources used in the model where treatment and assessment of outcomes regularly occur over a set number of weeks. Due to the short cycle length, no half-cycle correction is applied.

#### ***Perspective***

The NHS England and Personal and Social Services (PSS) perspective is used for the base case analysis, as per NICE recommendations (135). Direct healthcare costs consist of drug costs, AE costs, disease management costs, and end-of-life costs.

#### ***Discounting***

Costs and outcomes are both discounted at an annual rate of 3.5% in the base case analysis, as per NICE recommendations (135).

## Summary of features of the economic analysis

Table 39 summarises the features of the economic analysis. Further details for each factor are described in the relevant section and Appendix M.

**Table 39. Features of the economic analysis**

| Factor                    | Original submission (TA630)                                                                                                                                    | Current submission – chosen values                                                                                                                                     | Justification                                                                                                                                                         |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Model structure           | Partitioned survival model with stratification by tumour locations                                                                                             | Partitioned survival model with stratification by tumour locations                                                                                                     | As detailed in Section 3.2.2, the partitioned survival model approach allows direct use of key clinical trials' endpoints and additional data that has been collected |
| Time horizon              | 40 years for adult cohort engines and 80 years for paediatric cohort engines                                                                                   | 80 years                                                                                                                                                               | As detailed in Section 3.2.3, <1% survival is observed in most tumour locations by 80 years, reflecting a lifetime horizon                                            |
| Cycle length              | 7 days                                                                                                                                                         | 7 days                                                                                                                                                                 | As detailed in Section 3.2.3, a weekly cycle reflects treatment and assessment recurrence                                                                             |
| Discounting               | 3.5% for costs and outcomes                                                                                                                                    | 3.5% for costs and outcomes                                                                                                                                            | As detailed in Section 3.2.3, this is in line with NICE guidelines                                                                                                    |
| Source of clinical inputs | Larotrectinib clinical trials (studies 20288, 20289 and 20290), ePAS2 + SAS3 cohort<br><br>Indirect evidence from clinical trials identified in the literature | Larotrectinib clinical trials (studies 20288, 20289 and 20290), ePAS9 + SAS3 cohort<br><br>Indirect evidence from RWE and clinical trials identified in the literature | As detailed in Section 3.3 and Appendix M, additional trial data and RWE sources are now available                                                                    |
| Source of utility inputs  | Larotrectinib clinical trials (studies 20288, 20289 and 20290), ePAS2 + SAS3 cohort<br><br>Utilities identified in the literature and previous TAs             | Larotrectinib clinical trials (studies 20288, 20289 and 20290), ePAS9 + SAS3 cohort<br><br>Utilities identified in the literature and previous TAs                     | As detailed in Section 3.4 and Appendix M, additional trial data and updated NICE methods guidance for utility analysis are now available                             |
| Source of costs           | Resource use from previous TAs and costs from NHS reference costs, PSSRU, and BNF/eMIT                                                                         | Resource use from previous TAs and costs from NHS reference costs, PSSRU, and BNF/eMIT                                                                                 | As detailed in Section 3.5 and Appendix M, these costs reflect the NHS and PSS perspective. The latest cost sources and inflation indices have been used              |

BNF= British National Formulary; eMIT= electronic market information tool; ePAS= Extended primary analysis set; SAS= Supplemental analysis set; NHS= National Health Service; PSS= Personal Social Services; PSSRU= Personal Social Services Research Unit; RWE= real-world evidence; TA= technology appraisal



### 3.2.4 Intervention technology and comparators

#### *Intervention technology*

Larotrectinib is an orally bioavailable, ATP-competitive, potent and highly selective TRK inhibitor that was rationally designed to avoid activity against off-target kinase. The target for larotrectinib is the TRK family of proteins, inclusive of TRKA, TRKB, and TRKC, which are encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively. Larotrectinib was the first histology-independent drug approved in the EU.

#### *Comparator technologies*

There are no existing treatments for patients with NTRK gene fusion cancer routinely recommended in NHS clinical practice. The relevant comparators (treatments used in the absence of larotrectinib) typically depend on both tumour location and the line of treatment. Due to the number of tumour locations modelled in the stratified comparator arm, one comparator has been selected per tumour location. This reduces the number of potential combinations of comparator treatments, which can become unmanageable (over 100 combinations) if multiple comparators per tumour location are considered.

To account for larotrectinib's use in the real-world settings in the UK, the most appropriate source is the data from the SACT report (109). In the SACT report, we learn that 78% of patients (N=47) were treated with larotrectinib after receiving 1 line of systemic therapy. Given that the majority of patients were being treated in the second line, we use the assumption that all patients are treated in second line for each tumour type, unless there is a clear indication in the guidelines that TRK inhibitors should be used later in the treatment pathway (109). This positioning is further supported by real-world studies, as shown in Appendix E.

Tumour-specific European guidelines were leveraged to understand which treatment would be the most appropriate. If several treatments could be used, the final decision on which treatment would be selected in the model was made by UK clinicians during the advisory board, to reflect real-world practice (118). Each tumour type has been assessed separately:

### **Non-small cell lung cancer**

According to ESMO 2025 guidelines for metastatic NSCLC, the preferred first line of treatment is platinum doublet (119). There are various options in second line treatment in the absence of specific genetic mutations (non-oncogene addicted guidelines) including pemetrexed, docetaxel, nintedanib and docetaxel, ramucirumab and docetaxel or ICI rechallenge. A UK lung cancer specialist in the advisory board recommended nintedanib and docetaxel as the appropriate comparator for Larotrectinib (118). Notably, ESMO has published specific oncogene addicted guidelines in 2025 and recommends TRK inhibitors as a first-line treatment when a TRK fusion is detected earlier in the treatment pathway (119).

### **Salivary gland cancer**

According to ESMO 2022 guidelines for salivary gland cancer, the first treatment approach, when a patient is diagnosed, is surgical resection (39). When surgical resection is not an option due to local recurrence, metastatic disease or patient status, guidelines recommend chemotherapy or radiotherapy, without specifying any particular specific regimen. Clinical trials can also be an option for patients in the absence of effective treatment. Various regimens are used in the real-world, typically involving platinum-based chemotherapy. A UK head and neck clinical oncologist recommended cisplatin and vinorelbine as the most used combination in clinical practice. Of note, the same ESMO guidelines recommend that clinicians test for specific mutation and give a targeted treatment if surgical resection is not an option.

### **Melanoma**

According to ESMO 2024 guidelines for melanoma, patients at stage III/IV will receive treatment based on their prior adjuvant treatment received (46). The first-line treatment is nivolumab and ipilimumab and second-line treatment is not defined by a single agent. Options are mainly nivolumab or ipilimumab in monotherapy or pembrolizumab (46). A UK clinician in the advisory board recommends using pembrolizumab according to clinical practice (118).

## Colorectal

According to the ESMO 2023 guidelines for colorectal cancer, “*NTRK testing could be done at any time but will only influence treatment decisions after progression on at least two lines of treatment*” (45). Based on the guideline recommendations, we chose to position larotrectinib against a third-line comparator rather than a second-line comparator. Stage IV unresectable metastatic colorectal third-line treatments depend on mutation status (e.g., RAS-wt, BRAF-wt, RAS-mut) and include either single-agent anti-EGFR therapies (panitumumab or irinotecan-cetuximab), regorafenib, trifluridine-tipiracil or encorafenib-cetuximab (45). A UK oncologist in the advisory board recommended trifluridine-tipiracil as the most used regimen (118).

## STS adults (GIST)

According to the ESMO-EURACAN-GENTURIS clinical guidelines from 2021 for gastrointestinal stromal tumours, patients with advanced or metastatic GISTs are treated according to their imatinib-sensitivity mutation (42). If patients are not sensitive to imatinib mutation, the guidelines recommend testing for TRK mutations and use a TRK inhibitor if detected (42). Assuming that TRK inhibitors will be used as a second-line treatment, we are not looking at specific mutations and will consider that the first-line treatment in the advanced/metastatic setting is sunitinib, in the absence of targeted treatment. If there is no response to the first-line treatment with sunitinib, regorafenib is recommended as a second-line treatment. This treatment has been validated by clinicians in the advisory board (118).

## STS adult (non-GIST)

According to the ESMO-EURACAN-GENTURIS clinical guidelines from 2021 for soft tissue and visceral sarcomas, the first-line treatment for advanced/metastatic, clinically unresectable STS is doxorubicin, either as monotherapy or in combination with another agent (41). If patients progress, they can either continue this treatment or try further-line systemic therapies such as high-dose ifosfamide or trabectedin (41). Clinicians who attended the advisory board recommend trabectedin as a comparator (118).

## **STS paediatrics**

According to a joint EpSSG, CWS and ERN PaedCan project to write European standard clinical guidelines for children and adolescents with rhabdomyosarcoma (most common type of STS in children and young adults) in 2025, the only recommended treatment for progressive or relapsed disease is vincristine and irinotecan with temozolomide (VIT) (137). Since there are no other options, paediatric oncologists in the advisory board advised that it would be the preferred and only comparator in the absence of targeted treatment (118). As a result, VIT is the selected comparator in the model.

## **IFS**

In the absence of specific clinical guidelines for infantile fibrosarcoma (IFS) and considering the similarities with STS, the same comparator (VIT) has been chosen.

## **Breast cancer**

According to the ESMO guidelines for breast cancer from 2021, *“in metastatic breast cancer, standards therapies are personalised based on biomarkers [...] in addition, they are now several tissue and site agnostic approvals. For example, both larotrectinib and entrectinib [...] Biomarkers need to be checked once subtype specific standard therapy have been exhausted [...]”* (47). Based on this statement and the multiple options that exist for this tumour type, larotrectinib is likely to be used when a patient has no satisfactory treatment options; clinicians in the advisory board agree with this positioning (118). The chosen comparator in the model for breast cancer is “best supportive care”, represented by a mix of chemotherapies used in real-world.

## **Bone sarcoma**

According to the ESMO guidelines for bone sarcoma from 2021, the preferred approach is surgical resection (138). If surgery is not possible or the patient relapses, few treatments have antitumour activity in osteosarcoma (the single most common type of bone sarcoma): doxorubicin, cisplatin, high-dose methotrexate, ifosfamide and etoposide (138). For bone sarcoma, the advisory board recommended high-dose ifosfamide as the most appropriate comparator (118). However, due to insufficient

evidence available to inform the model inputs for this population, adult STS was used as a proxy instead. This assumption was considered acceptable in the previous appraisal and should remain relevant given the low percentage (<1%) of bone sarcoma patients in the recent dataset.

### **Cholangiocarcinoma (or biliary tract cancer)**

According to the ESMO clinical guidelines for biliary tract cancer from 2023, the first line of treatment for advanced or metastatic cancer is cisplatin-gemcitabine ± durvalumab (49). After progression, patients will be treated according to their genetic mutation. If none are identified or for all comers, FOLFOX or 5-FU ± irinotecan is recommended. Clinicians in the advisory board recommend that 5-FU combined with any chemotherapy (i.e., FOLFOX) would be the preferred option (118). Thus, FOLFOX has been selected as the model comparator.

### **CNS/glioma**

According to the ESMO guidelines for high-grade glioma from 2014, treatment depends on the grade and tumour location. The preferred approach is surgical resection (139). If surgical resection is not possible or the patient relapses, chemotherapies are recommended with either temozolomide, lomustine or PCV (procarbazine, lomustine and vincristine) (139). Clinicians in the advisory board recommended lomustine as a single agent for this specific population (118).

### **Pancreatic cancer**

According to the ESMO clinical guidelines for pancreatic cancer from 2023, patients are treated according to their ECOG performance score (48). For patients with a score of 0-1 (aligned with the larotrectinib patient population; section 2.3.2) who have no major comorbidity, the first line of treatment is FOLFIRINOX followed by gemcitabine and nab-paclitaxel or gemcitabine in second-line treatment (48). Clinicians in the advisory board recommended using gemcitabine as a relevant comparator in the model (118).

## Thyroid cancer

According to the ESMO clinical guidelines for advanced thyroid cancer from 2022, radioactive iodine (RAI) is used as a first-line treatment for differentiated thyroid cancer (40). If patients do not respond or stop responding, sorafenib, lenvatinib or both are recommended in Europe as second-line therapy (40). Based on UK clinical practice, clinicians in the advisory board recommend lenvatinib as a comparator (118).

For all identified comparators, the most recent source of data was selected to derive a comparator arm. The final comparators selected for each tumour location are summarised in Table 40.

**Table 40. Comparators by tumour location**

| Tumour location                                      | Included comparators                                 | Source                                          |
|------------------------------------------------------|------------------------------------------------------|-------------------------------------------------|
| NSCLC                                                | Nintedanib + docetaxel                               | TA347 (140)                                     |
| Salivary                                             | Cisplatin + vinorelbine                              | Airoldi <i>et al.</i> 2017 (141)                |
| Melanoma                                             | Pembrolizumab                                        | NICE TA357 (142)                                |
| Colorectal (including appendix proxy)                | Trifluridine-tipiracil                               | Mayer <i>et al.</i> 2015 (143)                  |
| STS adults (GIST)                                    | Regorafenib                                          | NICE TA488 (144)                                |
| STS adults (non-GIST) (including bone sarcoma proxy) | Trabectedin                                          | TA185 (145)<br>Demetri <i>et al.</i> 2016 (146) |
| STS paediatrics (including IFS proxy)                | Irinotecan + vincristine + temozolomide              | VIT-0910 trial (147)                            |
| Breast                                               | Vinorelbine (IV)                                     | NICE TA423 (148)                                |
|                                                      | Vinorelbine (oral)                                   |                                                 |
|                                                      | Gemcitabine                                          |                                                 |
|                                                      | Docetaxel                                            |                                                 |
|                                                      | Paclitaxel                                           |                                                 |
|                                                      | Doxorubicin                                          |                                                 |
| Cholangiocarcinoma                                   | 5-fluorouracil + oxaliplatin + folinic acid (FOLFOX) | ABC-06 trial (149)                              |
| CNS/Glioma                                           | Lomustine                                            | Batchelor <i>et al.</i> 2013 (150)              |
| Pancreas                                             | Gemcitabine                                          | Conroy <i>et al.</i> 2022 (151)                 |
| Thyroid                                              | Lenvatinib                                           | SELECT trial 2015 (152)                         |

GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= non-small cell lung cancer; STS= Soft tissue sarcoma

## 3.3 Clinical parameters and variables

### 3.3.1 Patient characteristics

#### **Baseline characteristics**

Baseline characteristics of the larotrectinib arm in the model are aligned with the population of the larotrectinib trials (Table 41). The modelled ePAS9 and SAS3 pooled cohort comprises ██████ paediatric and ██████ adult patients, based on the larotrectinib trials.

**Table 41. Baseline patient characteristics by tumour location**

| Tumour location                                      | Mean age (years) | Percentage female (%) |
|------------------------------------------------------|------------------|-----------------------|
| Larotrectinib pan-tumour adults                      | ████             | ████                  |
| Larotrectinib pan-tumour paediatrics                 | █                | ████                  |
| NSCLC                                                | ████             | ████                  |
| Salivary                                             | ████             | ████                  |
| Melanoma                                             | ████             | ████                  |
| Colorectal (including appendix proxy)                | ████             | ████                  |
| STS adults (GIST)                                    | ████             | ████                  |
| STS adults (non-GIST) (including bone sarcoma proxy) | ████             | ████                  |
| STS paediatrics (including IFS proxy)                | █                | ████                  |
| Breast                                               | ████             | ████                  |
| Cholangiocarcinoma                                   | ████             | ████                  |
| CNS/Glioma                                           | ████             | ████                  |
| Pancreas                                             | ████             | ████                  |
| Thyroid                                              | ████             | ████                  |

CNS= Central nervous system; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; STS= Soft tissue sarcoma

Source: ePAS9 + SAS3

For some tumour locations in the stratified comparator arm, some drugs were administered via the intravenous (IV) route and dosed according to average body surface area (BSA) or weight. The average BSA or weight was taken from the relevant NICE technology appraisal (TA), where applicable, or from a published clinical trial informing the efficacy inputs if this information was not available in the appraisal. For tumour locations where no NICE TA-based or literature-based BSA was available, the

average BSA of larotrectinib patients was used. The average adult and paediatric BSA from the ePAS9 and SAS3 datasets were ■■■ m<sup>2</sup> and ■■■ m<sup>2</sup>, respectively. The stratified comparator patient characteristics used in the model are included in Appendix I.

### ***Tumour location distribution***

As described in Section 3.2.2, larotrectinib is one of the first regulatory-approved tumour-agnostic treatment options, where no alternative NTRK tumour-agnostic comparator exists. As a result, larotrectinib is assessed in the model as a tumour-agnostic treatment option. However, comparators have been defined separately for each tumour location, necessitating the averaging of these individual comparator outcomes to enable comparison with the tumour-agnostic outcome of larotrectinib. For both clinical and cost outcomes, results for individual tumour locations were weighted by the distribution of the tumour locations within the total pooled population. An assumption is required for the optimal weighting used when averaging the comparator outcomes to ensure consistency and comparability with the larotrectinib arm outcomes. In the base case, the proportions of comparators were calculated using the ePAS9 and SAS3 datasets and were used to weigh the outcomes of individual tumour locations (Table 42). This aligns the outcomes with the clinical data supporting the model while still being reflective of NHS clinical practice, as discussed in section 3.2.1 and in the SACT data in section 2.13.2. Population generalisability was further validated in the clinical advisory board (118).

Total outcomes for larotrectinib are generated by combining the adult starting cohort and paediatric starting cohort outcomes using the ratio of adult to paediatric tumour locations in Table 42 (■■■% for paediatric tumour locations).

It should be noted that the ePAS9 dataset included 20 adult patients with different tumour locations, such as cervix, hepatic, cancer of unknown primary origin, prostate, urothelial, uterus, oesophageal, external auditory canal, gastric, lung cancer (excluding NSCLC). These patients were equally distributed (i.e., equi-proportionally) across the model tumour locations in lieu of creating a separate model engine.



**Table 42. Weighting used to aggregate different tumour location results based on ePAS9 and SAS3 datasets**

| Tumour location                                        | No. of patients in ePAS9 and SAS3 | Calculated weighting (%)       |
|--------------------------------------------------------|-----------------------------------|--------------------------------|
| NSCLC                                                  | ■                                 | ■                              |
| Salivary                                               | ■                                 | ■                              |
| Melanoma                                               | ■                                 | ■                              |
| Colorectal (used as proxy for appendix)                | ■                                 | ■                              |
| STS adults (GIST)                                      | ■                                 | ■                              |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | ■                                 | ■                              |
| STS paediatrics*                                       | ■                                 | ■                              |
| IFS (used as proxy for IFS)                            | ■                                 | Added to STS paediatrics       |
| Appendix                                               | ■                                 | Added to colorectal            |
| Breast                                                 | ■                                 | ■                              |
| Bone sarcoma                                           | ■                                 | Added to STS adults (non-GIST) |
| Cholangiocarcinoma                                     | ■                                 | ■                              |
| CNS/Glioma                                             | ■                                 | ■                              |
| Pancreas                                               | ■                                 | ■                              |
| Thyroid                                                | ■                                 | ■                              |
| Other                                                  | ■                                 | Redistributed evenly           |
| <b>Total</b>                                           | ■                                 | 100                            |

CNS= Central nervous system; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; ST= Soft tissue sarcoma

\*Includes two congenital nephroma patients

Source: Larotrectinib (BAY 2757566) Summary of clinical efficacy 2024 (89)

### 3.3.2 Summary of modelling approaches

The larotrectinib trials were single-arm trials with no randomised comparator arm. Therefore, it was necessary to synthesise a SOC comparator, and multiple methods exist to accomplish this, each with its own advantages and disadvantages. These methods are summarised in Table 43. The MAIC approach is used in the base case, and the inputs and additional detail regarding the methodology are detailed in Section 3.3.4 and 3.3.5. Scenario inputs and related methodology are described in Appendix M.

**Table 43. Modelling approaches to estimate larotrectinib and SOC survival data**

| Method                             | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Base case</b>                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| MAIC                               | <p>Larotrectinib is modelled using independent parametric models fitted to the ePAS9 and SAS3 datasets.</p> <p>SOC is modelled by applying a treatment effect, i.e. a HR, to the larotrectinib reference OS and PFS. The HR is estimated through a MAIC. The VICTORIA MAIC (Section 2.10.1.2) is used to model outcomes for adults and EPI VITRAKVI (Section 2.10.2.1) is used for paediatrics. The advantage of this approach is that the MAIC HR minimises the bias that results from prognostic or effect-modifying baseline characteristics that are imbalanced across study populations. However, this process reduces the sample size, which increases uncertainty in the HR. Using the ePAS9 and SAS3 datasets leverages the increased sample size and additional maturity of the latest data cut-off. It should also be noted that the MAIC analyses were conducted with the latest data cut-off available at the time of the analysis, with VICTORIA using ePAS7 (data cut-off July 2022) and EPI VITRAKVI using ePAS6 (data cut-off July 2021). However, this is expected to have a relatively low impact given the minimal differences in OS and PFS between an even earlier dataset (ePAS2 and SAS3) and the current ePAS9 and SAS3 dataset (Section 3.3.4 and 3.3.5).</p> <p>On balance, this is the most robust approach and hence is used in the base case. Scenario analyses were also conducted using alternative MAIC sources, including VICTORIA MAIC for paediatrics, and HMF and Flatiron MAICs for OS (Section 3.11.3).</p>                             |
| <b>Scenarios</b>                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Responder / non-responder analysis | <p>Responder and non-responder patients from the ePAS9 and SAS3 datasets are modelled separately using independent parametric models. A responder was defined as having achieved a complete response or partial response, and a non-responder was defined as having stable or progressive disease using the IRC.</p> <p>Larotrectinib is then modelled using either a mix of the responder and non-responder OS and PFS curves with the weighting based on an estimated ORR, or only using the responder OS and PFS curves.</p> <p>SOC is modelled by the non-responder OS and PFS curves.</p> <p>The advantage of this approach is that the patient population for larotrectinib and SOC is more similar than a naïve approach, as both arms are sourced from the larotrectinib trials. However, this analysis requires a strong assumption that treatment with SOC is equivalent to patients who do not achieve a response to treatment with larotrectinib. Furthermore, larotrectinib efficacy is skewed by assumptions regarding responders. If treatment with larotrectinib is assumed to be represented by 100% responders, then this can overestimate the efficacy of larotrectinib. This also ignores the benefits of stable disease, which are attributed to non-responders, hence overestimating SOC. Clinical feedback from the advisory board reported that stable disease holds strong value, especially in patients with a primary CNS tumour (118). Methods for estimating alternative ORRs from the trial are also uncertain, as discussed in Appendix M.</p> |

| Method                            | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intra-patient comparison (GMI)    | <p>Larotrectinib is modelled as per the base case.</p> <p>SOC PFS is modelled using the GMI analysis described in Section 2.6.1.4. The intra-patient comparison applies larotrectinib IPD, using patients' previous line of therapy PFS as a proxy for the comparator arm. SOC OS is modelled using the relative difference in larotrectinib OS and PFS hazard applied to SOC PFS as a conservative assumption.</p> <p>Previous analyses have shown patients with TRK fusion cancer treated with larotrectinib had a clinically meaningful improvement in PFS compared with time to progression for previous treatment. The disadvantage of this approach is that it cannot inform the OS endpoint without strong assumptions about the relationship between OS and PFS. Furthermore, there is a degree of subjectivity regarding the maximum size of the GMI applied.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Naïve literature-based comparator | <p>Larotrectinib is modelled as per the base case.</p> <p>SOC is modelled using OS and PFS identified in the literature for the comparator treatment in the relevant tumour location. NICE TAs are used to replicate the preferred modelling approach, and in the absence of NICE guidance, survival analysis was conducted on trial publications that reported endpoints of interest.</p> <p>The disadvantage of this approach is that the comparison is naïve and subject to bias from prognostic and treatment effect modifiers. For example, this patient population does not consist entirely of NTRK fusions. An attempt to reduce the bias in this comparison is explored by using the HRs from the Voyager 1 or Voyager 2 studies, which represent the difference in outcomes for patients with and without NTRK fusions. These are applied to tumour locations with low NTRK fusion rates (Figure 3) to adjust for the increased mortality associated with NTRK fusion. The model assumes that if tumour locations have high NTRK fusion rates e.g., STS paediatrics (&gt;91%), the OS curves will already capture the increased mortality associated with NTRK fusion in those populations, and thus the HRs are not applied. The HR is used to adjust the OS curves for the following tumour locations: NSCLC, salivary, melanoma, colorectal, STS adults (GIST), STS adults (non-GIST), breast, cholangiocarcinoma, CNS, pancreas, and thyroid.</p> |
| Mixture cure models               | <p>Larotrectinib adult cohort is modelled as per the base case. However, for paediatric patients, a mixture cure model is used to investigate a cure assumption as treatment with larotrectinib may provide a curative option for paediatric patients (118).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

CNS = central nervous system; GIST = gastrointestinal stromal tumour; GMI = growth modulation index; HR = hazard ratio; IPD = individual patient level data; IRC = independent review committee; MAIC = matching adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; NTRK = Neurotrophic Tyrosine Receptor Kinase; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SOC = standard of care; STS = soft tissue sarcoma; TA = technology appraisal

### 3.3.3 Survival analysis methods

Survival analyses of the IPD from the larotrectinib trials were performed to extrapolate OS and PFS for larotrectinib using the ePAS9 and SAS3 datasets. In line with NICE Decision Support Unit (DSU) (Technical Support Document [TSD] 14), the survival analyses included the standard parametric distributions commonly used in oncology models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and

generalised gamma) (153). In the base case approach, using the MAIC, the SOC arm is generated using HRs applied to the larotrectinib survival models.

The process for selecting the most appropriate parametric model required an assessment of both within-trial and extrapolation predictions. The suitability of each distribution and the choice of the most appropriate options was based on the NICE DSU (TSD 14) (Appendix L), which suggested a range of internal validation methods, including visual inspection, evaluation of fit using Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) testing, and clinical validation using feedback from the advisory board (118).

These methods were also used to extrapolate IPD in the scenario analyses, including those using alternative modelling approaches (Table 43). In addition, the survival analyses of the naïve literature based comparator required pseudo IPD, which was generated from the Guyot method (154), and the mixture cure models used methodology as described in NICE DSU (TSD 21) (155).

Separate analyses were also conducted using the updated data cut-off for the ePAS2 and SAS3 datasets that were used in the original submission. This was performed for adults and paediatric patients separately to reduce the heterogeneity of the sample while still maintaining a high sample size compared to stratification by tumour location. A scenario is presented where the adult and paediatric patients are modelled as one cohort. Finally, additional scenarios include modelling a waning treatment effect on the HR used to derive the SOC arm.

### **3.3.4 Overall survival (OS)**

OS in the model was bounded by background mortality using the 'England and Wales' life table reported by the Office for National Statistics (release date: 18<sup>th</sup> March 2025). This was applied by restricting the per-cycle hazard to not be lower than general population mortality, using the patient characteristics in Section 3.3.1.

#### ***Adult starting population***

The larotrectinib reference arm was generated using parametric models fitted to the adult cohort of the ePAS9 and SAS3 datasets. The Gompertz generates very

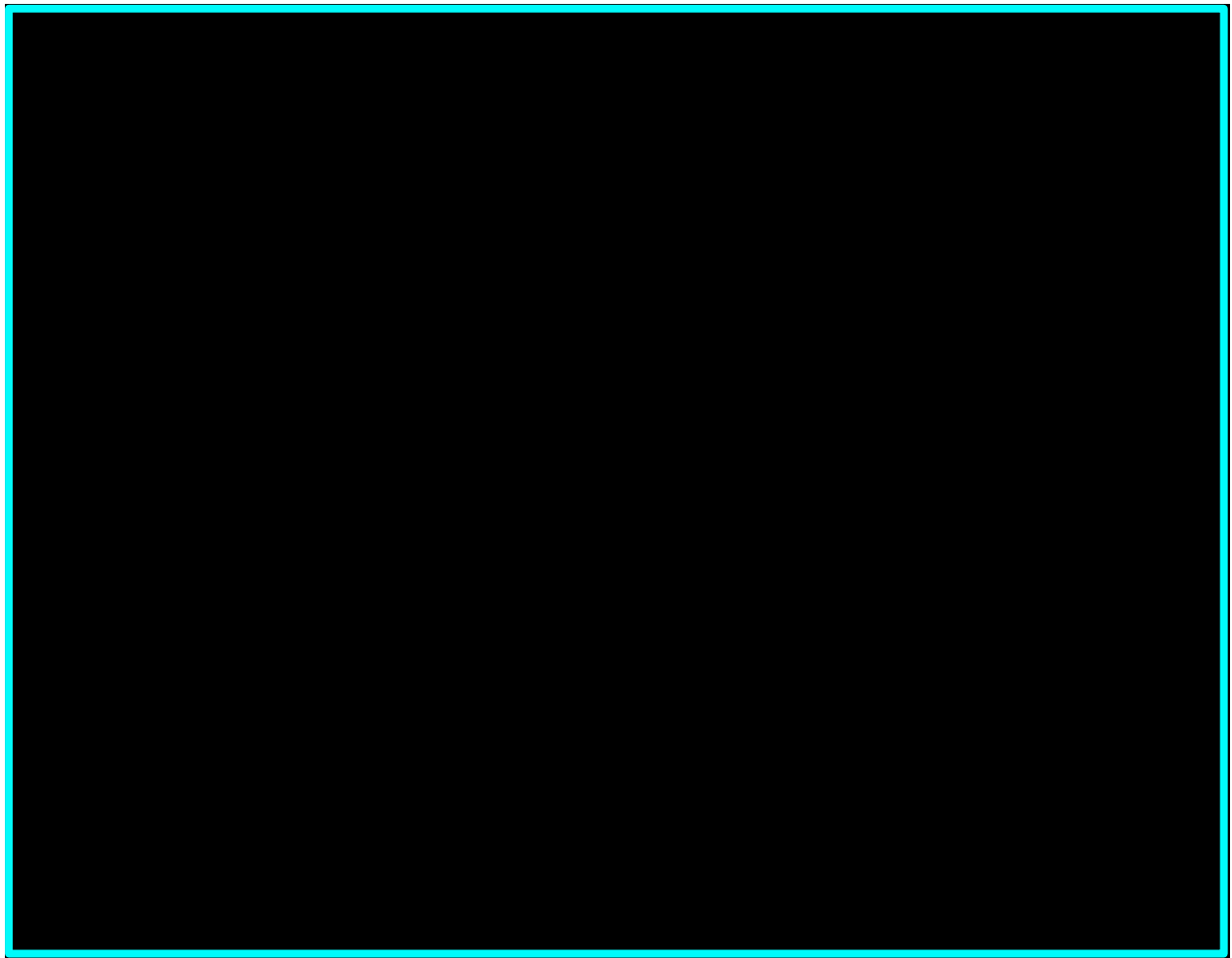
optimistic long-term survival. The log-normal, log-logistic, and generalised gamma models have a better fit to the trial period but generate more optimistic survival projections compared to the exponential, Weibull, and gamma models. The Weibull model was selected as the best-fitting option, representing the best statistical fitting model among the conservative extrapolation options, in line with clinician feedback that the models with higher tails were too optimistic (118). The AIC and BIC goodness-of-fit statistics for larotrectinib-treated adults are presented in Table 44, and an overlay of the KM curve for larotrectinib-treated adults with the parametric extrapolations is presented in Figure 23, which were validated with clinicians (118).

**Table 44. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to OS data for larotrectinib-treated adults from the ePAS9 and SAS3 datasets**

| Distribution      | AIC      | AIC ranking | BIC      | BIC ranking |
|-------------------|----------|-------------|----------|-------------|
| Exponential       | 1,132.00 | 7           | 1,135.50 | 7           |
| Gamma             | 1,127.70 | 6           | 1,134.50 | 6           |
| Weibull           | 1,125.70 | 5           | 1,132.50 | 5           |
| Log-logistic      | 1,120.10 | 4           | 1,126.90 | 3           |
| Gompertz          | 1,119.30 | 3           | 1,126.20 | 2           |
| Generalised gamma | 1,117.40 | 2           | 1,127.60 | 4           |
| Log-normal        | 1,116.10 | 1           | 1,122.90 | 1           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion; KM= Kaplan-Meier

**Figure 23. Parametric extrapolations of larotrectinib-treated adults OS based on ePAS9 and SAS3 datasets**



CI= Confidence interval; KM= Kaplan-Meier; OS = Overall survival

SOC was modelled using the OS HR from the VICTORIA study (Section 2.10.1.2).

### ***Paediatric starting population***

The larotrectinib reference arm was generated using parametric models fitted to the paediatric cohort of the ePAS9 and SAS3 data cut. The Gompertz and generalised gamma generate very optimistic long-term survival. The exponential, Weibull, and gamma models produce less optimistic long-term survival, and all have similar statistical fits (difference of approximately 3-5 in AIC and BIC). The Weibull model was selected as the best-fitting model based on clinician validation of long-term landmark survival (i.e., the percentage of patients alive at a particular timepoint) that preferred

the lower estimates from the different models. Additionally, the Weibull model was compatible with proportional hazards for application of the MAIC HR (118). The AIC and BIC goodness-of-fit statistics for larotrectinib-treated paediatrics are presented in Table 45, and an overlay of the KM curve for larotrectinib-treated paediatrics with the parametric extrapolations are presented in Figure 24.

**Table 45. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to OS data for larotrectinib-treated paediatrics from the ePAS9 and SAS3 datasets**

| Distribution      | AIC   | AIC ranking | BIC   | BIC ranking |
|-------------------|-------|-------------|-------|-------------|
| Gamma             | 334.3 | 7           | 340.3 | 7           |
| Weibull           | 334.1 | 6           | 340.0 | 6           |
| Log-logistic      | 333.2 | 5           | 339.1 | 5           |
| Exponential       | 333.2 | 4           | 336.2 | 2           |
| Log-normal        | 330.7 | 3           | 336.6 | 3           |
| Gompertz          | 330.1 | 2           | 336.0 | 1           |
| Generalised gamma | 327.9 | 1           | 336.8 | 4           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion; KM= Kaplan-Meier

**Figure 24. Parametric extrapolations of larotrectinib-treated paediatrics OS based on ePAS9 and SAS3 datasets**



CI= Confidence interval; KM= Kaplan-Meier; OS= Overall survival

SOC was modelled using the OS HR from the EPI VITRAKVI study (Section 2.10.2.1).

***Comparison between ePAS2+SAS3 and ePAS9+SAS3 datasets***

As shown in Figure 25, the ePAS2+SAS3 and ePAS9+SAS3 datasets have very similar OS KM curves, suggesting that the additional data collected are consistent with the initial survival analysis and conclusions from TA630 (118, 156). Furthermore, this suggests that the OS treatment effect from the MAICs and EPI VITRAKVI studies would be similar across datasets.



**Figure 25. OS KM comparison between ePAS2+SAS3 and ePAS9+SAS3 datasets**



KM= Kaplan-Meier; OS= overall survival

### **3.3.5 Progression-free survival (PFS)**

#### ***Adult starting population***

The larotrectinib reference arm was generated using parametric models fitted to the adult cohort of the ePAS9 and SAS3 datasets. The Gompertz and generalised gamma models generate overly optimistic long-term PFS. The Weibull model was selected as the best-fitting model, representing the best statistical fitting model amongst the conservative extrapolation options, in line with clinician feedback that the models with higher tails were too optimistic (118). The AIC and BIC goodness-of-fit statistics for larotrectinib-treated adults are presented in Table 46, and an overlay of the KM curve for larotrectinib-treated adults with the parametric extrapolations is presented in Figure 26.

**Table 46. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to PFS data for larotrectinib-treated adults from the ePAS9 and SAS3 datasets**

| Distribution      | AIC      | AIC ranking | BIC      | BIC ranking |
|-------------------|----------|-------------|----------|-------------|
| Exponential       | 1,213.20 | 7           | 1,216.60 | 7           |
| Gamma             | 1,183.20 | 6           | 1,190.00 | 6           |
| Weibull           | 1,175.10 | 5           | 1,181.90 | 5           |
| Gompertz          | 1,163.20 | 4           | 1,170.00 | 4           |
| Log-logistic      | 1,159.50 | 3           | 1,166.30 | 3           |
| Log-normal        | 1,150.20 | 2           | 1,157.00 | 2           |
| Generalised gamma | 1,137.60 | 1           | 1,147.80 | 1           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion; KM= Kaplan-Meier

**Figure 26. Parametric extrapolations of larotrectinib-treated adults PFS based on ePAS9 and SAS3 datasets**



SOC was modelled using the PFS HR from the VICTORIA study (Section 2.10.1.2).

### ***Paediatric starting population***

The larotrectinib-treated paediatric PFS reference arm was generated using parametric models fitted to the paediatric cohort of the ePAS9 + SAS3 data cut. The Gompertz model generates extremely optimistic long-term PFS. The remaining models are split into more optimistic predictions (log-normal, log-logistic, and generalised gamma models) and less optimistic predictions (Weibull, gamma, and exponential models). These less optimistic models had a similar statistical fit; therefore, the Weibull model was selected as the best-fitting model, aligned with clinician feedback (118). The AIC and BIC goodness-of-fit statistics for larotrectinib-treated paediatrics are presented in Table 47, and an overlay of the KM curve for larotrectinib-treated paediatrics with the parametric extrapolations are presented in Figure 27.

**Table 47. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to PFS data for larotrectinib-treated paediatrics from the ePAS9 and SAS3 datasets**

| Distribution      | AIC   | AIC ranking | BIC   | BIC ranking |
|-------------------|-------|-------------|-------|-------------|
| Gamma             | 603.2 | 7           | 609.1 | 7           |
| Exponential       | 602.7 | 6           | 605.7 | 4           |
| Weibull           | 602.4 | 5           | 608.3 | 6           |
| Log-logistic      | 599.0 | 4           | 605.0 | 3           |
| Gompertz          | 598.2 | 3           | 604.1 | 2           |
| Generalised gamma | 598.2 | 2           | 607.0 | 5           |
| Log-normal        | 596.7 | 1           | 602.6 | 1           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion; KM= Kaplan-Meier

**Figure 27. Parametric extrapolations of larotrectinib-treated paediatrics PFS based on ePAS9 and SAS3 datasets**



CI= Confidence interval; KM= Kaplan-Meier; PFS= Progression-free survival

SOC was modelled using the PFS HR from the EPI VITRAKVI study (Section 2.10.2.1)

***Comparison between ePAS2+SAS3 and ePAS9+SAS3 datasets***

As shown in Figure 28, the ePAS2+SAS3 and ePAS9+SAS3 datasets have very similar PFS KM curves, suggesting that the additional data collected are consistent with the initial survival analysis and conclusions from in TA630 (118). Furthermore, this suggests that the PFS treatment effect from the MAICs and EPI VITRAKVI studies would be similar across datasets.

**Figure 28. PFS KM comparison between ePAS2+SAS3 and ePAS9+SAS3 datasets**



KM= Kaplan-Meier; PFS= progression-free survival

### **3.3.6 Time-to-treatment discontinuation (TTD)**

TTD and PFS curves were very similar for larotrectinib (Figure 29), with only some patients treated post-progression in the tail. However, this period has a low number of patients and a large degree of censoring. Therefore, TTD was assumed to be equal to PFS, in line with clinician feedback that treatment is usually given until progression (118). Similarly, TTD was assumed to be equal to PFS for the indirect comparators to avoid the introduction of bias, since limited or no TTD data are available in the literature. In the case of a maximum treatment duration, SOC treatment costs were capped by the fixed schedule or the maximum duration for patients who have not progressed. These tumour locations are: salivary gland cancer (105 days, calculated from a median of 5 21-day cycles) (141), STS paediatrics (350 days, based on the fixed treatment schedule which spanned over 50 weeks) (157), breast cancer (6 months) (148), and cholangiocarcinoma (maximum treatment duration of 24 weeks) (158).

**Figure 29. KM PFS and TTD curves of ePAS9 and SAS3 datasets**



KM= Kaplan-Meier; PFS= Progression-free survival; TTD= Time-to-treatment discontinuation

### **3.3.7 Adverse events**

Grade 3-4 TEAEs that occurred in  $\geq 5\%$  of patients in the relevant treatment arm were included in the economic model. The 5% threshold was based on a common assumption used in NICE technology appraisals (144, 159, 160). TEAE rates for larotrectinib were taken from the NFCSAS of the larotrectinib trials (Section 2.11). AEs for the comparators were taken from the respective sources that informed clinical efficacy (Appendix I).

AEs that occur in  $\geq 5\%$  of patients in the relevant treatment arms were extracted for each tumour location comparator. A review of the rates across larotrectinib and the comparator tumour locations revealed that applying the 5% criterion to the individual tumour locations may bias the results, overestimating the AE rates and impact for the comparator arm. For example, an AE may have occurred in  $>5\%$  of population of the source publication, however, when pooled this reflected  $<5\%$  of the AEs in the comparator population.

To account for this, AE rates from the comparator sources were weighted based on the tumour distribution in the larotrectinib clinical trials. In the base case, only AEs with

a weighted rate in the full comparator sample of 5% or higher were included for model calculation. This represents a conservative approach, as different treatments have different AEs, weighting across multiple tumour locations reduces the chance of a given AE meeting the 5% threshold.

Table 48 outlines the AEs that occurred in  $\geq 5\%$  of patients in the treatment arm of the source references. The base case only includes AEs with a rate of  $\geq 5\%$  for larotrectinib or the pooled comparator after weighting by tumour location.

**Table 48. Percentage of grade 3+ TEAEs occurring in at least 5% of patients for larotrectinib and pooled comparator**

| Treatment emergent adverse event (Grade 3+) | Larotrectinib                                                                        | Pooled comparator |
|---------------------------------------------|--------------------------------------------------------------------------------------|-------------------|
| Anaemia                                     |    | 10.65%            |
| Diarrhoea                                   |     | 8.19%             |
| Febrile neutropenia                         |     | 6.34%             |
| Leukopenia                                  |     | 9.13%             |
| Lymphocyte count decreased (lymphopenia)    |   | 5.97%             |
| Neutropenia                                 |  | 29.47%            |
| Thrombocytopenia                            |   | 6.64%             |
| Vomiting                                    |   | 6.64%             |

TEAE= treatment emergent adverse event

### 3.4 Measurement and valuation of health effects

The impact of treatments on health-related quality of life (HRQoL) was tracked throughout the modelled time horizon by assigning differential health state utility values (HSUVs) to progression-free disease, progressed disease, and death. Results are presented as quality-adjusted life years (QALYs).

#### 3.4.1 Tumour location specific utilities

As described in Section 3.2.2, the model is stratified by tumour location for the comparator, thereby requiring utility inputs for each tumour location. Comparator utility values for progression-free and progressed health states were sourced from the literature. Key clinical trials for the comparator treatments in each tumour location were identified via the review of relevant NICE technology appraisals, thereby reflecting the relevant disease stage and line of therapy. The SLR and targeted literature searches

were used if data were not available from the NICE appraisals or clinical trial publications, prioritising EQ-5D-3L analyses for the population closest to the target population where feasible. The sourced inputs are outlined in Table 49.

**Table 49. Literature derived health state utility values by tumour location**

| Tumour location       | Progression-free | Progressive disease | Source                                                                |
|-----------------------|------------------|---------------------|-----------------------------------------------------------------------|
| NSCLC                 | 0.74             | 0.46                | NICE TA 347 (161)                                                     |
| Salivary              | 0.75             | 0.60                | Liberato 2012 (162)                                                   |
| Melanoma              | 0.75             | 0.69                | NICE TA357 (142)                                                      |
| Colorectal            | 0.73             | 0.59                | Recommended by ERG for NICE TA405; Grothey 2013 (CORRECT trial) (163) |
| STS adults (GIST)     | 0.77             | 0.65                | EQ-5D results from GRID                                               |
| STS adults (non-GIST) | 0.65             | 0.47                | Demetri 2013 (164); NICE TA185 (145)                                  |
| STS paediatrics       | 0.68             | 0.43                | Zuluga-Sanchez 2018; Delea 2014 (165)                                 |
| Breast                | 0.71             | 0.50                | NICE TA423 (148)                                                      |
| Cholangiocarcinoma    | 0.63             | 0.53                | Weighted average of other tumour locations                            |
| CNS/Glioma            | 0.60             | 0.60                | NICE TA23 (166)                                                       |
| Pancreas              | 0.67             | 0.60                | NICE TA440 (159)                                                      |
| Thyroid               | 0.72             | 0.64                | Bayer RAIR DTC NICE model                                             |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; NSCLC= Non-small cell lung cancer; RAIR DTC= Radioiodine-refractory differentiated thyroid cancer; STS= Soft tissue sarcoma

### 3.4.2 Health-related quality-of-life data from clinical trials

HRQoL data from the larotrectinib trials were available from studies 20289 and 20290. These data were used to estimate utility measures to populate the larotrectinib arm of the cost-effectiveness model. Note that information on HRQoL was not collected in 20288.

In study 20289 (patients aged 12 and older), HRQoL was assessed using EQ-5D-5L on day 1 of every other 28 days cycle during the first year of follow-up, and every 12 weeks after one year of follow-up. In the case of disease progression, the last HRQoL



assessment was performed in this visit but was not repeated in a subsequent visit in case of treatment continuation.

In study 20290 (patients aged 1 month to 21 years), HRQoL was assessed using PedsQL for all patients (the PedsQL Infant Scales [PedsQL IS] for infants aged 1-24 months, and PedsQL Generic Core Scales [PedsQL GCS] for children over 2 years old) as part of pre-treatment screening and then on day 1 of every 28-day cycle until the patient discontinues treatment. In case of disease progression and treatment continuation, HRQoL assessments were still implemented in each follow-up visit if still on treatment.

In line with the NICE position statement (167), data from these trials were mapped to EQ-5D-3L utilities (using the UK value set) as described in Section 3.4.3, and in more detail in Appendix J.

The data used to derive utility values are consistent with the methodology presented in TA630 (71). However, the current analysis is based on the recent ePAS9 and SAS3 datasets (data cut-off 20<sup>th</sup> July 2024) and therefore incorporates a larger patient cohort and extended follow-up (■■■ patients were included in the HRQoL analysis in total compared to ■■■ patients in TA630; see Appendix J). Notably, considerable data were available from long-term follow-up assessments post-progression from the larotrectinib trials (a total of ■■■ assessments were available for post-progression patients compared to ■■■ in TA630; see Appendix J), thereby contributing to the robust estimation of the average utility of larotrectinib treatment in the progressed disease state. As a result, the updated estimates reinforce previous findings and help reduce the uncertainty associated with the analysis presented in the original submission.

### **3.4.3 Mapping**

#### ***Derivation of utility values***

EQ-5D-5L responses obtained in study 20289 were used to derive utility values for patients 18 years of age and older. To ensure estimates were relevant to the UK population, the latest NICE DSU mapping framework developed by Hernández Alava

*et al.*, 2022 was utilised to derive mapped utility values from EQ-5D-5L to EQ-5D-3L (168).

A targeted literature review was conducted to identify mapping algorithms that could translate assessments from the PedsQL (PedsQL IS, PedsQL GCS) to EQ-5D-3L. The search yielded a single relevant publication by Khan *et al.* (2014) (169), where data from a cross-sectional survey among 11-15 year old children in four English secondary schools was used to generate a series of models to support mapping from PedsQL GCS to EQ-5D-3L (UK value set applied). No publications were identified that provided mapping algorithms for transforming PedsQL IS to EQ-5D scales. Therefore, for patients with assessments obtained using the PedsQL IS version only (including patients under the age of 2), utility values were not derived due to the lack of an available mapping algorithm.

### ***Patient disposition***

Eligible patients from studies 20289 and 20290 were restricted to those patients with at least one EQ-5D-5L or PedsQL GCS assessment. A total of [REDACTED] patients were included in the analysis and contributed a total of [REDACTED] assessments: [REDACTED] assessments were from paediatric patients ([REDACTED] patients), with [REDACTED] assessments from study 20290 ([REDACTED] patients) and [REDACTED] assessments from the 20289 study ([REDACTED] patients). The remaining [REDACTED] assessments were from adult patients ([REDACTED] patients), all from the study 20289.

The only missing data in the final sample of included patients was information on the school functioning domain for [REDACTED] patients from study 20290 and [REDACTED] patient from study 20289. For a total of [REDACTED] assessments ([REDACTED] pre-progression, [REDACTED] post-progression, and [REDACTED] with no progression date), the missing school function score was estimated by the mean of scores from the other available dimensions of the same subject.

### ***Statistical analysis***

The statistical analysis followed recommendations included in the NICE DSU Technical Support Documents (168). All analyses were conducted using R version 4.5.1.

EQ-5D-3L utility values were analysed using various regression modelling techniques (Ordinary Least Square (OLS) and Mixed Model Repeated Measures (MMRM)) to estimate the mean utility score for patients designated as either progression-free (and on treatment) or progressed disease.

The MMRM model was preferred as it reflects the repeated nature of measurements and resulted in better goodness-of-fit based on the AIC statistic. Using this model, the potential relationship (lower variability) between HRQoL assessments reported by the same patient (i.e., responses reported by the same patient can show a lower variability than with scores from other patients) was taken into account. The results of the OLS model, and the AIC statistic for each model are reported in Appendix J.

All HRQoL assessments were included in the analysis. A scenario assessing the impact of excluding HRQoL assessments from cycle 1, when the effects of larotrectinib may not yet be felt by the patient, is also provided in Appendix J. The scenarios estimate similar utilities and the scenario including cycle 1 was selected in the base case to be conservative.

Due to the small number of TEAEs, these could not be reliably evaluated within the regression models as a unique covariate. Instead, these are implicitly captured through the utility values derived from the larotrectinib trials. The economic model also conservatively applies TEAE disutilities from the literature for larotrectinib (Section 3.4.5), as this assumption avoids any introduction of bias in favour of larotrectinib.

### ***EQ-5D-3L utilities for larotrectinib***

The EQ-5D-3L utility values derived from the trial data and applied to larotrectinib in the base case for the progression-free and progressive disease health states are summarised in Table 50.

**Table 50. EQ-5D-3L utility values applied in the base case for larotrectinib – MMRM analysis including cycle 1**

| Health state       | Utility value (MMRM LS mean) | Standard error | 95% CI |
|--------------------|------------------------------|----------------|--------|
| Progression-free   | ████                         | ████           | ████   |
| Progressed disease | ████                         | ████           | ████   |

CI= confidence interval; EQ-5D-3L= EuroQol 5 dimension 3 level; LS= least squares; MMRM= mixed models for repeated measures

### 3.4.4 Health-related quality-of-life studies

The systematic literature search identified 16 unique HRQoL studies described in 16 publications from both original and updated SLRs (Appendix F). These publications, derived utility values from five common studies for patients with NTRK fusion-positive solid tumours treated with TRK inhibitors (Table 51).

**Table 51. Summary of utility study characteristics**

| Author Year        | Population and Country                                                                                                                                    | Treatment details                               | Utility value*                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Roth 2020 (170)    | Population: Patients with TRK fusion-positive metastatic NSCLC for second line treatment<br>Country: NR                                                   | Larotrectinib and entrectinib                   | <ul style="list-style-type: none"> <li>Health state utility <ul style="list-style-type: none"> <li>Pre-progression: 0.66</li> <li>Post-progression: 0.47</li> </ul> </li> </ul>                                                                                                                                                                                                                                          |
| Michels 2022 (129) | Population: Patients with cancer with NTRK fusion-positive tumour types<br>Country: The Netherlands                                                       | Larotrectinib                                   | <ul style="list-style-type: none"> <li>Utility value per health state: <ul style="list-style-type: none"> <li>Progression-free survival: 0.820</li> <li>Progressed disease: 0.730</li> </ul> </li> </ul>                                                                                                                                                                                                                 |
| Suh 2022 (171)     | Population: CRC with metastatic NTRK gene fusion cancers<br>Country: NR                                                                                   | Larotrectinib and entrectinib                   | <ul style="list-style-type: none"> <li>Progression-free/Stable disease <ul style="list-style-type: none"> <li>Base case (95% CI): 0.82 (0.78-0.86)</li> <li>Larotrectinib on-treatment utility: 0.83</li> <li>Entrectinib on-treatment utility: 0.83</li> </ul> </li> <li>Progressive disease <ul style="list-style-type: none"> <li>Base case (95% CI): 0.64 (0.55-0.75)</li> </ul> </li> </ul>                         |
|                    | Population: STS with metastatic NTRK gene fusion cancers<br>Country: NR                                                                                   | Larotrectinib and entrectinib                   | <ul style="list-style-type: none"> <li>Progression-free/Stable disease <ul style="list-style-type: none"> <li>Base case (off treatment) (95% CI): 0.43 (0.39-0.47)</li> <li>Larotrectinib on-treatment utility: 0.50</li> <li>Entrectinib on-treatment utility: 0.50</li> </ul> </li> <li>Progressive disease <ul style="list-style-type: none"> <li>Base case (95% CI): 0.30 (0.26-0.34)</li> </ul> </li> </ul>         |
| Suh 2024 (172)     | Population: Patients with NSCLC eligible for larotrectinib vs patients with unknown NTRK gene fusion status on nivolumab or pembrolizumab.<br>Country: NR | Larotrectinib versus nivolumab or pembrolizumab | <ul style="list-style-type: none"> <li>NSCLC: <ul style="list-style-type: none"> <li>Progression-free/Stable disease, base case (95% CI): 0.65 (0.61-0.70)</li> <li>Progressive disease, base case (95% CI): 0.47 (0.41-0.51)</li> </ul> </li> </ul>                                                                                                                                                                     |
|                    | Population: Patients with metastatic DTC eligible for larotrectinib vs patients with unknown NTRK gene fusion status on pembrolizumab<br>Country: NR      | Larotrectinib versus pembrolizumab              | <ul style="list-style-type: none"> <li>DTC: <ul style="list-style-type: none"> <li>Progression-free/Stable disease, base case (95% CI): 0.80 (0.77-0.84)</li> <li>Progressive disease, base case (95% CI): 0.50 (0.45-0.56)</li> </ul> </li> </ul>                                                                                                                                                                       |
| Suh 2025 (173)     | Population: Patients with locally advanced or metastatic NTRK gene fusion-positive cancers<br>Country: NR                                                 | Larotrectinib and Repotrectinib                 | <ul style="list-style-type: none"> <li>NSCLC <ul style="list-style-type: none"> <li>Pre-progression utility: 0.653</li> <li>Responsive utility increment: 0.019</li> <li>Progressive utility: 0.473</li> </ul> </li> <li>STS <ul style="list-style-type: none"> <li>Pre-progression utility: 0.43</li> <li>Responsive utility increment: 0.125</li> <li>Progressive utility: 0.3</li> </ul> </li> <li>Thyroid</li> </ul> |

| Author Year | Population and Country | Treatment details | Utility value*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------|------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             |                        |                   | <ul style="list-style-type: none"> <li>- Pre-progression utility: 0.8</li> <li>- Responsive utility increment: 0.06</li> <li>- Progressive utility: 0.5</li> <li>• CRC <ul style="list-style-type: none"> <li>- Pre-progression utility: 0.82</li> <li>- Responsive utility: 0.03</li> <li>- Progressive utility: 0.643</li> </ul> </li> <li>• Prevalence-weighted average <ul style="list-style-type: none"> <li>- Pre-progression utility: 0.67</li> <li>- Responsive utility: 0.05</li> <li>- Progressive utility: 0.47</li> </ul> </li> </ul> |
|             |                        | Larotrectinib     | <ul style="list-style-type: none"> <li>• On-Treatment Health State utility: 0.697</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|             |                        | Repotrectinib     | <ul style="list-style-type: none"> <li>• On-Treatment Health State utility: 0.701</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

CI = Confidence interval; CRC = colorectal cancer; DTC = differentiated thyroid cancer; NR = not reported; NSCLC = non-small cell lung cancer; NTRK = neurotrophic tropomyosin receptor kinase; STS = soft tissue sarcoma; TRK = tropomyosin receptor kinase; US = United States

\*Utility values were incorporated in the model for the comparator

### 3.4.5 Adverse reactions

The economic model considers the HRQoL impact of AEs by means of applying disutilities relating to the included grade 3/4 AEs occurring in  $\geq 5\%$  of patients (Section 3.3.7). The disutilities for each grade 3/4 AE sourced from the literature are provided in Table 52. To capture the full impact of the AEs, disutilities were applied to the full modelled cohort within the first cycle for each arm based on the event rates from the relevant clinical trials. AE disutilities were assumed to be the same for the same type of AE across each tumour location in line with previous accepted modelling approach in TA630 (118).

**Table 52. Grade 3/4 adverse event disutilities**

| Adverse event                            | Disutility | Source            | Assumption                        |
|------------------------------------------|------------|-------------------|-----------------------------------|
| Anaemia                                  | -0.090     | Nafees 2008 (174) | NSCLC - neutropenia               |
| Diarrhoea                                | -0.047     | Nafees 2008 (174) | NSCLC - diarrhoea                 |
| Febrile neutropenia                      | -0.090     | Nafees 2008 (174) | NSCLC - febrile neutropenia       |
| Leukopenia                               | -0.090     | Nafees 2008 (174) | NSCLC - neutropenia               |
| Lymphocyte count decreased (lymphopenia) | 0          | -                 | Laboratory AE, assumed equal to 0 |
| Neutropenia                              | -0.090     | Nafees 2008 (174) | NSCLC - neutropenia               |
| Thrombocytopenia                         | -0.090     | Nafees 2008 (174) | NSCLC - neutropenia               |
| Vomiting                                 | -0.048     | Nafees 2008 (174) | NSCLC - nausea and vomiting       |

AE= adverse event; CLL= Chronic lymphocytic leukaemia; NSCLC= Non-small cell lung cancer

### 3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

The comparator and larotrectinib utility values used in the base case are shown in Table 53. A scenario explores using an equal utility in the PD health state for larotrectinib and SOC derived from a weighted average of the PD health state utilities, equal to 0.53.

**Table 53. Comparator and larotrectinib health state utility values used in the base case**

| Tumour location               | Progression-free | Progressive disease | Source                                                                |
|-------------------------------|------------------|---------------------|-----------------------------------------------------------------------|
| Larotrectinib tumour agnostic | ■                | ■                   | ePAS9 and SAS3                                                        |
| NSCLC                         | 0.74             | 0.46                | NICE TA 347 (161)                                                     |
| Salivary                      | 0.75             | 0.60                | Liberato 2012 (162)                                                   |
| Melanoma                      | 0.75             | 0.69                | NICE TA357 (142)                                                      |
| Colorectal                    | 0.73             | 0.59                | Recommended by ERG for NICE TA405; Grothey 2013 (CORRECT trial) (163) |
| STS adults (GIST)             | 0.77             | 0.65                | EQ-5D results from GRID                                               |
| STS adults (non-GIST)         | 0.65             | 0.47                | Demetri 2013 (164); NICE TA185 (145)                                  |
| STS paediatrics               | 0.68             | 0.43                | Zuluga-Sanchez 2018; Delea 2014 (165)                                 |
| Breast                        | 0.71             | 0.50                | NICE TA423 (148)                                                      |
| Cholangiocarcinoma            | 0.63             | 0.53                | Weighted average of other tumour locations                            |
| CNS/Glioma                    | 0.60             | 0.60                | NICE TA23 (166)                                                       |
| Pancreas                      | 0.67             | 0.60                | NICE TA440 (159)                                                      |
| Thyroid                       | 0.72             | 0.64                | Bayer RAIRDTC NICE model                                              |

CNS= Central nervous system; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; STS= Soft tissue sarcoma

In addition, the model applies general population utility adjustment for age-related declines in HRQoL. The model uses a multiplicative method as described in the NICE DSU (TSD 12):

- The multiplicative method (the base case method recommended by NICE) – the baseline health state utility values are adjusted in proportion with the change in general population utility values over time.

The model base case used the general population utility values derived from the Health Survey for England 2014 dataset in line with recommendations from the NICE DSU.

### 3.5 Cost and healthcare resource use identification, measurement and valuation

Only direct medical costs were included, as per the NICE reference case (135). The direct medical costs considered in the model are drug acquisition, administration, follow-up cost (e.g., tests, doctor visits) and AE-related costs.

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3.5.1 Drug acquisition costs

Drug acquisition costs were sourced from the electronic market information tool (eMIT) (175) for generic compounds and British National Formulary (BNF) (176) for all other compounds, where available; otherwise, targeted searches were conducted for economic inputs.

Larotrectinib drug costs

To allow for use across the adult and paediatric populations, larotrectinib is available in different presentations (100mg capsules, 25mg capsules and oral solution). Dose (mg) per cycle was based on the relative dose intensity for the adult and paediatric patients as observed in the larotrectinib trials and aligns treatment used with health outcomes observed. Presentations of larotrectinib used in the economic model reflect those received in the larotrectinib clinical trial programme and are presented within Table 54. The cost of larotrectinib reflected in the model includes a discount of [REDACTED]%, offered to the NHS through a simple Patient Access Scheme.

Table 54. Larotrectinib drug cost (expected Patient Access Scheme price)

| Larotrectinib formula | Formulation        | Pack size   | Total mg per pack | List price per pack | Expected Patient Access Scheme price per pack | Average dose per day (mg) | Expected Patient Access Scheme price per day |
|-----------------------|--------------------|-------------|-------------------|---------------------|-----------------------------------------------|---------------------------|----------------------------------------------|
| Adults                | 100mg capsules     | 56 capsules | 5,600             | £14,000.00          | [REDACTED]                                    | [REDACTED]                | [REDACTED]                                   |
| Paediatric            | 100mg capsules     | 56 capsules | 5,600             | £14,000.00          | [REDACTED]                                    | [REDACTED]                | [REDACTED]                                   |
|                       | 25mg capsules      | 56 capsules | 1,400             | £3,500.00           | [REDACTED]                                    |                           | [REDACTED]                                   |
|                       | Bottle of solution | 1 bottle    | 2,000             | £5,000.00           | [REDACTED]                                    |                           | [REDACTED]                                   |

mg = milligram

SOC drug costs

Drug acquisition costs were sourced from the electronic market information tool (eMIT) (175) for generic compounds and British National Formulary (BNF) (176) for all other compounds, where available; otherwise, targeted searches were conducted for economic inputs. The least expensive cost per mg of drug was used to represent the unit cost. SOC dosage and drug costs are presented in Table 55 (detail in Appendix M).

**Table 55. Treatments to be included in the active comparator arm of the economic model**

| Tumour location       | Included comparators   | Dose                                                                                                                                                                                             | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source                                     |
|-----------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|-------------|------------|-------------------------------------------------|
| NSCLC                 | Nintedanib             | 200 mg twice daily on days 2 to 21 of a standard 21-day docetaxel treatment cycle                                                                                                                | Oral        | 8,000                        | 12,000      | £2,151.10  | TA347 (140)                                     |
|                       | Docetaxel              | 75 mg/m <sup>2</sup> once per 21-day cycle                                                                                                                                                       | IV          | 139.1                        | 80          | £9.48      |                                                 |
| Salivary              | Cisplatin              | 80 mg/m <sup>2</sup> on day 1                                                                                                                                                                    | IV          | 147.78                       | 10          | £3.68      | Airoldi <i>et al.</i> 2017 (141)                |
|                       | Vinorelbine            | 25 mg/m <sup>2</sup> on days 1 and 8                                                                                                                                                             | IV          | 92.37                        | 500         | £175.52    |                                                 |
| Melanoma              | Pembrolizumab          | 2 mg/kg once every 3 weeks                                                                                                                                                                       | IV          | 140                          | 100         | £2,630.00  | NICE TA357 (142)                                |
| Colorectal            | Trifluridine-tipiracil | 35 mg/m <sup>2</sup> twice a day on days 1-5 and days 8-12 of 28-day cycle                                                                                                                       | Oral        | 1,190                        | 400         | £666.67    | Mayer <i>et al.</i> 2015 (143)                  |
| STS adults (GIST)     | Regorafenib            | 160 mg taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.                                                                          | Oral        | 3,360                        | 3,360       | £3,744.00  | NICE TA488 (144)                                |
| STS adults (non-GIST) | Trabectedin (1mg)      | 1.22 mg/m <sup>2</sup> body surface area, administered as IV over 24 hours with a 3-week interval between cycles.                                                                                | IV          | 2                            | 1           | £1,229.40  | TA185 (145)<br>Demetri <i>et al.</i> 2016 (146) |
|                       | Trabectedin (0.25mg)   |                                                                                                                                                                                                  | IV          | 0.1                          | 0.25        | £326.70    |                                                 |
| STS paediatrics       | Irinotecan             | 50 mg/m <sup>2</sup> per day for 5 days at weeks 1, 4, 13, 25, 34, 46, 49;                                                                                                                       | IV          | 35.46                        | 500         | £16.59     | VIT-0910 trial (147)                            |
|                       | Vincristine            | 1.5 mg/m <sup>2</sup> on day 1 of weeks 1, 2, 4, 5, 13, 14, 25, 26, 34, 35, 46, 47, 49, 50.                                                                                                      | IV          | 1.06                         | 5           | £63.72     |                                                 |
|                       | Temozolomide           | 125 mg/m <sup>2</sup> /day<br>Dose will be escalated to 150 mg/m <sup>2</sup> /day at cycle 2 TMZ will be given orally, prior to vincristine and irinotecan, on days 1-5 repeated every 3-weeks. | Oral        | 1,350                        | 5           | £20.15     |                                                 |

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| Tumour location    | Included comparators | Dose                                                                                                                                                                            | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source                        |
|--------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|-------------|------------|------------------------------------|
| Breast             | Vinorelbine (IV)     | 30 mg/m <sup>2</sup> weekly for 6 months;                                                                                                                                       | IV          | 156.6                        | 100         | £75.42     | NICE TA423 (148)                   |
|                    | Vinorelbine (oral)   | 60 mg/m <sup>2</sup> weekly for first 3 administrations and 80mg/m <sup>2</sup> weekly for subsequent administrations for 6 months                                              | Oral        | 313.2                        | 500         | £175.52    |                                    |
|                    | Gemcitabine          | 1250 mg/m <sup>2</sup> two times per 21-day cycle for 6 months                                                                                                                  | IV          | 4,350                        | 2000        | £19.74     |                                    |
|                    | Docetaxel            | 100 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                        | IV          | 174                          | 80          | £16.59     |                                    |
|                    | Paclitaxel           | 175 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                        | IV          | 304.5                        | 300         | £18.75     |                                    |
|                    | Doxorubicin          | 75 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                         | IV          | 130.5                        | 200         | £19.01     |                                    |
| Cholangiocarcinoma | 5-fluorouracil       | 400 mg/m <sup>2</sup> (5–10 min bolus) completed on day 1, and fluorouracil 2400 mg/m <sup>2</sup> as continuous intravenous infusion starting on day 1 and finishing on day 2. | IV          | 696                          | 5,000       | £6.13      | ABC-06 trial (149)                 |
|                    | Oxaliplatin          | 85 mg/m <sup>2</sup> (2-h intravenous infusion)                                                                                                                                 | IV          | 148                          | 200         | £28.24     |                                    |
|                    | Folinic acid         | 350 mg; 2-h intravenous infusion concurrently with oxaliplatin infusion                                                                                                         | IV          | 350                          | 3500        | £62.62     |                                    |
| CNS/Glioma         | Lomustine            | 110 mg/m <sup>2</sup> day on 1 every 6 weeks                                                                                                                                    | Oral        | 187                          | 800         | £780.82    | Batchelor <i>et al.</i> 2013 (150) |
| Pancreas           | Gemcitabine          | 2000 mg/m <sup>2</sup> administered 4 times every 6-week cycle                                                                                                                  | IV          | 5,400                        | 2,000       | £19.74     | Conroy <i>et al.</i> 2022 (151)    |
| Thyroid            | Lenvantinib (10mg)   | 24 mg once daily                                                                                                                                                                | Oral        | 20                           | 300         | £1,437.00  | SELECT trial 2015 (152)            |
|                    | Lenvantinib (4mg)    |                                                                                                                                                                                 | Oral        | 4                            | 120         | £1,437.00  |                                    |

AUC= area under the curve; GIST= gastrointestinal stromal tumour; IFS= infantile fibrosarcoma; IV= intravenous; STS= soft tissue sarcoma

Source: British national formulary 2021 (176).

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### ***Subsequent treatment costs***

As detailed in Section 2.7, very few patients (■%) received subsequent therapy after treatment with larotrectinib. Therefore, no subsequent treatment costs for larotrectinib are included. To reduce bias and apply a conservative assumption for larotrectinib's cost-effectiveness, an equivalent assumption was applied to the SOC arm. It is expected to have a reduced impact as the cost of including cheap and/or generic next-line treatments would be low.

### **3.5.2 Drug administration costs**

Administration costs for comparators were calculated based on the administration procedure(s) required in each treatment cycle and the number of administrations. Drugs administered orally were assumed to incur no administration cost. The reference cost for simple chemotherapy delivery was used for all IV chemotherapies, except for FOLFOX, which used the reference cost for complex chemotherapy and a district nurse. Drugs were assumed to require an administration procedure every treatment cycle. A simple parenteral chemotherapy administration was applied for most IV administrations as it was most commonly used in the NICE technology appraisals and provided a conservative approach for estimating comparator costs (142, 145, 148, 159). The unit costs for treatment administration are presented in Table 56.

**Table 56. Drug administration costs**

| Variable                                                                                | Code       | Unit cost (£) | Reference                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------|------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Simple Chemotherapy (IV); first attendance                                              | CHEM SB12Z | £255.49       | Weighted average of all entries under SB12Z source: National Cost Collection Data Publication: National Schedule 2023/2024 – Outpatient Procedures                                                                        |
| Tablet                                                                                  | N/A        | £0.00         | N/A                                                                                                                                                                                                                       |
| District nurse visit to remove pump after each cycle                                    | N/A        | £57.00        | PSSRU 2024; <a href="https://www.pssru.ac.uk/unitcostsreport/">https://www.pssru.ac.uk/unitcostsreport/</a> ; Table 6.2.1: National average unit costs for community health services, District Nurse, Adult, Face to Face |
| Complex Chemotherapy (IV); including prolonged infusional treatment at first attendance | SB14Z      | £598.00       | National Cost Collection Data Publication: National Schedule 2023/2024 – Summary: HRG Cost                                                                                                                                |

HRG= Healthcare resource group; IV= intravenous; N/A= not applicable

### 3.5.3 Health state unit costs and resource use

Each health state is associated with corresponding HCRU. This varies by tumour location under conventional care (see Appendix M for detailed sources). HCRU costs covers disease management costs including oncology visits, testing, e.g., X-rays, and pain management. Recognising that there are currently no published estimates of HCRU or prior clinical experience of tumour-agnostic treatments in England, healthcare resource use for larotrectinib is assumed to be equal to that of the weighted comparator arm for each health state. This assumption is considered to potentially overestimate resource use for larotrectinib, as expected resource use may be lower with a targeted oral therapy.

UK-specific unit costs were based on 2023/2024 NHS reference costs for healthcare resource use (177) and Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2024 report (177, 178). Where a NICE appraisal was available, the approach selected was to use the HCRU inputs used to inform the committee's preferred assumptions. Data collection for HCRU inputs for the tumour locations without a NICE appraisal was based on the SLR output where possible; otherwise, broader targeted searches were conducted for published articles where no evidence was found in the SLR.

The cost of the progression-free or progressive disease health states take the form of a one-off cost at state initiation (start-up costs) and recurrent costs per cycle. The cost of death was applied as a one-off lump-sum. The CEM includes palliative care costs as part of end-of-life costs.

Aggregated costs with a paucity of information around individual components or costs from alternative sources could not be updated from national databases. In these cases, costs were inflated using the PSSRU reported inflation indices. Based on PSSRU recommendations, the 'New Health Services Index using Consumer Price Index' values were used to inflate prices between 2014-2021, with the 'Hospital and Community Health Services Index' (HCHS) applied prior to 2014. The details of these costs are listed in Appendix M.

Where a source for a tumour location provided an aggregate cost or HCRU details for start-up costs, these were implemented in the model. If the source did not present a start-up cost, start-up costs were assumed null, remaining consistent with the replication of methodology used within the specific TA or evidence source.

End-of-life costs could not be identified for glioma, STS non-GIST, STS in paediatric patients, and cholangiocarcinoma patients. The targeted literature review identified a modelling study for end-of-life cost among cancer patients, which was used to inform this input (179). The healthcare cost and social care cost from this modelling study were included to align with the resources accounted for in other TAs for consistency. Because the larotrectinib HCRU was the weighted average based on tumour location of all comparators, absolute values for comparator tumour location were not expected to impact the incremental result between intervention and the comparators.

The detailed list of resource use associated with the comparator arm and the unit costs is presented in Appendix M.

Table 57 shows the calculated health state costs for the tumour locations.

**Table 57. Health state costs by tumour location**

| <b>Tumour locations</b>       | <b>Progression-free, start-up</b> | <b>Progression-free, per cycle</b> | <b>Progressed, start-up</b> | <b>Progressed, per cycle</b> | <b>Death/End-of-life</b> |
|-------------------------------|-----------------------------------|------------------------------------|-----------------------------|------------------------------|--------------------------|
| Larotrectinib tumour agnostic | £94.10                            | £41.16                             | £156.08                     | £57.39                       | £7,201.90                |
| NSCLC                         | £0.00                             | £106.07                            | £0.00                       | £223.50                      | £8,575.58                |
| Salivary                      | £2.67                             | £107.58                            | £335.00                     | £82.37                       | £7,802.79                |
| Colorectal/Appendix           | £0.00                             | £52.55                             | £1,877.10                   | £65.63                       | £8,722.76                |
| Melanoma                      | £516.11                           | £115.10                            | £856.27                     | £115.10                      | £9,814.31                |
| STS (GIST)                    | £34.75                            | £36.09                             | £728.55                     | £38.51                       | £10,920.87               |
| Non-GIST/Bone sarcoma         | £0.00                             | £27.58                             | £0.00                       | £55.16                       | £7,775.11                |
| Breast                        | £0.00                             | £65.74                             | £0.00                       | £65.74                       | £7,208.03                |
| Glioma                        | £516.21                           | £0.00                              | £0.00                       | £0.00                        | £7,775.11                |
| Pancreas                      | £358.75                           | £96.72                             | £0.00                       | £94.10                       | £5,073.34                |
| STS paediatric/IFS            | £0.00                             | £27.28                             | £0.00                       | £54.57                       | £7,775.11                |
| Cholangiocarcinoma            | £94.10                            | £41.16                             | £156.08                     | £57.39                       | £6,858.62                |
| Thyroid                       | £0.00                             | £81.76                             | £0.00                       | £81.76                       | £9,872.17                |

NSCLC= non-small-cell lung cancer; GIST= gastrointestinal stromal tumours; STS= soft tissue sarcoma; IFS= infantile fibrosarcoma.

Health state costs are based on the source NICE TA or literature.

Start-up cost is the one-time cost of health resources required for assessment and/or treatment initiation when patients enter a health state. Start-up cost is assumed £0 if the source does not mention any HRU details or aggregate health state cost.

Glioma TA reported monitoring cost over the treatment period by a fixed schedule that did not fit a per cycle calculation. Thus, the total costs were applied as a one-off cost to glioma health states. Round 2015 was used to inform end-of-life cost for tumour locations that did not have this data in the TA or literature sources.

### 3.5.4 Adverse reaction unit costs and resource use

The cost of treating an AE was assumed not to vary based on the patient's tumour location. This approach has been applied in previous NICE appraisals, where the cost of treating AEs were based on reported costs for other tumour locations (180).

Healthcare Resource Group (HRG) codes were used for AEs. When multiple codes for the same adverse reaction were identified, the codes were weighted using the 'Activity' information from the NHS reference costs (177). If the evidence source only provided HCRU details rather than the codes, the HCRU terms were searched in the NHS reference schedule to identify relevant codes.

In the event that the evidence source estimated the AE cost based on activity codes that were no longer used or there was no information on HCRU or cost at all, assumptions were made. These assumptions included either estimating HCRU (then

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codes are identified), to equate to the cost of another AE that was considered to have similar cost impact, where applicable, or inflation rates were applied based on the 2024 PSSRU report (178).

Table 58 provides the details for AE costs included in the economic model base case for both larotrectinib and comparators. For the full cost breakdown and sources used for costing the impact of AEs, see Appendix M.

**Table 58. Adverse event costs**

| Adverse event                          | Total cost | Source                                                                                                                   |
|----------------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------|
| Anaemia                                | £ 1,544.29 | NICE TA 405 ERG report. Weighted average                                                                                 |
| Diarrhoea                              | £ 702.63   | NICE TA 405 ERG report. Average of grade 3 (code PF26B) and grade 4/5 events (weighted average of codes PF26A and PF26B) |
| Febrile neutropenia                    | £ 7,137.45 | NICE TA 405 ERG report. Weighted average                                                                                 |
| Leukopenia                             | £ 171.23   | Assumption based on NICE TA 405 and TA 423                                                                               |
| Lymphocyte count decreased/lymphopenia | £ 171.23   | Assumption                                                                                                               |
| Neutropenia                            | £ 171.23   | Assumption                                                                                                               |
| Thrombocytopenia                       | £ 2,515.70 | NICE TA 405 ERG report. Weighted average                                                                                 |
| Vomiting                               | £ 171.23   | NICE TA 405                                                                                                              |

### 3.5.5 Miscellaneous unit costs and resource use

The cost of NTRK testing was not included in the base case analysis, as genomic testing at diagnosis is increasingly integrated into routine care to guide optimal treatment and uncover actionable targets across a broad range of genes, with NTRK fusions representing only a small subset. NTRK fusion testing capability already exists within the NHS infrastructure and is expanding according to plans by the NHS England's Genomic Medicine Service, which commits to offering genomic testing to all cancer patients as part of routine care (181). Furthermore, the National Genomic Test Directory specifies that NTRK testing is commissioned by the NHS (182). Genomics England also supports the integration of genomic data into clinical decision-making to enable personalised and predictive healthcare (183). Therefore, the



requirement for NTRK testing reflects the evolution of precision oncology in the NHS rather than a wholly new or exceptional resource need specific to this indication.

A scenario analysis was conducted to incorporate the cost of NTRK fusion testing for patients treated with larotrectinib, representing an extreme scenario in which the entire additional testing costs are attributed to larotrectinib rather than at least partially absorbed by the NHS for testing of other treatments requiring NTRK fusions.

The calculation for testing costs was based on methods employed by the ERG in the original NICE submission (71). First, the number of patients requiring screening to identify an eligible larotrectinib patient was estimated as the inverse of the NTRK fusion rate for each tumour type (Table 59). Testing strategies and unit costs for each tumour type were then informed by clinical advice and a published testing algorithm used by the ERG in TA630 (Table 60 and Table 61). The cost of NTRK fusion testing with next-generation sequencing (NGS) was incurred for all tumour types where there is no screening stage, and by 9% of patients who undergo screening with immunohistochemistry (IHC) or WGS, reflecting rates reported from a study assessing the diagnostic accuracy of IHC (184). After weighted according to the distribution of tumour types in the ePAS9 and SAS3 datasets, the overall cost of testing for larotrectinib applied in the scenario analysis is £28,952.

**Table 59. Number of NTRK fusion screenings by tumour location**

| Tumour location       | NTRK fusion rate | Number needed to screen | Source                                                                                                                                                                                                                                      |
|-----------------------|------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NSCLC                 | 0.09%            | 1,111                   | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Salivary              | 1.72%            | 58                      | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Melanoma              | 0.21%            | 476                     | TA630 ERG report; Okamura <i>et al.</i> (2018) (186)                                                                                                                                                                                        |
| Colorectal            | 0.12%            | 833                     | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Appendix              | 4.00%            | 25                      | TA630 ERG report; Amatu <i>et al.</i> (2016) (assumed same as pancreatic) (22)                                                                                                                                                              |
| STS adults (GIST)     | 1.28%            | 78                      | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| STS adults (non-GIST) | 0.56%            | 179                     | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Bone sarcoma          | 1.00%            | 100                     | TA630 ERG report; ERG Assumption                                                                                                                                                                                                            |
| STS paediatrics       | 0.56%            | 179                     | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| IFS                   | 90.90%           | 1                       | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Breast                | 0.07%            | 1429                    | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| Cholangiocarcinoma    | 0.10%            | 1000                    | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| CNS/Glioma            | 0.05%            | 2000                    | TA630 ERG report; larotrectinib FDA submission (185)                                                                                                                                                                                        |
| CNS paediatric        | 5.30%            | 19                      | TA630 ERG report; Okamura <i>et al.</i> (2018) (186)                                                                                                                                                                                        |
| Pancreas              | 0.26%            | 385                     | TA630 ERG report; Okamura <i>et al.</i> (2018) (186)                                                                                                                                                                                        |
| Thyroid               | 4.94%            | 20                      | TA630 ERG report; assumption, weighted average of fusion rates for papillary and generic thyroid tumours in larotrectinib FDA submission (weighted by UK cancer incidence statistics for all thyroid tumours and papillary thyroid tumours) |

CNS= Central Nervous System; ERG= Evidence review group; FDA= Food and Drug Administration; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; NTRK= Neurotrophic tropomyosin receptor kinase; STS= Soft tissue sarcoma

**Table 60. Unit costs of NTRK fusion testing**

| Test                                                             | Unit cost | Source                                                         |
|------------------------------------------------------------------|-----------|----------------------------------------------------------------|
| IHC                                                              | £350      | TA630 ERG report; TA406 (187)                                  |
| NGS panel                                                        | £75*      | TA630 ERG report                                               |
| Expansion of existing RNA-based NGS panel to detect NTRK fusions | £0        | TA630 ERG report                                               |
| WGS via NHS Testing Directory                                    | £0        | TA630 ERG report; assumption, WGS is conducted in all patients |

ERG= Evidence review group; IHC= Immunohistochemistry; NGS= Next-generation sequencing; NHS= National Health Service; WGS= Whole genome sequencing

\*Cost for RNA-based panel for all types of NTRK fusion.

**Table 61. NTRK fusion testing costs by tumour type**

| Tumour location       | Testing strategy | Cost per patient | Tumour type weight |
|-----------------------|------------------|------------------|--------------------|
| NSCLC                 | NGS+             | £0               | ■                  |
| Salivary              | IHC + NGS        | £6,192           | ■                  |
| Melanoma              | WGS + NGS        | £15,000          | ■                  |
| Colorectal            | IHC + NGS        | £88,750          | ■                  |
| Appendix              | IHC + NGS        | £2,663           | ■                  |
| STS adults (GIST)     | WGS + NGS        | £2,461           | ■                  |
| STS adults (non-GIST) | WGS + NGS        | £5,625           | ■                  |
| Bone sarcoma          | WGS + NGS        | £3,150           | ■                  |
| STS paediatrics       | WGS + NGS        | £5,625           | ■                  |
| IFS                   | NGS              | £385             | ■                  |
| Breast                | IHC + NGS        | £152,143         | ■                  |
| Cholangiocarcinoma    | IHC + NGS        | £106,500         | ■                  |
| CNS/Glioma            | IHC + NGS        | £213,000         | ■                  |
| CNS paediatric        | WGS + NGS        | £594             | ■                  |
| Pancreas              | IHC + NGS        | £40,962          | ■                  |
| Thyroid               | IHC + NGS        | £2,156           | ■                  |

CNS= Central Nervous System; ERG= Evidence review group; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; IHC= Immunohistochemistry; NSCLC= Non-small cell lung cancer; NGS= Next-generation sequencing; NGS+= Expansion of existing RNA-based NGS panel to detect NTRK fusions; NHS= National Health Service; STS= Soft tissue sarcoma; WGS= Whole genome sequencing

## 3.6 Severity

Using NICE's recommended methods and severity modifier calculator, the absolute and proportional QALY shortfalls were calculated for each tumour type (188). Starting ages and sex distributions (Table 62) were based on observations from the larotrectinib trials outlined in Section 3.3.1, and utility values (Table 63) were sourced

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from the literature described in Section 3.4.1. Mortality estimates for patients receiving SOC were aligned with the final survival curves used in the naïve literature-based comparator scenario. Details of the survival curves are provided in Appendix M. This scenario was chosen to estimate the severity modifier as it is the closest absolute estimate of QALYs that has been used in previous NICE TAs to determine severity modifiers and end-of-life criteria. However, this could be conservative as patients with NTRK+ fusions have a worse prognosis than patients with NTRK- status (Section 1.3.1). The MAIC used in the base case remains the best option to model the incremental outcomes.

The results of the QALY shortfall analysis are presented in Table 64. Based on NICE's severity modifier criteria, a 1.2x severity modifier was applied across the following indications: NSCLC, salivary gland cancer, melanoma, STS in adults (GIST) and thyroid cancer. A higher 1.7x modifier was applied to colorectal cancer, STS in adults (non-GIST), STS in paediatrics, breast cancer, cholangiocarcinoma, and CNS/glioma tumours.

As the previous assessment of larotrectinib was conducted before the introduction of QALY shortfall considerations, it did not include calculations for a severity modifier (71). However, the former end-of-life criteria were satisfied in TA630, supporting the application of a higher severity multiplier under the current QALY shortfall framework.

**Table 62. Summary features of QALY shortfall analysis**

| Tumour location                                        | Starting age (years) | Percentage female (%) | Reference to section in submission |
|--------------------------------------------------------|----------------------|-----------------------|------------------------------------|
| NSCLC                                                  | ■                    | ■                     | Section 3.3.1, Table 41            |
| Salivary                                               | ■                    | ■                     | Section 3.3.1, Table 41            |
| Melanoma                                               | ■                    | ■                     | Section 3.3.1, Table 41            |
| Colorectal (used as proxy for appendix)                | ■                    | ■                     | Section 3.3.1, Table 41            |
| STS adults (GIST)                                      | ■                    | ■                     | Section 3.3.1, Table 41            |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | ■                    | ■                     | Section 3.3.1, Table 41            |
| STS paediatrics (used as proxy for IFS)                | ■                    | ■                     | Section 3.3.1, Table 41            |
| Breast                                                 | ■                    | ■                     | Section 3.3.1, Table 41            |

| Tumour location    | Starting age (years) | Percentage female (%) | Reference to section in submission |
|--------------------|----------------------|-----------------------|------------------------------------|
| Cholangiocarcinoma | ■                    | ■                     | Section 3.3.1, Table 41            |
| CNS/Glioma         | ■                    | ■                     | Section 3.3.1, Table 41            |
| Pancreas           | ■                    | ■                     | Section 3.3.1, Table 41            |
| Thyroid            | ■                    | ■                     | Section 3.3.1, Table 41            |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma

**Table 63. Summary of health state benefits and utility values for QALY shortfall analysis**

| Tumour location                                        | Utility value for PF health state | Utility value for PD health state | Reference to section in submission |
|--------------------------------------------------------|-----------------------------------|-----------------------------------|------------------------------------|
| NSCLC                                                  | 0.74                              | 0.46                              | Section 3.4.1, Table 49            |
| Salivary                                               | 0.75                              | 0.60                              | Section 3.4.1, Table 49            |
| Melanoma                                               | 0.75                              | 0.69                              | Section 3.4.1, Table 49            |
| Colorectal (used as proxy for appendix)                | 0.73                              | 0.59                              | Section 3.4.1, Table 49            |
| STS adults (GIST)                                      | 0.77                              | 0.65                              | Section 3.4.1, Table 49            |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | 0.65                              | 0.47                              | Section 3.4.1, Table 49            |
| STS paediatrics (used as proxy for IFS)                | 0.68                              | 0.43                              | Section 3.4.1, Table 49            |
| Breast                                                 | 0.71                              | 0.50                              | Section 3.4.1, Table 49            |
| Cholangiocarcinoma                                     | 0.63                              | 0.53                              | Section 3.4.1, Table 49            |
| CNS/Glioma                                             | 0.60                              | 0.60                              | Section 3.4.1, Table 49            |
| Pancreas                                               | 0.67                              | 0.60                              | Section 3.4.1, Table 49            |
| Thyroid                                                | 0.72                              | 0.64                              | Section 3.4.1, Table 49            |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; PD= Progressed disease; PF= Progression-free; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma

**Table 64 Summary of QALY shortfall analysis**

| <b>Tumour location</b>                                 | <b>Expected total QALYs for the general population</b> | <b>Total QALYs that people living with a condition would be expected to have with current treatment</b> | <b>Absolute QALY shortfall</b> | <b>Proportional QALY shortfall</b> | <b>QALY weight</b> |
|--------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------|--------------------|
| NSCLC                                                  | 14.39                                                  | 0.73                                                                                                    | 13.66                          | 94.93%                             | 1.2                |
| Salivary                                               | 14.63                                                  | 0.78                                                                                                    | 13.85                          | 94.67%                             | 1.2                |
| Melanoma                                               | 15.06                                                  | 1.37                                                                                                    | 13.69                          | 90.90%                             | 1.2                |
| Colorectal (used as proxy for appendix)                | 10.32                                                  | 0.48                                                                                                    | 9.84                           | 95.35%                             | 1.7                |
| STS adults (GIST)                                      | 15.56                                                  | 1.4                                                                                                     | 14.16                          | 91.00%                             | 1.2                |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | 18.66                                                  | 0.71                                                                                                    | 17.95                          | 96.19%                             | 1.7                |
| STS paediatrics (used as proxy for IFS)                | 24.30                                                  | 1.43                                                                                                    | 22.87                          | 94.11%                             | 1.7                |
| Breast                                                 | 15.99                                                  | 0.61                                                                                                    | 15.38                          | 96.19%                             | 1.7                |
| Cholangiocarcinoma                                     | 14.43                                                  | 0.41                                                                                                    | 14.02                          | 97.16%                             | 1.7                |
| CNS/Glioma                                             | 22.67                                                  | 0.75                                                                                                    | 21.92                          | 96.69%                             | 1.7                |
| Pancreas                                               | 12.34                                                  | 2.65                                                                                                    | 9.69                           | 78.53%                             | 1.0                |
| Thyroid                                                | 14.42                                                  | 2.37                                                                                                    | 12.05                          | 83.56%                             | 1.2                |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma

QALY shortfalls and modifiers calculated using the QALY shortfall calculator recommended by the NICE DSU (188).

### 3.7 Uncertainty

The cost-effectiveness analysis presented herein is based on longer follow-up and a larger sample size from the ePAS9 and SAS3 datasets, compared to the original submission. The key uncertainties in the clinical and cost-effectiveness of larotrectinib highlighted in TA630 are addressed in this company submission (Section 2.17.2). The data and results presented herein strongly indicate that larotrectinib provides a cost-effective use of NHS resources.

There are two areas of uncertainty in the cost-effectiveness model presented in this company submission:

- Due to the rarity of TRK fusion cancers and the tumour-agnostic indication, the larotrectinib trials (studies 20288, 20289 and 20290) were single-arm studies with no randomised comparator arm. Nevertheless, multiple methods for generating a comparator from the data have been explored (Section 3.3.2), and an extensive set of additional RWE has been collected to generate comparative data, including the MAICs, which are the most robust approach the company could have undertaken to generate comparative effectiveness data (Section 2.10). These analyses are presented in Section 3.3.2. Therefore, this analysis represents an appropriate and robust approach to model the cost-effectiveness of larotrectinib.
- The heterogeneous nature of the tumour locations presents another uncertainty in this analysis. The additional data collected in the ePAS9 and SAS3 datasets have increased the sample size across tumour locations, reducing the uncertainty in survival estimates. Furthermore, these patients have been modelled as separate paediatric and adult cohorts to reflect the difference in age on treatment effect and other clinical outcomes, including exploring curative effects. In addition, as described in Section 3.3.2, a response-based analysis has been conducted to explore the heterogeneity of response.

The uncertainties surrounding the assessment of the cost-effectiveness of larotrectinib in patients with NTRK fusion-positive solid tumours were extensively explored in this

company submission, and the results presented suggest that larotrectinib represents a cost-effective use of NHS resources.

### 3.8 Managed access proposal

Larotrectinib is currently available under the CDF MAA. There is no managed access proposed in this company submission.

### 3.9 Summary of base case analysis inputs

A summary of the base case settings and inputs used within the model are presented in Table 65. A full list of larotrectinib and comparator-specific inputs that inform the base case analysis are further detailed in Appendix M.

**Table 65. Summary of the base case settings and inputs used within the model**

| Variable                           | Setting/Input                                                                                                                                                                                                                                                                                               | Justification                                                                                                                                                                                                                                                            | Detailed section                |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Discount rate - costs and outcomes | 3.50%                                                                                                                                                                                                                                                                                                       | As per NICE reference case                                                                                                                                                                                                                                               | Section 3.2.3                   |
| Time horizon                       | 80 years (Lifetime)                                                                                                                                                                                                                                                                                         | As per NICE reference case                                                                                                                                                                                                                                               | Section 3.2.3                   |
| Cycle length                       | 1 week                                                                                                                                                                                                                                                                                                      | To reflect dosing/administration of treatments                                                                                                                                                                                                                           | Section 3.2.3                   |
| Severity modifier                  | Included by tumour location, calculated using naïve literature-based comparator                                                                                                                                                                                                                             | As per NICE reference case. The naïve literature-based comparator scenario was chosen to estimate the severity modifier as it is the closest absolute estimate of QALYs that has been used in previous NICE TAs to determine severity modifiers and end-of-life criteria | Section 3.4                     |
| Patient characteristics            | Sourced from the larotrectinib clinical trial programme and the literature                                                                                                                                                                                                                                  | To reflect the target population and align with survival inputs                                                                                                                                                                                                          | Section 3.3.1                   |
| Weighting of tumour locations      | Larotrectinib clinical trial programme                                                                                                                                                                                                                                                                      | To reflect the target population and align with survival inputs                                                                                                                                                                                                          | Section 3.3.1                   |
| Larotrectinib OS and PFS           | Survival analysis of ePAS9+SAS3 split by adult and paediatric patients<br>Adult starting population: <ul style="list-style-type: none"> <li>OS: Weibull</li> <li>PFS: Weibull</li> </ul> Paediatric starting population <ul style="list-style-type: none"> <li>OS: Weibull</li> <li>PFS: Weibull</li> </ul> | Stratification by adult and paediatric patients reduces heterogeneity for the survival extrapolations. Curve selection was aligned with statistical criteria, NICE methods, and clinical feedback.                                                                       | Section 3.3.4;<br>Section 3.3.5 |
| SOC OS and PFS                     | MAIC HR applied to larotrectinib survival curves <ul style="list-style-type: none"> <li>Adult starting population: VICTORIA</li> <li>Paediatric starting population: EPI</li> </ul>                                                                                                                         | The MAIC approach minimises bias that results from prognostic or effect-modifying baseline characteristics that are imbalanced across study populations. Using a HR from the MAIC allowed the maturity and large                                                         | Section 3.3.4;<br>Section 3.3.5 |

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| Variable               | Setting/Input                                                                                                                                                                                                                                                              | Justification                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Detailed section |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
|                        | VITRAKVI                                                                                                                                                                                                                                                                   | sample size of the ePAS9 and SAS3 datasets to be leveraged.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                  |
| TTD                    | Larotrectinib: treat to progression<br>SOC: treat to progression with stopping rules as per comparator treatment                                                                                                                                                           | Observed TTD and PFS from the ePAS9 and SAS3 datasets were similar, and this was confirmed by clinical feedback. To avoid bias, this assumption was applied to SOC where no TTD was available.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Section 3.3.6    |
| Treatment waning       | No waning of the treatment effect                                                                                                                                                                                                                                          | This was assumed given the maturity of the data in the VICTORIA MAIC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Section 3.3.3    |
| Price of larotrectinib | Expected price of [REDACTED] for 5,600 mg pack (100mg tablets x 56)<br>Other packs/vials priced at same cost per mg                                                                                                                                                        | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Section 3.5.1    |
| Larotrectinib dosing   | Larotrectinib: <ul style="list-style-type: none"> <li>Adults: 191.72 mg per day</li> <li>Paediatric: 134.48 mg per day</li> </ul>                                                                                                                                          | To reflect real-world dosing of larotrectinib.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Section 3.5.1    |
| Costs                  | <p>Excluding cost of drug wastage</p> <p>No testing costs included</p> <p>Health state costs</p> <ul style="list-style-type: none"> <li>Larotrectinib: average of SOC tumour location inputs</li> <li>SOC: costs reported in the literature per tumour location</li> </ul> | <p>Drug cost wastage was excluded for both larotrectinib and SOC to avoid bias of additional drug cost for one treatment versus another as per the costing methodology in the previous larotrectinib appraisal.</p> <p>Testing costs were not included as genomic testing at diagnosis is increasingly integrated into routine care to guide optimal treatment and uncover actionable targets across a broad range of genes, with NTRK fusions representing only a small subset. NTRK gene fusion testing capability already exists within the NHS infrastructure and is expanding according to plans by the NHS England's Genomic Medicine Service, which commits to offering genomic testing to all cancer patients as part of routine care. Furthermore, the National Genomic Test Directory specifies that NTRK testing is commissioned by the NHS. Genomics England also supports the integration of genomic data into clinical decision-making to enable personalised and predictive healthcare. Therefore, the requirement for NTRK testing reflects the evolution of precision oncology in the NHS rather than a wholly new or exceptional resource need specific to this indication. Testing costs are included in scenario analysis.</p> <p>Health state costs for larotrectinib were assumed equal to the average of SOC tumour location inputs as a conservative assumption in the</p> | Section 3.5      |

| Variable  | Setting/Input                                                                                                                                                                                                                               | Justification                                                                                                                                                                                                                             | Detailed section |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
|           |                                                                                                                                                                                                                                             | absence of healthcare resource use data that was applied in the previous appraisal of larotrectinib.                                                                                                                                      |                  |
| Utilities | Larotrectinib: Mixed Model Repeated Measures analysis of EQ-5D-3L utility values from larotrectinib trials (PF: 0.77 (95% CI: 0.75, 0.80); PD: 0.74 (95% CI: 0.72, 0.75)).<br>SOC: Utilities reported in the literature per tumour location | Larotrectinib trial data reflects the target population and uses the large sample size of ePAS9 and SAS3 datasets. SOC utility was sourced from the literature as no utilities were obtained for comparators in the larotrectinib trials. | Section 3.4      |

CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; SOC = standard of care; TTD = time to treatment discontinuation

### 3.10 Base case results (deterministic)

Larotrectinib was associated with a gain in LYs of 5.005 and QALYs of 3.962 compared to SOC (7.779 vs. 2.774 for LYs, 5.626 vs. 1.663 for QALYs). After applying the QALY severity modifiers calculated in section 3.6, this translated into an additional 6.324 QALYs (8.936 vs. 2.612). The severity modifier is included in all QALYs and ICERs reported in this company submission unless specified otherwise. Total costs in the base case were higher with larotrectinib versus SOC (£[REDACTED] vs. £[REDACTED]), resulting in an incremental cost of £[REDACTED].

The incremental results for costs and health effects indicate that at the expected PAS price, larotrectinib was associated with a cost per QALY of £[REDACTED]. Detailed results are presented in Table 66.

**Table 66. Base case cost-effectiveness results (deterministic)**

| Source of results                                  | Larotrectinib | SOC          | Incremental  |
|----------------------------------------------------|---------------|--------------|--------------|
| Progression-free survival (£)                      | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| Progressed disease (£)                             | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| Death (£)                                          | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| Adverse event (£)                                  | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| Treatment cost (£)                                 | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| Testing cost (£)                                   | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| <b>Total costs (£)</b>                             | [REDACTED]    | [REDACTED]   | [REDACTED]   |
| <b>Total life years</b>                            | <b>7.779</b>  | <b>2.774</b> | <b>5.005</b> |
| Progression-free QALYs without severity modifier   | 2.695         | 1.030        | 1.665        |
| Progressed disease QALYs without severity modifier | 2.949         | 0.696        | 2.253        |

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| Source of results                              | Larotrectinib | SOC          | Incremental  |
|------------------------------------------------|---------------|--------------|--------------|
| Adverse events QALYs without severity modifier | -0.018        | -0.063       | 0.045        |
| <b>Total QALYs without severity modifier</b>   | <b>5.626</b>  | <b>1.663</b> | <b>3.962</b> |
| Progression-free QALYs                         | 4.213         | 1.689        | 2.525        |
| Progressed disease QALYs                       | 4.751         | 1.028        | 3.723        |
| Adverse events QALYs                           | -0.028        | -0.104       | 0.077        |
| <b>Total QALYs with severity modifier</b>      | <b>8.936</b>  | <b>2.612</b> | <b>6.324</b> |
| <b>ICER (£/QALY)</b>                           |               |              |              |

ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life years; SOC= standard of care

## 3.11 Exploring uncertainty

### 3.11.1 Deterministic sensitivity analysis (DSA)

In order to assess the most influential parameters and uncertainty around the cost-effectiveness of larotrectinib, the model includes DSA, whereby parameters are iteratively varied. The results of the DSA are presented using a tornado diagram. The parameters varied in the DSA are summarised in Appendix L. The parameters were varied either using their standard error/reported upper and lower ranges, or by 20% from the mean value.

The results of the DSA show that the cost-effectiveness of larotrectinib is sensitive to the OS HRs but relatively stable for other key parameters. The cost-effectiveness of larotrectinib was most sensitive to the MAIC HR for OS in paediatric patients, driven by the parameters wide CIs due to the immaturity of OS data in EPI-VITRKVI. This has an impact on the accumulation of post progression QALYs for SOC paediatric patients, as well as treatment costs, since the time on treatment is bounded by the OS curve. The OS MAIC HR for adults was also influential for similar reasons but had less of an effect due to the reduced QALYs accrued for an older cohort. Similarly, STS paediatric progression-free utility was relatively influential due to the time in the progression-free health state. PFS HR parameters were less influential but had an impact mainly through additional time on SOC treatment, hence higher treatment costs and lower incremental costs when compared to the larotrectinib arm.

The top five parameters that the ICER was most sensitive to are presented in Table 67 and the tornado diagram in Figure 30.

**Table 67. Deterministic sensitivity analysis**

| Variable                                   | Lower bound<br>ICER* | Upper bound<br>ICER* |
|--------------------------------------------|----------------------|----------------------|
| Base case (deterministic)                  |                      |                      |
| MAIC paediatrics - OS HR                   |                      |                      |
| MAIC adults - OS HR                        |                      |                      |
| STS paediatrics - progression-free utility |                      |                      |
| MAIC adults - PFS HR                       |                      |                      |
| MAIC paediatrics - PFS HR                  |                      |                      |

HR = hazard ratio; ICER= incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; STS = soft tissue sarcoma.  
\* The ICERs include the severity modifier adjustment

**Figure 30. Deterministic sensitivity analysis – tornado diagram**



HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; STS = soft tissue sarcoma.

**3.11.2 Probabilistic sensitivity analysis (PSA)**

Probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model. The uncertainties in the individual parameters for

treatment effect, costs, and utilities were characterised using probability distributions and analysed using a Monte Carlo simulation using 1,000 simulations, which were deemed sufficient to produce convergence in the PSA results.

The following groups of parameter values were included in the PSA:

- Parametric survival models and MAIC HRs
- Adverse event costs, disutilities
- Health state costs, utilities

Appendix L presents the specific parameters varied in the PSA. Parametric survival models were varied using a multivariate normal distribution, and HRs were varied using a lognormal distribution. Disutilities and health state costs were varied using a gamma distribution. Utilities were varied using a Beta distribution (189).

The probabilistic results (Table 68) are similar to those presented in the base case analysis (Table 66), providing confidence in the results. The cost-effectiveness plane is presented in Figure 31. The clustering of results demonstrates relatively low variation in both costs and QALYs, with all iterations positioned in the north-east quadrant of the cost-effectiveness plane (i.e., larotrectinib has higher costs but also higher QALYs than SOC).

**Table 68. Base case cost-effectiveness results (probabilistic, severity modifier)**

| Source of results             | Larotrectinib | SOC   | Incremental |
|-------------------------------|---------------|-------|-------------|
| Progression-free survival (£) | ■■■■          | ■■■■  | ■■■■        |
| Progressed disease (£)        | ■■■■■         | ■■■■■ | ■■■■■       |
| Death (£)                     | ■■■■          | ■■■■  | ■■■■        |
| Adverse event (£)             | ■■■           | ■■■   | ■■■         |
| Treatment cost (£)            | ■■■■■         | ■■■■■ | ■■■■■       |
| Testing cost (£)              | ■             | ■     | ■           |
| <b>Total costs (£)</b>        | ■■■■■         | ■■■■■ | ■■■■■       |
| <b>Total life years</b>       | ■■■■          | ■■■■  | ■■■■        |
| Progression-free QALYs*       | ■■■■          | ■■■■  | ■■■■        |
| Progressed disease QALYs*     | ■■■■          | ■■■■  | ■■■■        |
| Adverse events QALYs*         | ■■■■■         | ■■■■■ | ■■■■■       |
| <b>Total QALYs*</b>           | ■■■■■         | ■■■■■ | ■■■■■       |

| Source of results | Larotrectinib | SOC | Incremental |
|-------------------|---------------|-----|-------------|
| ICER (£/QALY)*    |               |     | ██████      |

ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life years; SOC= standard of care

\* The QALYs and ICER include the severity modifier adjustment

**Figure 31. Cost-effectiveness plane (severity modifier)**



PSA= Probabilistic sensitivity analysis; QALYs= quality-adjusted life years

At the expected Patient Access Scheme price, the probability of larotrectinib being cost-effective at £30,000 per QALY is █████%, with an 80% probability at a willingness-to-pay of approximately £████ per QALY. The probability of cost-effectiveness at different willingness-to-pay thresholds is presented in the cost-effectiveness acceptability curve (CEAC) in Figure 32.

Figure 32. Larotrectinib CEAC (severity modifier)



3.11.3 Scenario analysis

Several scenario analyses presented in Table 69 were conducted to test structural and input assumptions in the model. The results, shown in Table 70, indicate that the ICER remains relatively consistent across the tested scenarios, with variances in the range of [redacted] to [redacted]. This consistency supports confidence in the robustness of the findings, even when alternative data sources are applied.

Table 69. Scenarios inputs compared to base case

| No. | Scenario    | Base case input                               | Scenario input                                                                                   | Justification                                                                                           |
|-----|-------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| 1.1 | MAIC source | Adults: VICTORIA<br>Paediatrics: EPI-VITRAKVI | Adults: VICTORIA (106)<br>Paediatrics: VICTORIA (106)                                            | Investigate the uncertainty in the estimation of OS and PFS in SOC by using alternative MAIC HR sources |
| 1.2 |             |                                               | OS: HMF (103)<br>PFS: applying the relative difference in larotrectinib OS and PFS to the SOC OS |                                                                                                         |
| 1.3 |             |                                               | OS: Flatiron (104)                                                                               |                                                                                                         |

| No. | Scenario                                               | Base case input                                            | Scenario input                                                                                                                                  | Justification                                                                                                                                           |
|-----|--------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |                                                        |                                                            | PFS: applying the relative difference in larotrectinib OS and PFS to the SOC OS                                                                 |                                                                                                                                                         |
| 2.1 | Modelling approach (responder/non-responder analysis)  | MAIC                                                       | Responder/non-responder analysis<br>Weight for responder curve for larotrectinib:100%                                                           | Test the impact of alternative modelling approaches to generating a comparator using the responder/non-responder analysis with different response rates |
| 2.2 |                                                        |                                                            | Responder/non-responder analysis<br>Weight for responder curve for larotrectinib: █████% using BHM excluding tumour locations with < 5 patients |                                                                                                                                                         |
| 2.3 |                                                        |                                                            | Responder/non-responder analysis<br>Weight for responder curve for larotrectinib: █████% using BHM excluding tumour locations with < 2 patients |                                                                                                                                                         |
| 2.4 |                                                        |                                                            | Responder/non-responder analysis<br>Weight for responder curve for larotrectinib: █████% using BHM for all patients in ePAS9 and SAS3 datasets  |                                                                                                                                                         |
| 3   | Modelling approach (intra-patient comparison)          | MAIC                                                       | Intra-patient comparison<br>SOC OS: applying the relative difference between larotrectinib OS and PFS curves to the SOC PFS                     | Test the impact of alternative modelling approaches to generating a comparator using the intra-patient comparison (GMI)                                 |
| 4.1 | Modelling approach (naïve-literature based comparator) | MAIC                                                       | Naïve literature-based comparator<br>Adjustment for NTRK+ fusions: No                                                                           | Test the impact of alternative modelling approaches to generating a comparator using the naïve literature based comparator                              |
| 4.2 |                                                        |                                                            | Naïve literature-based comparator<br>Adjustment for NTRK+ fusions: Yes, using VOYAGER 1                                                         |                                                                                                                                                         |
| 4.3 |                                                        |                                                            | Naïve literature-based comparator<br>Adjustment for NTRK+ fusions: Yes, using VOYAGER 2                                                         |                                                                                                                                                         |
| 5.1 | Modelling approach (mixture cure modelling)            | No cure modelling                                          | Using a cure model for paediatric patients with continued treatment with larotrectinib in the progression-free cure health state                | To explore the possible curative potential of larotrectinib in paediatric patients                                                                      |
| 5.2 |                                                        |                                                            | Using a cure model for paediatric patients with larotrectinib treatment discontinuation after 10 years                                          |                                                                                                                                                         |
| 6.1 | Treatment waning                                       | No treatment waning                                        | Immediate waning after the end of the KM data to a treatment effect of 0                                                                        | Explore the impact of waning the treatment effect (MAIC HR)                                                                                             |
| 6.2 |                                                        |                                                            | Treatment waning over the entire time horizon                                                                                                   |                                                                                                                                                         |
| 7   | PD utility source                                      | Larotrectinib PD utility: utility from larotrectinib trial | Larotrectinib PD: weighted average of literature utility<br>SOC PD: weighted average of literature utility                                      | Investigate the effect of assuming equal post-progression utilities.                                                                                    |



| No.  | Scenario                 | Base case input                                             | Scenario input                               | Justification                                                                                                                        |
|------|--------------------------|-------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
|      |                          | SOC PD: literature utility specific to each tumour location |                                              |                                                                                                                                      |
| 8    | NTRK testing cost        | No costs of NTRK fusion testing included                    | Costs of NTRK fusion testing included        | Explore the impact of testing cost inclusion                                                                                         |
| 9    | Stratification of cohort | Split by adults and paediatrics                             | Mixed adults and paediatrics                 | Investigate the impact of the heterogeneity of the patient population by combining adults and paediatrics into a mixed cohort        |
| 10   | Trial cohort dataset     | ePAS9 + SAS3                                                | ePAS2 + SAS3                                 | Explore the impact of using more mature data for the cohort used in the previous appraisal of larotrectinib in the survival analysis |
| 11.1 | Discount rates           | 3.5% for costs and outcomes                                 | 0% discount rate for both costs and outcomes | Explore the effect of discounting on cost-effectiveness                                                                              |
| 11.2 |                          |                                                             | 6% discount rate for both costs and outcomes |                                                                                                                                      |
| 12.1 | Time horizon             | 80 years (lifetime)                                         | 20-year horizon                              | Explore the effect of the time horizon on the cost-effectiveness                                                                     |
| 12.2 |                          |                                                             | 40-year horizon                              |                                                                                                                                      |

BHM = Bayesian Hierarchical Model; ePAS9 = extended primary analysis set 9; GMI = growth modulation index; HMF = Hartwig Medical Foundation; HR = hazard ratio; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NTRK = neurotrophic tyrosine receptor kinase; OS = overall survival; PD = progressive disease; PFS = progression-free survival; QALYs = quality-adjusted life years; SAS3 = statistical analysis system 3; SOC = standard of care

**Table 70. Scenario analyses results (deterministic)**

| No.  | Scenario                                                                                                                              | Inc. costs (£) | Inc. QALYs* | ICER (£/QALY)* | Change from base case ICER* |
|------|---------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------|----------------|-----------------------------|
|      | Base case (deterministic)                                                                                                             | ██████         | ██████      | ██████         |                             |
| 1.1  | MAIC source: VICTORIA for paediatric patients                                                                                         | ██████         | ██████      | ██████         | ██████                      |
| 1.2  | MAIC source: HMF (Bokemeyer 2024)                                                                                                     | ██████         | ██████      | ██████         | ██████                      |
| 1.3  | MAIC source: Flatiron (Bokemeyer 2023)                                                                                                | ██████         | ██████      | ██████         | ██████                      |
| 2.1  | Modelling approach (responder/non-responder; 100% responders in larotrectinib)                                                        | ██████         | ██████      | ██████         | ██████                      |
| 2.2  | Modelling approach (responder/non-responder BHM ORR excluding tumour locations with < 5 patients; 65.2% responders in larotrectinib)  | ██████         | ██████      | ██████         | ██████                      |
| 2.3  | Modelling approach (responder/non-responder; BHM ORR excluding tumour locations with < 2 patients; 55.2% responders in larotrectinib) | ██████         | ██████      | ██████         | ██████                      |
| 2.4  | Modelling approach (responder/non-responder; BHM ORR all ePAS9+SAS3; 47.0% responders in larotrectinib)                               | ██████         | ██████      | ██████         | ██████                      |
| 3    | Modelling approach (Intra-patient comparison)                                                                                         | ██████         | ██████      | ██████         | ██████                      |
| 4.1  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: No)                                              | ██████         | ██████      | ██████         | ██████                      |
| 4.2  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: Yes, using VOYAGER 1)                            | ██████         | ██████      | ██████         | ██████                      |
| 4.3  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: Yes, using VOYAGER 2)                            | ██████         | ██████      | ██████         | ██████                      |
| 5.1  | Modelling approach (mixture cure modelling with no restriction on treatment duration)                                                 | ██████         | ██████      | ██████         | ██████                      |
| 5.2  | Modelling approach (mixture cure modelling with a stopping rule for cured patients)                                                   | ██████         | ██████      | ██████         | ██████                      |
| 6.1  | Treatment waning (Immediate treatment waning)                                                                                         | ██████         | ██████      | ██████         | ██████                      |
| 6.2  | Treatment waning (Waning over entire time horizon)                                                                                    | ██████         | ██████      | ██████         | ██████                      |
| 7    | PD utility (weighted average of literature utility)                                                                                   | ██████         | ██████      | ██████         | ██████                      |
| 8    | NTRK testing costs (included)                                                                                                         | ██████         | ██████      | ██████         | ██████                      |
| 9    | Stratification of cohort (mixed adults and paediatrics)                                                                               | ██████         | ██████      | ██████         | ██████                      |
| 10   | Trial cohort dataset (ePAS2 + SAS3)                                                                                                   | ██████         | ██████      | ██████         | ██████                      |
| 11.1 | Discount rates (0% discount rate)                                                                                                     | ██████         | ██████      | ██████         | ██████                      |
| 11.2 | Discount rates (6% discount rate)                                                                                                     | ██████         | ██████      | ██████         | ██████                      |
| 12.1 | Time horizon (20-year horizon)                                                                                                        | ██████         | ██████      | ██████         | ██████                      |
| 12.2 | Time horizon (40-year horizon)                                                                                                        | ██████         | ██████      | ██████         | ██████                      |

BHM = Bayesian Hierarchical Model; HMF = Hartwig Medical Foundation; ICER = incremental cost-effectiveness ratio; MAIC = Matching-Adjusted Indirect Comparison; NTRK = Neurotrophic Tyrosine Receptor Kinase; ORR = Objective Response Rate; PD = Progressive Disease; QALYs = quality-adjusted life years; SOC = standard of care  
 \* The QALYs and ICER include the severity modifier adjustment

### **3.12 Subgroup analysis**

Not applicable given histology-independent nature of the intervention and no identifiable subgroups.

### **3.13 Benefits not captured in the QALY calculation**

The QALY calculation captures the majority of benefits directly related to the patient, such as delayed progression, extension of life and improved quality-of-life. However, it can overlook some emotional and psychological benefits described in Section 2.15, such as reduced anxiety and a sense of hope.

Larotrectinib's oral administration constitutes a strong advantage over injectable treatments, as evidence suggests that oncology patients prefer oral treatment over IV for various reasons, including the absence of pain from needles, the possibility of working during the treatment, and the autonomy it provides to patients (190). The risk of serious complications, including fatal outcomes, associated with chemotherapy administration are also important considerations.

In their review, Eek *et al.* (2016) (191) found that cancer patients also reported a general preference for the convenience of treatment intake. Indeed, outpatient management of larotrectinib reduces the logistical and emotional burden of treatment, which may result in lower caregiver burden - particularly important in paediatric populations, where parents or family members are heavily involved in managing hospital visits, toxicities, and supportive care, as described in Section 2.15. The reduction in caregiver time, stress, and potential income loss is not captured within the QALY framework but represents a meaningful health and societal benefit.

For paediatric patients specifically, avoiding intensive chemotherapy or radiotherapy may also reduce the risk of late effects on growth, cognitive development, and long-term organ function, with implications for lifetime health outcomes not fully captured within the model. In 2016, a meta-analysis of the neuropsychological effects of chemotherapy in the treatment of childhood cancer demonstrated deficits in attentional capacity among children with cancer who received chemotherapy (192).

Disutility caused by mutilating surgery can partially be captured in QALYs, but the impact of its avoidance is likely not, especially the impact on future productivity gains in adulthood.

Treatment with larotrectinib has been shown to extend a patient's lifespan, which may provide a bridge to a future or alternative effective therapy, thereby offering additional value beyond its immediate clinical benefit. These additional elements of value are potentially sizeable and are not captured in the QALY calculation (193). As a result, the base case ICER is a conservative estimate of the cost-effectiveness of larotrectinib (193).

## **3.14 Validation**

### **3.14.1 Validation of cost-effectiveness analysis**

The model was developed in line with best modelling practices (194) and in alignment with NICE preferred methods. It aligns with the NICE reference case (167). An advisory board reviewed the model, offering feedback, which informed the model development (118). This advisory board, consisting of UK oncologists, covered the following topics:

- Treatment pathway including testing practices
- Population generalisability from the trial to NHS patients
- CDF criteria for use of larotrectinib
- Patient response with larotrectinib and the value of stable disease
- Comparators
- Treatment discontinuation in real-world settings
- Curative potential for paediatric patients and the effect and use of mutilating surgery
- Utility and HRQoL
- Survival extrapolations

Importantly, the model forming part of this submission was adapted from the model used in TA630 which has previously been extensively reviewed by the EAG (71).

The model outcomes were validated with the RWE outcomes (section 2.10 and 2.13). As the ePAS9 and SAS3 datasets had the longest follow-up for patients treated with larotrectinib, it was not possible to compare extrapolated survival to a reported landmark survival in the literature. Instead, clinical feedback was prioritised. The SOC arm generated in the model was compared with the RWE data for SOC reported in the MAICs. In the EPI-VITRAKVI study, the median OS was not reached and the median PFS has high uncertainty (105). Similarly, the median OS in the VICTORIA study has a wide CI as only six patients are at risk at 36 months (106). It is difficult to compare median estimates directly due to the low sample size in the RWE and differences in population characteristics. Furthermore, as larotrectinib is tumour-agnostic, heterogeneity between studies is to be expected. The SOC median OS and PFS estimates are not statistically different from the RWE given the overlapping CIs, supporting its external validity. A comparison of medians for OS and PFS are shown in Table 71.

**Table 71. Comparison of median OS and PFS with RWE for SOC**

|                                        | Median OS (months),<br>(95% CI) | Median PFS (months),<br>(95% CI) |
|----------------------------------------|---------------------------------|----------------------------------|
| <b>Adult populations</b>               |                                 |                                  |
| SOC from model base case (adults)      | 15.9 (7.1; 35.0)                | 3.0 (1.6; 5.7)                   |
| VICTORIA (106)                         | 37.2 (12.5; NE)                 | 5.2 (3.5; 6.8)                   |
| HMF (103)                              | 13.0 (6.4; 18.3)                | NA                               |
| Flatiron (104)                         | 10.2 (7.2; 14.1)                | NA                               |
| <b>Paediatric populations</b>          |                                 |                                  |
| SOC from model base case (paediatrics) | 37.7 (2.3; 799.4)               | 36.1 (2.3; 80.2)                 |
| EPI VITRAKVI (105)                     | Not reached                     | 16 (16; NE)                      |

CI = confidence interval; HMF = Hartwig Medical Foundation; NA = not applicable; NE = not estimable; OS = overall survival; PFS = progression-free survival; SOC = standard of care

In addition, following the finalisation of the model, a full quality control assessment was conducted. This included a review of all calculations and inputs used in the model by independent internal and external third-party health economic modellers. The internal review followed a technical checklist (Appendix R), based on TECH-VER (195). This guided the reviewer in the examination of formulae, equations, cross-checking of inputs (clinical, resource use, utility), Visual Basic for Applications (VBA) coding, and

face validity of results. Stress tests were also conducted to ensure that the results returned were robust to extreme values.

### **3.15 Interpretation and conclusions of economic evidence**

The clinical and health economic evidence presented in this submission seeks to address the uncertainties outlined in Table 72 that were highlighted in the original submission (TA630) (71). Most notably, the evidence generated since larotrectinib's entry into the CDF includes extended follow-up data from the clinical trials (i.e., ePAS9 and SAS3 datasets, data cut-off 20<sup>th</sup> July 2024). Not only do the recent datasets from the trials address uncertainties caused by limited follow-up at the time of the original submission, but they also include a substantially larger sample size due to the open enrolment during this time and inclusion of a study population reflecting broader tumour type representation.

To complement the recent data cut-offs of the larotrectinib trials, a number of RWE studies were conducted in the meantime to generate evidence for the outcomes of patients with NTRK fusion-positive solid tumours treated with larotrectinib or SOC. Larotrectinib was compared with active comparator treatments versus end-of-line (best supportive care) comparators in the original appraisal of larotrectinib. These comparators of interest reflect the proposed positioning of larotrectinib. This positioning is supported by RWE, and SACT data (Section 2.13.2), where 78% of patients received larotrectinib as a 2L therapy.

Combining the recent clinical trial datasets and comparative effectiveness evidence for the SOC in this patient population, the revised economic assessment described above maintains the conclusion that larotrectinib is a life-extending, cost-effective treatment option for patients with NTRK fusion-positive solid tumours, supporting its continued availability to NHS England patients beyond the CDF.

**Table 72. Key uncertainties addressed in this Company submission**

| Key uncertainties in TA630                                    | Details of how this Company submission addresses the uncertainties                                                                                                                                                                                                     |
|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Short follow-up in the larotrectinib trials                   | Data cut-off 20 <sup>th</sup> July 2024, median follow-up of [REDACTED] months (vs [REDACTED] months in the original submission)                                                                                                                                       |
| Small sample size                                             | [REDACTED] patients (vs [REDACTED] in the original submission)                                                                                                                                                                                                         |
| Limited patients with CNS tumours                             | [REDACTED] patients (vs [REDACTED] in the original submission)                                                                                                                                                                                                         |
| Limited tumour type representation                            | 28 tumour types (vs [REDACTED] in the original submission), with larger sample size in all tumour types that were presented in the original submission                                                                                                                 |
| Immature survival data                                        | 72-month OS rate of [REDACTED] % in ePAS9, [REDACTED] % in SAS3                                                                                                                                                                                                        |
| Heterogeneity of response between tumour types                | Bayesian hierarchical model developed by the Company as a scenario analysis in the cost-effectiveness model demonstrated instability and was found to be unsuitable for exploring heterogeneity                                                                        |
| Unclear impact of NTRK gene fusions on cancer prognosis       | Real-world data from VOYAGER 1 and 2 reported a higher risk of death for patients with NTRK gene fusion versus patients without NTRK gene fusion                                                                                                                       |
| Lack of comparative effectiveness data                        | Multiple indirect treatment comparisons versus real-world standard of care therapies consistently demonstrated the robust effectiveness and safety of larotrectinib                                                                                                    |
| Unclear positioning of larotrectinib in the treatment pathway | Availability of real-world data (i.e., SACT, ON-TRK) showing that larotrectinib is used in earlier lines of therapy in practice, aligned with its proposed positioning                                                                                                 |
| Generalisability of larotrectinib trial population to the NHS | Similar patient characteristics (e.g., age, tumour types, performance status) between larotrectinib trials and SACT. Key outcomes are broadly aligned and supportive of those reported in the larotrectinib trials (i.e., ORR, OS)                                     |
| Modelling cure                                                | Scenario analyses performed using a mixture cure model to investigate a cure assumption, as treatment with larotrectinib may provide a curative option for paediatric patients                                                                                         |
| Inclusion of NTRK gene fusion testing in the model            | A conservative scenario was conducted that included testing costs for larotrectinib                                                                                                                                                                                    |
| Treatment post progression                                    | Clinical feedback was sought from an advisory board, which advised that treatment would be given until progression in practice. This aligns with a comparison of the TTD and PFS data, utilising the increased sample size and follow-up from the larotrectinib trials |

EAG = Evidence assessment group; ePAS = Extended primary analysis set; NHS = National Health Service; NTRK = Neurotrophic tropomyosin receptor kinase; OS = Overall survival; ORR = Overall response rate; PFS = Progression-free survival; SACT = Systematic Anti-Cancer Therapy; SAS = supplementary analysis set; TTD = Time-to-treatment discontinuation

Consistent with the original submission, the model employs an established and validated PSM structure, with key clinical inputs validated through a clinician advisory board. To address the uncertainty around comparative effectiveness versus the SOC in this patient population, a number of data sources were generated during the period of CDF access to larotrectinib. Being the most robust source available, MAIC methodology comparing larotrectinib to a real-world SOC comparator was applied in the base case. The VICTORIA and EPI VITRAKVI studies were selected for the base case MAIC due to the availability of both OS and PFS data for both adult and paediatric

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patients. Although EPI VITRAKVI includes only patients with IFS, its inclusion was justified based on its relevance to the paediatric group within the broader NTRK fusion-positive population and relaxing the assumptions of the base case MAIC source was not found to alter the conclusions, with larotrectinib remaining cost-effective. The MAIC OS HRs were key drivers of the model; thus, investigating the uncertainty by exploring further scenarios using other MAICs (Scenario 1.2 to 1.3) (HMF (103); Flatiron (104)), remained consistent with the base case cost-effectiveness conclusion for larotrectinib, despite requiring conservative assumptions due to the lack of PFS data.

At the request of the EAG, methods to inform comparative effectiveness that were presented in the previous submission were explored as additional scenarios, despite having greater limitations due to the reliance on very strong assumptions. To inform the responder/non-responder analysis submitted originally, a BHM analysis was conducted as an attempt to adjust for the heterogeneity of the ORR that may be caused by tumour location. However, the ORR generated from the BHM varied significantly depending on the tumour locations included in the model, suggesting instability in a BHM analysis-informed responder/non-responder analysis. Most notably, when patients from all tumour locations were included, the ORR was █%; however, excluding tumour locations with a sample size < 2 █ the ORR to █%. Furthermore, when using a larger sample size threshold of excluding tumour types with fewer than 5 patients, the ORR █ to █%. Such a wide range in results reveals sensitivity and instability of the BHM to its underlying assumptions; it is unclear why this would be preferred over the larotrectinib trials' ORR, which are based on observed outcomes from actual patients, with no requirement for assumptions. Regardless, results of the responder/non-responder analysis showed little difference between ORR scenarios (Scenario 2.2 to 2.4). While the responder/non-responder analysis (Scenario 2.1 to 2.4) was less cost-effective than the base case, this approach ignores the benefit of stable disease in a locally advanced or metastatic population generated from larotrectinib, an impact considered valuable by clinicians (118). Furthermore, the analysis assumes that non-responders are representative of patients who do not receive larotrectinib, potentially underestimating the benefit of larotrectinib. The company further believes that the responder/ non-responder



analysis should be disregarded on account of the additional robust sources of comparative effectiveness as applied in the provided MAICs.

The intra-patient comparison (Scenario 3) was also updated since the original submission, using the most recent data set from the larotrectinib trial, which was also shown to be consistent with the base case. The company similarly believes that this analysis is limited due to the lack of an OS estimate for SOC and that it disregards part the whole dataset, as it relies on the subset of trial patients with a prior PFS event.

Finally, the naïve literature-based comparator originally submitted was also updated. This data source is also marked by important methodological limitations as it does not control for NTRK gene fusion status. Nonetheless, this scenario generated an improvement to the cost-effectiveness of larotrectinib (Scenario 4.1). Further attempts to adjust the naïve literature-based comparator to consider the difference in OS between NTRK+ versus NTRK- generated an even more cost-effective ICER (Scenario 4.2 to 4.3).

Regardless of comparative effectiveness source, the conclusions for cost-effectiveness remained consistent across the base case and scenarios (i.e., £[REDACTED] per QALY to £[REDACTED] per QALY). Larotrectinib consistently showed QALY gains over SOC but was associated with a higher total cost, mainly driven by its longer TTD and higher drug acquisition costs per cycle combined with the additional disease management costs from delayed progression and extended survival.

The cost-effectiveness results are sensitive to a few key inputs. Unsurprisingly, the analysis is sensitive to the utility estimates (Scenario 7), as was the case in the original submission (71). The updated analysis for larotrectinib-specific utilities presented in this submission, however, is based on a larger dataset that includes longer follow-up and additional patients reporting EQ-5D and PedsQL scores, resulting in more certain health state utility estimates than those used in the original submission, given the very narrow CIs (Section 3.4). Also consistent with the original submission, the inclusion of NTRK fusion testing costs resulted in a large increase in the ICER (Scenario 8). However, this represents an extreme scenario where NTRK fusion testing is entirely associated with the availability of larotrectinib. This is counterintuitive given that NTRK

fusions are not the only biomarkers included in gene testing panels and the NHS England's goal to expand access to genetic testing to support treatment decision making in oncology along the treatment pathway (132, 181).

Modelling the cohort as a combined mix of adults and paediatrics was explored to investigate the heterogeneity with respect to age (Scenario 9). A combined cohort was not able to accurately reflect the change in hazards for the survival extrapolations compared to the base case approach of stratifying survival by adults and paediatrics. Consequently, leveraging some of the RWE data sources that only had aggregate data available (e.g., SACT data) for survival extrapolations would have been limiting. The aggregate outcomes from the SACT data did align with the larotrectinib trials and so the use of the trial data seems valid and representative of the NHS setting.

A cure model was explored for paediatric patients to explore the potential of a cure effect, given the high response observed in paediatric patients (Scenario 5.1 to 5.2). While this scenario relies on strong assumptions, it demonstrates the additional potential value of larotrectinib.

Challenges remain in translating clinical benefit into equitable access under the current CDF criteria. Specifically, the restriction on treatment breaks, where larotrectinib cannot be restarted after a gap exceeding six weeks, may not reflect the clinical realities of managing patients with rare and complex cancers and could be a reason for clinicians' hesitancy to prescribe larotrectinib. The model may overestimate treatment costs with larotrectinib, as it does not account for any interruptions in treatment.

Additionally, the subjective interpretation of the phrase "no satisfactory treatment options" within the indication can lead to inconsistent application across treatment centres, potentially resulting in inequities in access. These limitations are particularly concerning given the high unmet need in this patient population, as demonstrated by the high severity modifier and the many patients who have exhausted standard therapies or face disfiguring surgical options such as amputation. Addressing these barriers is essential to ensure that patients who could benefit from larotrectinib are not excluded due to administrative constraints

In conclusion, the clinical and health economic evidence presented in this company submission demonstrates that larotrectinib offers substantial benefits in terms of clinical and patient-reported outcomes. It is further found to be a cost-effective use of NHS England's resources, as it has consistently shown to be cost-effective versus SOC across a range of sources informing comparative effectiveness and altered assumptions. Larotrectinib's availability to NHS England patients should also be maintained irrespective of prior treatments received, as the evidence generated during its availability through the CDF demonstrates greater clinical and patient benefits with earlier access. The evidence submitted here supports the mandate that NICE and NHS England do everything possible to remove barriers and facilitate access to larotrectinib, allowing all eligible patients to receive the benefits it offers. This aligns with NHS England's objective to be a global pioneer in targeted therapies and precision oncology.

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# **NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

## **Single technology appraisal**

### **Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]**

## **Summary of Information for Patients (SIP)**

October 2025

| <b>File name</b>                                 | <b>Version</b> | <b>Contains<br/>confidential<br/>information</b> | <b>Date</b>       |
|--------------------------------------------------|----------------|--------------------------------------------------|-------------------|
| <b>ID6292_larotrectinib_NICE_SIP<br/>[noCON]</b> | <b>v.1</b>     | <b>no</b>                                        | <b>01/10/2025</b> |

**RESTRICTED**

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

### **SECTION 1: Submission summary**

#### **1a) Name of the medicine** (generic and brand name):

Response: Larotrectinib (Vitrakvi®)

#### **1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

Response: Larotrectinib is indicated for the treatment of adult and paediatric patients with solid tumours who have:

- a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and
- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- no satisfactory treatment options

#### **1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Larotrectinib is recommended for use within the Cancer Drugs Fund (CDF) since 2020 as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children if:

- the disease is locally advanced or metastatic or surgery could cause severe health problems and
- they have no satisfactory treatment options.

EU regulatory approval was received 09/2019 and UK regulatory approval 03/2021

The European commission decision is available [here](#).

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: N/A

## **SECTION 2: Current landscape**

### **2a) The condition – clinical presentation and impact**

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response: The condition being assessed by NICE in this submission is NTRK fusion-positive advanced solid tumours, which are characterised by the presence of neurotrophic tyrosine receptor kinase (NTRK) gene fusions that drive cancer growth. These tumours can occur across various solid tumour types, affecting both adults and children. NTRK fusion-positive cancer is considered a rare disease, with a low percentage of solid tumours harbouring an NTRK gene fusion. A paper published by Westphalen et al. (1) in 2021 reports that 1.34% of paediatric cancers and 0.28% of adult cancers display an NTRK gene fusion. Larotrectinib is considered a tumour agnostic treatment.

The impact of NTRK fusion-positive tumours on the quality of life for patients and their families can be significant. Patients often experience a range of physical, emotional, and psychological challenges due to the advanced nature of their disease and the aggressive treatment regimens required. This can lead to considerable distress not only for the patients but also for their caregivers and families, who may face emotional strain and logistical challenges in providing support. Furthermore, the rarity of these tumours means that patients may feel isolated in their experiences, which can exacerbate feelings of anxiety and depression.

### **2b) Diagnosis of the condition (in relation to the medicine being evaluated)**

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response: In order to be eligible for precision medicine using targeted therapies, patients need to be tested to detect the presence of this specific oncogenic driver. For this purpose, diagnostic testing for NTRK gene fusions is routinely available in the NHS, primarily via the National Genomic Test directory. The test is nationally approved, funded and available for adult and paediatric patients with solid tumours to support the use of precision medicine and harmonise access across the country as part of the NHS Genomic

Laboratory Hub (GLH). According to ESMO recommendations, multiple standard testing methods are available to identify patients with tumours harbouring NTRK gene fusions (2). However, as discussed with clinicians, in routine clinical practice, the extent to which this testing is actively performed may vary based on some factors. Testing is generally prioritised for selected tumour types where NTRK fusions are either more prevalent or where standard treatments options are limited (e.g., rare cancers, paediatric tumours). In common tumour types (e.g., lung, breast), broad panel Next-Generation Sequencing (NGS) assays may incidentally detect NTRK fusions if NGS is performed for other molecular markers (e.g., KRAS, EGFR) (3). Nevertheless, it is not uniformly applied across all patients or tumour types and dependent on local genomic strategies, availability of comprehensive genomic profiling, tissue availability, clinical indications, clinicians' awareness or clinical urgency (in late-stage disease, rapid decisions may prevent full testing). This is primarily due to the fact that NTRK fusions are extremely rare in common cancers. Due to this rarity, oncologists may not prioritise NTRK testing unless common options have been ruled out (e.g., no common driver mutation, tumour has an unusual histology).

## 2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

**Response:** There are no treatment options routinely available in the NHS that specifically target TRK fusion-driven cancers.

In the absence of TRK-fusion specific treatments, it is assumed that patients with TRK fusion-driven cancer are currently treated according to guideline recommendations based on the tumour location, with standard of care available for advanced or metastatic solid tumour cancers such as chemotherapy, immunotherapy, molecularly targeted treatment or best supportive care.

## 2d) Patient-based evidence (PBE) about living with the condition

### Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include

the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response: Three different (anonymous) telephone interviews with one patient, and two caregivers of patients with NTRK fusion positive cancer were led in July and September 2025 to understand the disease impact on daily activities and any change reported since the start of the treatment.

Caregivers observed that after starting larotrectinib, patients (i.e., their child) experienced a significant improvement in their HRQoL. The need for hospital visits was significantly reduced, and families found themselves able to return to more typical routines, such as the patient attending school and participating in family activities, which had previously been disrupted by the disease and its treatment.

Before larotrectinib, the burden of care was significant, as the side effects of chemotherapy and the frequency of medical interventions made caregiving extremely demanding. Additionally, the caregivers were overwhelmed by hospital visits and intensive care, leaving little time to care for their other children.

After starting the treatment, caring for the patient became much more manageable and parents could also spend time with their other children, greatly improving their quality of life. The stability offered by the treatment allowed at least one caregiver to return to work, and life at home became less dictated by the illness. Larotrectinib's effectiveness at maintaining disease control reduced the anxiety caused by the fear of progression.

Another important aspect was how well the patients tolerated larotrectinib. Unlike previous treatments, which often brought severe side effects, patients on larotrectinib experienced few or no significant side effects. This made the daily routine of taking the medication easier and contributed further to a sense of normalcy for the whole family. The simplicity of the dosing regimen, such as its liquid formulation and twice-daily schedule, also made administration more manageable, allowing caregivers to fit doses around school timings and daily routines with minimal disruption.

These testimonials showed that larotrectinib has been transformative for these patients and their families, enabling them to engage more fully in daily life and allowing caregivers to regain some balance and optimism. The treatment's predictability and tolerability have provided both practical and emotional relief, allowing families to focus less on illness and more on living their lives together. This renewed stability and hope have had a lasting, positive impact on the entire family dynamic.

In a recent conversation with a NTRK fusion positive salivary gland cancer patient treated with larotrectinib, the patient shared profound insights into the impact of their disease on daily life and treatment experiences.

Initially, the patient faced significant challenges, including debilitating symptoms, deteriorating mental health, and financial difficulties following a diagnosis of metastasised salivary gland cancer at 32 years old.

After transitioning from ineffective and emotionally and physically draining chemotherapy to the oral treatment larotrectinib, the patient reported a remarkable turnaround in both physical and mental well-being. They highlighted the ease of the new treatment regimen, which allows for greater flexibility and autonomy, significantly improving their quality of life. The patient's renewed sense of hope and optimism is evident, as they now feel capable of returning to work and engaging in social activities, ultimately reclaiming a sense of normalcy and vitality after a tumultuous period.

## **SECTION 3: The treatment**

### **3a) How does the new treatment work?**

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

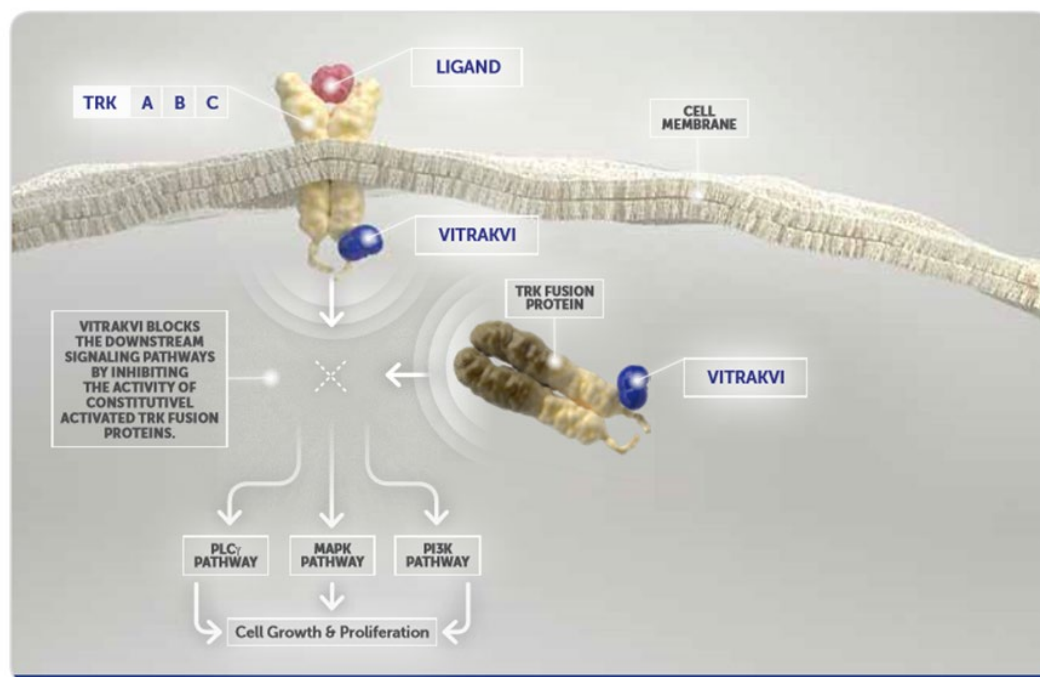
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response: Larotrectinib is an innovative medicine that blocks a group of proteins called TRKs (TRKA, TRKB, TRKC), which are made by the NTRK genes (figure 1). In some cancers, changes in these genes create abnormal TRK fusion proteins that are always switched on. This makes cancer cells grow and survive.

By specifically targeting and blocking these abnormal TRK proteins, larotrectinib can stop the signals that drive cancer growth. It has been shown to shrink tumours in patients whose cancers have these gene fusions, but not in cancers without them. Because larotrectinib is highly selective, it tends to have fewer effects on other proteins, which may explain its favourable safety profile.

The summary of product characteristics is available [here](#).

Figure 1: Mechanism of action - larotrectinib



Source: Bayer – Data on file

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

Response: No

### 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response: Larotrectinib is available as hard capsules (25 mg, 100 mg) to be taken orally, or as an oral solution (20 mg/mL).

- **Adults:** The recommended dose is 100 mg larotrectinib twice daily, until disease progression or unacceptable toxicity occurs.

- **Paediatric population:** Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m<sup>2</sup> larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or unacceptable toxicity occurs.

Existing treatments are predominantly infusions, an oral treatment represents a major shift in patient autonomy, gain in terms of time and decreased risks link to injections related adverse events.

### 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

| Name                   | LOXO-TRK-14001 (20288)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | NAVIGATE (20289)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | SCOUT (20290)                                                                                                                                                                                                                                                                                                                                  |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical trial Number  | NCT 02122913                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | NCT02576431                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | NCT02637687                                                                                                                                                                                                                                                                                                                                    |
| Link                   | <a href="#">Study Details   A Study to Test the Safety of the Investigational Drug Larotrectinib in Adults That May Treat Cancer   ClinicalTrials.gov</a>                                                                                                                                                                                                                                                                                                                                                                          | <a href="#">Study Details   A Study to Test the Effect of the Drug Larotrectinib in Adults and Children With NTRK-fusion Positive Solid Tumors   ClinicalTrials.gov</a>                                                                                                                                                                                                                                                                                                                                                             | <a href="#">Study Details   A Study to Test the Safety and Efficacy of the Drug Larotrectinib for the Treatment of Tumors With NTRK-fusion in Children   ClinicalTrials.gov</a>                                                                                                                                                                |
| Start date             | May 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | September 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | December 2015                                                                                                                                                                                                                                                                                                                                  |
| Phase                  | Phase I                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Phase II                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Phase I/II                                                                                                                                                                                                                                                                                                                                     |
| Comparator             | Single arm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Single arm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Single arm                                                                                                                                                                                                                                                                                                                                     |
| Label                  | Open label                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Open label                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Open label                                                                                                                                                                                                                                                                                                                                     |
| Population             | Adults with NTRK positive solid tumours                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Patients >12 years old with NTRK-fusion positive solid tumours                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Paediatrics (max 21) with advanced solid tumours or primary CNS NTRK-positive tumours                                                                                                                                                                                                                                                          |
| Number of patients     | 75                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 215                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 154                                                                                                                                                                                                                                                                                                                                            |
| Location               | Multicentre in the US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | International                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | International                                                                                                                                                                                                                                                                                                                                  |
| Key inclusion criteria | <ul style="list-style-type: none"> <li>- Adult patients with a locally advanced or metastatic solid tumour that has progressed or was nonresponsive to available therapies, are unfit for standard chemotherapy or for which no standard or available curative therapy exists</li> <li>- Proof of a malignancy harbouring a NTRK fusion</li> <li>- Eastern Cooperative Oncology Group (ECOG) score of 0, 1 or 2 and a life expectancy of at least 3 months</li> <li>- Adequate hematologic, hepatic, and renal function</li> </ul> | <ul style="list-style-type: none"> <li>- Locally advanced or metastatic NTRK gene fusion</li> <li>- Having received prior standard therapy or have no satisfactory treatment option</li> <li>- Subjects have at least one measurable lesion as defined by RECIST</li> <li>- At least 18 years of age</li> <li>- ECOG score ≤3. If primary CNS tumours, Karnofsky performance score (KPS) ≥50%</li> <li>- Adequate organ function</li> <li>- For patients in the bone health cohort: life expectancy of at least 6 months</li> </ul> | <ul style="list-style-type: none"> <li>- Patients with solid tumour or primary CNS tumours or cerebral metastasis</li> <li>- Karnofsky (those 16 years and older) or Lansky (those younger than 16 years) performance score of at least 50.</li> <li>- Adequate hematologic function</li> <li>- Adequate hepatic and renal function</li> </ul> |



|                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Key exclusion criteria</i> | <ul style="list-style-type: none"> <li>- Patients with unstable primary central-nervous-system tumours or metastasis, exceptions possible</li> <li>- Clinically significant active cardiovascular disease or history of myocardial infarction</li> <li>- Active uncontrolled systemic bacterial, viral, or fungal infection</li> <li>- Current treatment with a strong CYP3A4 inhibitor or inducer</li> <li>- Pregnancy or lactation</li> </ul> | <ul style="list-style-type: none"> <li>- Investigational or anticancer therapy intake within 2 weeks prior to start</li> <li>- Prior progression while receiving approved or investigational tyrosine kinase inhibitors</li> <li>- Systematic or unstable brain metastases</li> <li>- Uncontrolled concurrent malignancy</li> <li>- Active uncontrolled infection (bacterial, viral, fungal)</li> </ul> | <ul style="list-style-type: none"> <li>- Major surgery within 14 days (2 weeks) prior to C1D1</li> <li>- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to C1D1, ongoing cardiomyopathy</li> <li>- Active uncontrolled systemic bacterial, viral, or fungal infection</li> <li>- Current treatment with a strong CYP3A4 inhibitor or inducer.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Primary endpoint</i>       | <ul style="list-style-type: none"> <li>- Number of participants with adverse events</li> <li>- Severity of adverse events (<i>The severity of adverse events will be assessed according to the NCI CTCAE version 4.03</i>)</li> <li>- Maximum tolerated dose (MTD)</li> <li>- Recommended dose for dose expansion</li> </ul>                                                                                                                    | Best overall response of confirmed complete response (CR) or partial response (PR) as determined by an independent radiology review committee using RECIST v1.1 or RANO criteria, as appropriate to tumour type.                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>- Phase 1: Number of participants in an assigned dose cohort with treatment emergent adverse events (TEAEs) by grade assessed by NCI-CTCAE v 4.03 who experience a DLT (DLT: Dose-limiting toxicity)</li> <li>- Phase 1: Number of participants with TEAEs</li> <li>- Phase 1: Severity of TEAEs</li> <li>- Phase 2: Overall response rate (ORR) by IRRC (Proportion of participants with a best overall response of complete response (CR) or partial response (PR) as determined by an independent radiology review committee (IRRC) based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1,</li> <li>- Response Assessment in Neuro Oncology (RANO) or International Neuroblastoma Response Criteria (INRC) as appropriate to tumor type who express NTRK gene fusions)</li> </ul> |
| <i>QoL</i>                    | Not collected                                                                                                                                                                                                                                                                                                                                                                                                                                   | EORTC QLC-C30<br>EQ-5D 5L<br>PedsQL core                                                                                                                                                                                                                                                                                                                                                                | PedsQL core<br>FACES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <i>Ongoing</i>                | No (completed)                                                                                                                                                                                                                                                                                                                                                                                                                                  | Yes                                                                                                                                                                                                                                                                                                                                                                                                     | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <i>LPLV (estimated)</i>       | May-21                                                                                                                                                                                                                                                                                                                                                                                                                                          | Oct-25                                                                                                                                                                                                                                                                                                                                                                                                  | Sep-26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

The pooled analysis of efficacy is presented as two datasets – ePAS9 and SAS3. ePAS9 or ‘Extended Primary Analysis set 9’ reflects an updated version of ePAS2, used in the original submission, including data from additional patients recruited since that data cut of July 2018. As of July 2024, ePAS9 consists of 304 patients. SAS3 or ‘Supplementary analysis set 3’ consists of 60 paediatric and adult patients with primary CNS tumours but who otherwise met PAS eligibility criteria (Appendix N) and were enrolled before the data cut-off. In the original submission, there were 9 patients in the SAS dataset.

### 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in

confidence information but where necessary reference the section of the company submission where this can be found.

**Response:** Efficacy was consistent across key subgroups such as age, tumour type, and number of prior systemic therapy received.

Only results for non-primary CNS patients are publicly available at this time (4). The overall response rate for non-primary CNS patients was 65% (95% CI 59-70):

- 66 (22%) complete responses (CR),
- 20 (7%) pathological CR,
- 112 (37%) partial responses,
- 56 (18%) stable disease,
- 32 (11%) progressive disease,
- 18 (6%) not evaluable/undefined.

Median time to response was 1.8 months (range 0.9–22.9 months). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 43 months (95% CI 34–not estimable), 28 months (95% CI 22–38), and not reached, respectively, at median follow-ups of 45, 42, and 57 mo. The 4-year rates for DoR, PFS, and OS were 48% (95% CI 40–57), 39% (95% CI 32–46), and 63% (95% CI 57–68), respectively. Response to larotrectinib was rapid and durable, with short median time to response. Survival data also showed durability of efficacy. Positive response rate and extended survival were also observed in primary-CNS patients. Please refer to section 2.6 of the company dossier for details.

Since all three trials are non-comparative, results are only provided for larotrectinib, not considering different treatment options based on the tumour type. Indirect comparison methods all demonstrated additional benefit for larotrectinib over standard of care (tumour specific treatments).

### 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

**Response:**

Two out of the three larotrectinib clinical trials integrated measure of the quality of life using EORTC-QLQ-C30, EQ-5D 5L, PedsQL and FACES.

EQ-5D collected in the trial covers various aspects of the patient's life and is considered to sufficiently capture quality of life even though some aspects might be missed e.g., sense of hope patients can feel when starting a targeted therapy.

The extended follow-up data of larotrectinib showed a rapid and sustained improvement in health-related quality of life compared to baseline. For most patients, questionnaire scores

indicated a meaningful improvement in their quality of life (see section 2.6.1.3 in the company submission).

Larotrectinib, as an oral treatment, has a strong advantage over traditional chemotherapies as evidence showed that patients are preferring oral treatments over injections (5). It has also been echoed by the interviewed patients and caregivers (see question 2d).

### 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

**Response:** Larotrectinib is well tolerated in patients with NTRK fusion-positive solid tumours. The latest data cut-off showed a very low rate of Grade 3 and 4 TEAE, with no fatal TEAE attributed to larotrectinib. TEAEs that led to permanent discontinuation of larotrectinib occurred in rare cases.

Safety data for larotrectinib are publicly available for non-primary CNS patients in whom treatment-related adverse events (TRAEs) were mainly Grade 1/2 (n = 189; 62%). Grade 3/4 TRAEs occurred in 71 (23%) patients. Five (2%) pts discontinued due to TRAEs (4).

The safety profile of larotrectinib is characterised by manageable and reversible adverse events (AEs) that can be monitored, and it is comparable across adult and paediatric patients, as well as across tumour types.

### 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

**Response:**

#### 1. Patient Benefits:

- **Targeted Action:** Larotrectinib specifically inhibits TRK proteins linked to NTRK gene fusions, providing a tailored treatment approach that is effective across various solid tumours, regardless of their origin.
- **Efficacy:** Clinical trials and indirect treatment comparison indicate the efficacy of larotrectinib with rapid and durable responses as well as increased survival compared with standard of care (SOC).

- **Safety Profile:** Larotrectinib is associated with a low incidence of severe adverse effects, allowing patients to maintain a better quality of life compared to traditional chemotherapy.
- **Convenient Administration:** Available as an oral medication, it simplifies treatment regimens for both adults and children.

## 2. Caregiver Benefits:

- **Reduced Burden:** Improved patient outcomes and fewer side effects lessen the emotional and physical demands on caregivers.
- **Empowerment:** Caregivers can feel more engaged in treatment decisions, knowing their loved ones have access to an effective therapy.

## 3. Community Benefits:

- **Cost-Effectiveness:** Larotrectinib can optimise public healthcare expenditure by minimising ineffective treatments and hospitalizations due to side effects.
- **Equitable Access:** As a histology-independent therapy, it ensures that all patients with NTRK fusion-positive tumours, regardless of tumour type, have access to effective treatment options.
- **Advancement in Precision Medicine:** The introduction of larotrectinib supports the NHS's goals for personalised medicine and enhances cancer treatment strategies within the community.

In summary, larotrectinib represents a significant advancement in cancer therapy, benefiting patients, caregivers, and the healthcare system as a whole.

### 3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response: Larotrectinib is an oral treatment compared to most comparative treatments, it is also associated with low rate of adverse events and is effective in NTRK fusion positive patients. There is no disadvantage.

### 3i) Value and economic considerations

#### Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

### **Model structure**

- The analysis employed a partitioned survival model (PSM) with three health states (progression-free, progressed and death). This technique is commonly used in oncology modelling, as noted in the literature identified in Section 3.1 of the company submission, and is appropriate for capturing progressive, chronic conditions described by clinical outcomes that require an ongoing, time-dependent risk, such as progression and death.

### **Treatment life extension**

- Larotrectinib was shown to delay progression and extended survival in the cost effectiveness analysis leveraging clinical trial data and indirect treatment comparisons (6, 7) (MAIC – see glossary) vs standard of care.
- Number of patients alive, having progressed and who died have been captured throughout the clinical trial length.

### **Treatment's quality of life improvement**

- The impact of treatments on health-related quality of life was tracked throughout the modelled time horizon by assigning differential health state utility values to progression-free disease, progressed disease, and death. These utility values also differ based on the treatment administered. In addition, adverse events from treatments are captured in terms of disutility (see glossary). Since larotrectinib is associated with lower rates of adverse events, there is less disutility associated with this treatment compared to standard of care treatments.
- EQ-5D-3L was used to estimate a person's quality of life. The QALY calculation (see glossary) captures the majority of benefits directly related to the patient, such as delayed progression, extension of life and improved quality-of-life. However, it can overlook some emotional and psychological benefits described in Section 2.15 of the company submission, such as reduced anxiety and a sense of hope. Preference towards an oral treatment might also not be fully captured in QALY calculation. Finally, disutility caused by mutilating surgery can partially be captured in QALYs, but the impact of its avoidance is likely not, especially the impact on future productivity gains in adulthood.

### **Modelling how the costs of treatment differ with the new treatment**

- Larotrectinib consistently showed QALY gains over standard of care but was associated with a higher total cost, mainly driven by its longer time to treatment discontinuation and higher drug acquisition costs per cycle combined with the additional disease management costs from delayed progression and extended survival.

- Most standard of care treatments are given intravenously. This mode of administration incurs drug administration costs (see Section 3.5.2 of the company submission). Because larotrectinib is given orally, it does not incur any administration cost.

### Uncertainty

- The main assumption about comparative effectiveness for the base case analysis of larotrectinib versus standard of care is based on two MAICs – one for adult and one for paediatric patients (6, 7).
- The results from the two MAICs have an important influence in the cost-effectiveness results as shown in Section 3.11 of the company submission. This led the company to use alternative assumptions to derive a comparator for larotrectinib. This includes using other MAICs or other modelling approaches (responder/non responder analysis, intra-patient comparison or a naïve literature-based approach – see glossary). Regardless of comparative effectiveness source, the conclusions for cost-effectiveness remained consistent across the base case and scenarios.
- To complement the recent data cut-offs of the larotrectinib trials, a number of real-world studies were conducted in the meantime to generate evidence for the outcomes of patients with NTRK fusion-positive solid tumours treated with larotrectinib or SOC. Because of the relatively short length of these studies, long-term cost-effectiveness results cannot be confirmed. However, unpublished real-world evidence (e.g., efficacy data of patients treated through the Cancer Drugs Fund) are consistent with the response and time to response rates of the larotrectinib trials.

### Additional factors

- Since NTRK fusion positive cancers are very debilitating cancers, a case for severity modifiers has been made (see table 1).

Table 1: Summary of severity modifiers analysis

| Tumour location                                        | Expected total QALYs for the general population | Total QALYs that patients would be expected to have* | Absolute QALY shortfall | Proportional QALY shortfall | QALY weight |
|--------------------------------------------------------|-------------------------------------------------|------------------------------------------------------|-------------------------|-----------------------------|-------------|
| NSCLC                                                  | 14.39                                           | 0.73                                                 | 13.66                   | 94.93%                      | 1.2         |
| Salivary                                               | 14.63                                           | 0.78                                                 | 13.85                   | 94.67%                      | 1.2         |
| Melanoma                                               | 15.06                                           | 1.37                                                 | 13.69                   | 90.90%                      | 1.2         |
| Colorectal (used as proxy for appendix)                | 10.32                                           | 0.48                                                 | 9.84                    | 95.35%                      | 1.7         |
| STS adults (GIST)                                      | 15.56                                           | 1.4                                                  | 14.16                   | 91.00%                      | 1.2         |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | 18.66                                           | 0.71                                                 | 17.95                   | 96.19%                      | 1.7         |
| STS paediatrics (used as proxy for IFS)                | 24.30                                           | 1.43                                                 | 22.87                   | 94.11%                      | 1.7         |
| Breast                                                 | 15.99                                           | 0.61                                                 | 15.38                   | 96.19%                      | 1.7         |

|                          |       |      |       |        |     |
|--------------------------|-------|------|-------|--------|-----|
| Cholangiocarcinoma       | 14.43 | 0.41 | 14.02 | 97.16% | 1.7 |
| CNS/Glioma               | 22.67 | 0.75 | 21.92 | 96.69% | 1.7 |
| Pancreas                 | 12.34 | 2.65 | 9.69  | 78.53% | 1.0 |
| Thyroid                  | 14.42 | 2.37 | 12.05 | 83.56% | 1.2 |
| * With current treatment |       |      |       |        |     |

### 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response: Larotrectinib is an innovative therapy and a 'step change' in the management of NTRK fusion-positive cancers. It is a precision medicine, designed to selectively target NTRK fusion cancer, providing a specific treatment for NTRK fusion-positive solid tumours where previously no treatment was available.

Larotrectinib can be described as a histology-independent therapy, offering treatment for both adults and children under a single indication. It is approved by EMA as the first histology independent drug in the EU.

### 3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

[Find more general information about the Equality Act and equalities issues here](#)

Response: Larotrectinib is a new type of cancer treatment that targets the genetic cause of certain tumours (NTRK fusions), rather than where the cancer starts in the body. Because these cancers are rare and testing is not offered equally across the UK, some patients face barriers to diagnosis and treatment. This creates inequalities based on region, hospital size, ethnicity, and language.

If larotrectinib is not routinely funded by the NHS, patients may be forced to pay privately, which would further increase health inequalities. Routine access through the NHS would ensure that all eligible patients, regardless of background or location, can benefit from this targeted treatment and from advances in personalised cancer care.

## **SECTION 4: Further information, glossary and references**



#### 4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Response: N/A

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: [http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA\\_Policy\\_brief\\_on\\_HTA\\_Introduction\\_to\\_Objectives\\_Role\\_of\\_Evidence\\_Structure\\_in\\_Europe.pdf](http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf)

#### 4b) Glossary of terms

Response:

- **MAIC (Matching-Adjusted Indirect Comparison):** A way of comparing two treatments from different studies by making the groups of patients more similar, so the results are fairer.
- **Disutility:** The negative effect on quality of life caused by a health problem or side effect.
- **QALY (Quality-Adjusted Life Year):** A measure that combines how long people live with how good their quality of life is.
- **Non responder/responder analysis:** Looking at how many patients improved with a treatment (responders) compared with those who did not (non-responders).
- **Intra-patient comparison:** Comparing how the same patient feels or functions before and after progression, rather than comparing different patients.
- **Naïve literature-based approach:** Using published results from different studies to compare treatments, without adjusting for differences between the studies.



#### 4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. **Westphalen CB, Krebs MG, Le Tourneau C, Sokol ES, Maund SL, Wilson TR, Jin DX, Newberg JY, Fabrizio D, Veronese L, Thomas M, de Braud F.** Genomic context of NTRK1/2/3 fusion-positive tumours from a large real-world population. *NPJ Precis Oncol.* 2021;5(1):69. doi:10.1038/s41698-021-00206-y.
2. **Marchiò C, Scaltriti M, Ladanyi M, lafrate AJ, Bibeau F, Dietel M, et al.** ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. *Ann Oncol.* 2019;30(9):1417-27.
3. **Zito Marino F, Pagliuca F, Ronchi A, Cozzolino I, Montella M, Berretta M, et al.** NTRK Fusions, from the Diagnostic Algorithm to Innovative Treatment in the Era of Precision Medicine. *Int J Mol Sci.* 2020;21(10)
4. **Xu RH, et al.** Efficacy and safety of larotrectinib in patients with non-primary central nervous system TRK fusion cancer: an updated analysis. *J Clin Oncol.* 2025;43(16\_suppl):3148. doi:10.1200/JCO.2025.43.16\_suppl.3148.
5. **Holko P, Kawalec P, Mossakowska M.** Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. *Eur J Gastroenterol Hepatol.* 2018;30(2):174–80. doi:10.1097/MEG.0000000000001031.
6. **Brose MS, Westphalen CB, Pan X, Bernard-Gauthier V, Kurtinecz M, Guo H, Aris V, Brett NR, Majdi A, Subbiah V, Pennell NA, Kehl KL, Drilon A.** Larotrectinib compared with real-world non-tropomyosin receptor kinase inhibitor therapies in patients with tropomyosin receptor kinase fusion cancer. *JCO Precis Oncol.* 2025;9:e2400500. doi:10.1200/PO-24-00500.
7. **Orbach D, Carton M, Khadir SK, Feuilly M, Kurtinecz M, Phil D, Vokuhl C, Koscielniak E, Pierron G, Lemelle L, Sparber-Sauer M.** Therapeutic benefit of larotrectinib over the historical standard of care in patients with locally advanced or metastatic infantile fibrosarcoma (EPI VITRAKVI study). *ESMO Open.* 2024;9(5):103006. doi:10.1016/j.esmoop.2024.103006.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

#### Company response to clarification questions

November 2025

| File name                                                                             | Version | Contains<br>confidential<br>information | Date       |
|---------------------------------------------------------------------------------------|---------|-----------------------------------------|------------|
| ID6292<br>Larotrectinib<br>Company<br>response to<br>clarification<br>questions [CON] | 1       | Yes                                     | 10/11/2025 |

### **Notes for company**

#### **Highlighting in the template**

Square brackets and ■ highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in ■ with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

**To delete grey highlighted text, click anywhere within the text and press DELETE.**

## **Section A: Clarification on effectiveness data**

### ***Decision problem***

**A1. Priority question: Company submission (CS) Table 1, states that the comparator “is in line with the final scope”. Please clarify what established clinical management is for each the tumour types included in the CS.**

Table 1 below presents the methodology used to choose the appropriate comparator in the cost-effectiveness analysis. As highlighted in question A16 of this clarification letter, European guidelines were utilised to select the comparator, and when several options were available, the advice of UK clinicians was sought to determine the treatment that was most suitable for UK clinical practice. Please refer to question 6 of the advisory board minutes (1).

**Table 1. Methodology for the selection of appropriate comparator by tumour type**

| Tumour site                       | Methodology for comparator selection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Non-small cell lung cancer</b> | <p>According to the ESMO 2025 guidelines for metastatic NSCLC:</p> <ul style="list-style-type: none"> <li>- The preferred first line of treatment is platinum doublet (2).</li> <li>- There are various options in second line treatment in the absence of specific genetic mutations (non-oncogene addicted guidelines) including: <ul style="list-style-type: none"> <li>o pemetrexed,</li> <li>o docetaxel,</li> <li>o <b>nintedanib and docetaxel</b>,</li> <li>o ramucirumab and docetaxel or</li> <li>o ICI rechallenge.</li> </ul> </li> </ul> <p>A UK lung cancer specialist in the advisory board recommended <b>nintedanib and docetaxel</b> as the appropriate comparator for larotrectinib (1).</p>                                                                                                                                      |
| <b>Salivary gland cancer</b>      | <p>According to the ESMO 2022 guidelines for salivary gland cancer:</p> <ul style="list-style-type: none"> <li>- The first treatment approach, when a patient is diagnosed, is surgical resection (3).</li> </ul> <p>When surgical resection is not an option due to local recurrence, metastatic disease or patient status, guidelines recommend:</p> <ul style="list-style-type: none"> <li>- <b>Chemotherapy or radiotherapy</b>, without specifying any particular specific regimen.</li> <li>- Clinical trials can also be an option for patients in the absence of effective treatment.</li> </ul> <p>Various regimens are used in the real-world, typically involving platinum-based chemotherapy. A UK head and neck clinical oncologist recommended <b>cisplatin and vinorelbine</b> as the most used combination in clinical practice.</p> |

| Tumour site              | Methodology for comparator selection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Melanoma</b>          | <p>According to the ESMO 2024 guidelines for melanoma, patients at stage III/IV will receive treatment based on their prior adjuvant treatment received (4).</p> <ul style="list-style-type: none"> <li>- The first-line treatment is nivolumab and ipilimumab and Second-line treatment is not defined by a single agent. Options are mainly:</li> <li>- nivolumab or ipilimumab in monotherapy</li> <li>- or <b>pembrolizumab</b> (4).</li> </ul> <p>A UK clinician in the advisory board recommended using <b>pembrolizumab</b> according to clinical practice (1).</p>                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Colorectal cancer</b> | <p>According to the ESMO 2023 guidelines for colorectal cancer, “<i>NTRK testing could be done at any time but will only influence treatment decisions after progression on at least two lines of treatment</i>” (5). Based on the guideline recommendations, since a genetic test is required for larotrectinib, we chose to position it against a third-line comparator rather than a second-line comparator.</p> <p>Same guidelines mention that stage IV unresectable metastatic colorectal third-line treatments depend on mutation status (e.g., RAS-wt, BRAF-wt, RAS-mut) and include:</p> <ul style="list-style-type: none"> <li>- Either single-agent anti-EGFR therapies (panitumumab or irinotecan-cetuximab), regorafenib,</li> <li>- <b>trifluridine-tipiracil</b> or</li> <li>- encorafenib-cetuximab (5).</li> </ul> <p>A UK oncologist in the advisory board recommended <b>trifluridine-tipiracil</b> as the most used regimen (1).</p> |
| <b>STS adults (GIST)</b> | <p>According to the ESMO-EURACAN-GENTURIS clinical guidelines from 2021 for gastrointestinal stromal tumours, patients with advanced or metastatic GISTs are treated according to their imatinib-sensitivity mutation (6).</p> <ul style="list-style-type: none"> <li>- The first-line treatment in the advanced/metastatic setting is sunitinib, in the absence of targeted treatment.</li> <li>- If there is no response to the first-line treatment with sunitinib, <b>regorafenib</b> is recommended as a second-line treatment.</li> </ul> <p><b>Regorafenib</b> has been validated by clinicians in the advisory board as an appropriate comparator (1).</p>                                                                                                                                                                                                                                                                                       |

| Tumour site                                         | Methodology for comparator selection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>STS adult (non-GIST)</b>                         | <p>According to the ESMO-EURACAN-GENTURIS clinical guidelines from 2021 for soft tissue and visceral sarcomas, the first-line treatment for advanced/metastatic, clinically unresectable STS is:</p> <ul style="list-style-type: none"> <li>- doxorubicin, either as monotherapy or in combination with another agent (7).</li> </ul> <p>If patients progress, they can either continue this treatment or try further-line systemic therapies such as:</p> <ul style="list-style-type: none"> <li>- high dose ifosfamide or</li> <li>- <b>trabectedin</b> (7).</li> </ul> <p>Clinicians who attended the advisory board recommend <b>trabectedin</b> as a comparator (1).</p>                                                                                                                                      |
| <b>STS paediatrics</b>                              | <p>According to a joint EpSSG, CWS and ERN PaedCan project to write European standard clinical guidelines for children and adolescents with rhabdomyosarcoma (most common type of STS in children and young adults) in 2025, the only recommended treatment for progressive or relapsed disease is <b>vincristine and irinotecan with temozolomide (VIT)</b> (8).</p> <p>Since there are no other options, paediatric oncologists in the advisory board advised that it would be the preferred and only comparator in the absence of targeted treatment (1). As a result, <b>VIT</b> is the selected comparator in the model.</p>                                                                                                                                                                                  |
| <b>Breast cancer</b>                                | <p>According to the ESMO guidelines for breast cancer from 2021, <i>“in metastatic breast cancer, standards therapies are personalised based on biomarkers [...] in addition, they are now several tissue and site agnostic approvals. For example, both larotrectinib and entrectinib [...]. Biomarkers need to be checked once subtype specific standard therapy have been exhausted [...]”</i> (9).</p> <p>Based on this statement and the multiple options that exist for this tumour type, larotrectinib is likely to be used when a patient has exhausted all treatment options; clinicians in the advisory board agree with this positioning (1). The chosen comparator in the model for breast cancer is <b>“best supportive care”</b>, represented by a mix of chemotherapies used in the real-world.</p> |
| <b>Cholangiocarcinoma (or biliary tract cancer)</b> | <p>According to the ESMO clinical guidelines for biliary tract cancer from 2023:</p> <ul style="list-style-type: none"> <li>- The first line of treatment for advanced or metastatic cancer is cisplatin-gemcitabine ± durvalumab (10).</li> </ul> <p>After progression, patients will be treated according to their genetic mutation.</p> <ul style="list-style-type: none"> <li>- If no mutations are identified, or for all comers, <b>FOLFOX</b> or 5-FU ± irinotecan is recommended.</li> </ul> <p>Clinicians in the advisory board recommend that 5-FU combined with any chemotherapy (i.e., FOLFOX) would be the preferred option (1). Therefore, <b>FOLFOX</b> has been selected as the model comparator.</p>                                                                                              |

| Tumour site              | Methodology for comparator selection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CNS/glioma</b>        | <p>According to the ESMO guidelines for high-grade glioma from 2014, treatment depends on the grade and tumour location.</p> <ul style="list-style-type: none"> <li>- The preferred approach is surgical resection (11).</li> </ul> <p>If surgical resection is not possible or the patient relapses, chemotherapies are recommended with either:</p> <ul style="list-style-type: none"> <li>- temozolomide</li> <li>- <b>lomustine</b> or</li> <li>- PCV (procarbazine, lomustine and vincristine) (11).</li> </ul> <p>Clinicians in the advisory board recommended <b>lomustine</b> as a single agent for this specific population (1).</p>                                                           |
| <b>Pancreatic cancer</b> | <p>According to the ESMO clinical guidelines for pancreatic cancer from 2023, patients are treated according to their ECOG performance score (12). For patients with a score of 0-1 (aligned with the larotrectinib patient population; section 2.3.2 of company CS) who have no major comorbidities:</p> <ul style="list-style-type: none"> <li>- the first line of treatment is FOLFIRINOX, followed, in the second line treatment (12) by: <ul style="list-style-type: none"> <li>o gemcitabine and nab-paclitaxel, or</li> <li>o <b>gemcitabine</b>.</li> </ul> </li> </ul> <p>Clinicians in the advisory board recommended using <b>gemcitabine</b> as a relevant comparator in the model (1).</p> |
| <b>Thyroid cancer</b>    | <p>According to the ESMO clinical guidelines for advanced thyroid cancer from 2022:</p> <ul style="list-style-type: none"> <li>- radioactive iodine (RAI) is used as a first-line treatment for differentiated thyroid cancer (13).</li> </ul> <p>If patients do not respond or stop responding, the following options are recommended in Europe as second-line therapy (13):</p> <ul style="list-style-type: none"> <li>- sorafenib,</li> <li>- <b>lenvatinib</b>, or</li> <li>- both</li> </ul> <p>Based on UK clinical practice, clinicians in the advisory board recommended <b>lenvatinib</b> as the comparator (1).</p>                                                                           |

## Data cuts

A2. Please clarify whether data cuts more recent than 20<sup>th</sup> July 2024 are available for ePAS9 and SAS3.

a) If so, please provide an update for the clinical analyses; this includes updating Tables 9 – 14, 18-19, and Kaplan-Meier curves (Figures 8-10).

b) If not, please explain why, and clarify whether and when an updated analysis may be presented.

The 20<sup>th</sup> of July 2024 is the most recent data cut available. We had an additional data cut-off in July 2025, comprising the same patients included in the ePAS9 and SAS3 summary (since enrolment had stopped in 2023 for both ongoing studies, SCOUT and

NAVIGATE). The dataset is still under analysis and is expected to be submitted to the EMA in March 2026.

### ***Applicability of the trial evidence to the NHS***

**A3. Priority question: Compared with ePAS9 and SAS3, the SACT population differed significantly. Amongst other variables, the sex distribution differed, most SACT patients had one prior line of therapy; ECOG status and rates of metastatic disease also differed between the SACT and trial evidence.**

**Analyses of ORR, PFS and OS that align with the baseline characteristics of the SACT cohort are needed. Analyses need to account for heterogeneity in tumour sites (as evidenced in CS Appendix Q) and differences in paediatric and adult populations (Appendix C). Please provide an indirect comparison between the SACT evidence and SoC evidence. If the company chooses to conduct an unanchored MAIC, please ensure that the reporting of methods and results matches the information requested in Question A24.**

The company led a feasibility assessment of conducting a Matching-Adjusted Indirect Comparison (MAIC) using the CDF data and real-world evidence (RWE). There are four different reasons why this assessment led to a negative recommendation:

#### **1. Data Availability and Quality**

The aggregate data from the CDF lack granularity, with no stratification by key characteristics (e.g., adult vs. paediatric), making adjustment for patient characteristics impossible. The Eastern Cooperative Oncology Group (ECOG) performance status is incomplete (less than 50%), which prevents adjustment for baseline disease severity — a known prognostic factor. Additionally, patient characteristics by tumour site (e.g., age, sex) are unavailable, further limiting the ability to adjust for case-mix differences between populations. Subgroup-specific outcomes (e.g., paediatric, primary-CNS) outcomes are also unavailable (please see response to question A17 and A18).

#### **2. Population Overlap and Comparability**

The VICTORIA study includes patients with non-small cell lung cancer (NSCLC), colorectal cancer (CRC), soft tissue sarcoma (STS), thyroid, and salivary gland



tumours. The CDF population covers overlapping tumour types but with very small numbers in each category and incomplete classification (NSCLC: 4; CRC: 2; STS: unknown; thyroid: 5; salivary gland: 2). Given the imprecise reporting of tumour sites and minimal overlap, meaningful reweighting of the individual patient data (IPD) to the CDF population is not feasible. This extremely low sample size makes it unlikely that a reliable hazard ratio (HR) could be generated, as any estimate would be highly unstable.

### **3. Methodological Constraints**

The MAIC would need to be unanchored due to the absence of a common comparator arm. This approach requires the strong assumption that all relevant effect modifiers and prognostic factors are accounted for, which cannot be met given the missing ECOG data. Consequently, the validity of any unanchored MAIC would be highly questionable, with a substantial risk of bias.

### **4. Practical Limitations**

Individual patient data are available only for the VICTORIA and EPI VITRAKVI studies, while other MAICs lack corresponding IPD datasets, further constraining analytical options. In addition, time constraints prevent extensive global data collection or additional data requests that would be needed to improve feasibility.

### **Overall Assessment**

Given the combination of a small and incomplete aggregate dataset, partial overlap between tumour populations with the MAIC, missing key covariate (notably ECOG performance status), and the requirement for an unanchored comparison, a quantitative MAIC is not feasible. Any resulting estimates would lack robustness and interpretability. A qualitative comparison is therefore the only defensible approach.

### ***Clinical trial evidence***

A4. Please provide clinical study reports at the latest available data cut for studies 20288, 20289 and 29290.

These are still in preparation for the most recent data-cut (July 2025). The latest CSRs (data cut-off July 2024) have been added to the references (14-16).

A5. Please clarify the numbers and proportions of patients in ePAS9 and SAS3 at baseline with:

- a. brain metastases;
  - b. 1 previous line of therapy;
  - c. 2 previous lines of therapy;
- or clarify why this data was not available.

The Company did not collect information about brain metastases in the CRF; however, a medical review of the baseline data identified █ patients with brain metastases, all of whom were in the ePAS9 cohort. There are █ patients with brain metastases at baseline in SAS3.

As requested, Table 2 below breaks down the number of patients who had 1 previous line of therapy or 2 previous lines of therapy at baseline, based on the July 2024 data cut-off:

**Table 2. Prior systemic regimen received at baseline in ePAS9 and SAS3 (data cut-off 20 July 2024)**

| Number of prior systemic regimen n (%) | Pooled analysis of patients from Studies 20288, 20289 and 20290 |             |
|----------------------------------------|-----------------------------------------------------------------|-------------|
|                                        | ePAS9<br>n=█                                                    | SAS3<br>n=█ |
| 0                                      | █                                                               | █           |
| 1                                      | █                                                               | █           |
| 2                                      | █                                                               | █           |
| 3 or more                              | █                                                               | █           |

Source: Bayer. Data on file. Tables, figures and listings for Integrated Summary of Efficacy.

2731953\_ise\_jul2024\_8\_1 (1) table 8.1 / 14 and 8.1 / 15 (17)

A6. Table 6 combines patients with 0 prior systemic therapy and missing data.

Please clarify why these were combined and provide a breakdown as appropriate.

The company has double-checked the data, and all patients have records. Therefore, there is no missing data, and all patients reported in this row have 0 prior lines of therapy.

A7. CS Table 5 does not list OS as an outcome for the Phase 1 of study 20290.

Please clarify why, and whether any OS events were missed as a result.

This table reflects the endpoints as specified in the protocol, but all patients are included in the OS analysis, regardless of phase, so no events are missed.

A8. Please clarify why health-related quality of life (HRQoL) was not available for ePAS9.

Health-related quality of life (HRQoL) data were collected for ePAS9; however, a formal analysis has not yet been conducted. Due to the extensive nature of this analysis, priority was given to completing the EQ-5D analysis required for the economic model. Therefore, the most recent HRQoL analysis available (from ePAS6) was presented in the submission. The number of patients included in ePAS9 is comparable to that in ePAS6, and no material differences in patient characteristics are expected.

## ***Censoring***

A9. CS Table 18, p73, shows that [REDACTED] of patients in ePAS9 OS analyses were censored because they started taking a subsequent NTRK inhibitor. This censoring is likely to be informative and was not stated in the statistical analysis plan (v6.0). Please explain why these patients were censored and provide updated OS analyses that do not censor for this reason.

This analysis is a post-hoc analysis conducted to understand the effect of censoring patients who received a TRKi before they received it. This was done to appraise if there is a difference in survival between patients having received a TRKi compared to the main analysis, where patients are still censored but only on the basis that they're alive. Because of the small number of patients who take a subsequent NTRK inhibitor and the small difference in censoring time, [REDACTED], there is little difference in the milestone estimates compared to the main analysis. The main analysis conducted according to the SAP which does not censor for this reason is presented in table 14 of the CS.

Subsequent therapies

A10. Please clarify whether SAS3 patients received any subsequent therapies (including systemic and surgery), and if so, provide evidence of their potential effect on OS.

Please find below the subsequent therapies received in SAS3, as presented in Table 3.

Table 3. Summary of subsequent therapies (SAS3, data cut-off 20<sup>th</sup> July 2024)

| Subsequent Therapy         | Paediatrics (Age < 18 years)<br>N= (100%) | Adults (Age ≥ 18 years)<br>N= (100%) | Total<br>N= (100%) |
|----------------------------|-------------------------------------------|--------------------------------------|--------------------|
| Other systemic therapies   |                                           |                                      |                    |
| Radiotherapy               |                                           |                                      |                    |
| Radioactive iodine therapy |                                           |                                      |                    |
| Surgery                    |                                           |                                      |                    |
| Systemic and radiotherapy  |                                           |                                      |                    |

Patients may be counted in more than one row.

Table 4 below presents the adjusted OS for SAS3 patients who are censored based on receiving subsequent treatment (13% of the population). other metrics (e.g., CI, min and max) are . As a result, the impact of subsequent therapies on survival is .

Table 4. Overall Survival (SAS3, data cut-off 20<sup>th</sup> July 2024)

| Status                                | SAS3 (N= ) |
|---------------------------------------|------------|
| Vital Status                          |            |
| Dead                                  |            |
| Censored                              |            |
| Reason Censored                       |            |
| Alive                                 |            |
| Study discontinuation                 |            |
| Start taking a subsequent therapy     |            |
| Duration of Overall Survival (months) |            |
| Median                                |            |
| 95% confidence interval for median    |            |
| Minimum, Maximum                      |            |
| Duration of Follow-up (months)        |            |

| Status                 | SAS3 (N=■) |
|------------------------|------------|
| Median                 | ■          |
| 25th, 75th percentiles | ■■■■■      |

A11. For ePAS9 and SAS3, please provide PFS2 data and corresponding Kaplan-Meier curves, where available.

Unfortunately, this is not something the company can provide for all patients, as patients are not re-baselined (target lesions identified) upon progression. All assessments (target lesions, non-target lesions and new lesions) are relative to the original baseline.

## ***Heterogeneity***

**A12. Priority question: The Bayesian hierarchical analyses in CS Appendix Q showed evidence of heterogeneity in ORR between tumour types. Subgroup analyses in CS Appendix C showed numerical differences in ORR in ■■■■■ subgroups, by ■■■■■, ■■■■■ and ■■■■■. Given this evidence, please discuss the clinical relevance of ORR, PFS and OS estimates pooled across these diverse patient populations.**

Heterogeneity in outcomes is expected within this evidence base, as larotrectinib is a tumour-agnostic treatment by definition, utilised across populations with very different background prognoses, disease kinetics and prior therapy exposure. The observed variation in ORR is primarily explained by prognostic factors rather than differential drug activity.

Specifically, ORR is ■■■ in patients who have received  $\geq 3$  lines of therapy (■■■■ vs. ■■■■ in patients without prior systemic regimen). This is expected and aligns with previous literature (Garcia et al., 2025), which indicates that response rates decrease as patients become heavily pre-treated (18). As patients undergo more treatments and experience relapses, the likelihood of responding to subsequent therapies diminishes.

In patients with poorer performance status (■■■■■ for ECOG 3 vs. ■■■■■ for ECOG 0), we also observe poorer outcomes. This finding is consistent with

conclusions drawn from studies of other treatments for advanced solid tumours, such as checkpoint inhibitors in the study by Krishnan et al. (2022), where the overall response rate (ORR) for patients with ECOG PS 0-1 was 23% compared with 8% for those with poor PS ( $P = 0.005$ ) (19). Similarly, this conclusion has been found in the study by Galan et al. (2019) where the rate of response, median overall survival (OS) and progression-free survival (PFS) were significantly higher in patients with ECOG PS 0–1 than in those with ECOG PS  $\geq 2$  (20). These findings collectively reinforce the strong association between poorer performance status and worse clinical outcomes across tumour types and treatments.

Outcomes are also lower in patients with metastatic disease at baseline (██████████ vs. ██████████ for locally advanced patients), likely due to the aggressiveness of metastatic disease. Lower treatment response has also been observed in other cancer types as well; for instance, in basal cell carcinoma, the ORR was 35.0% for locally advanced patients compared to 22.2% for metastatic patients, as reported in a paper from 2022 (21). This pattern underscores the impact of disease burden and biological aggressiveness on treatment effectiveness across tumour types.

It is worth noting that the mechanism of action is consistent across histologies, leading to the interpretation that the observed differences in ORR, PFS and OS are primarily prognostic rather than predictive. To ensure appropriate representation of clinical differences, adult and paediatric patients were modelled separately in the base case analysis. Tumour-level variation was addressed in a scenario using a Bayesian hierarchical framework, which preserves genuine heterogeneity while allowing for the estimation of a coherent average treatment effect relevant to a tumour-agnostic decision problem.

The pooled estimates are clinically meaningful, as they encapsulate the expected range of outcomes across the diverse population eligible for tumour-agnostic therapy in NHS practice.

**A13. Priority question: The main analysis of the Bayesian Hierarchical Model (BHM) is based on the ePAS9 database which contains both adults ( $n=$ ██████████) and**

children (n=■). Given the subgroup differences mentioned in question A12, please:

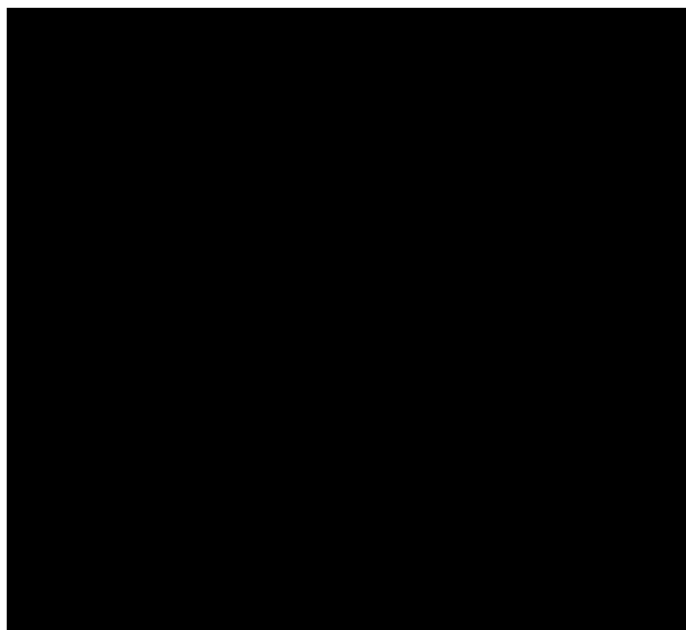
- a) re-run the base-case BHM analysis for adults and children separately (including overall and tumour-specific responses).
- b) provide a separate BHM analysis for the SAS3 database, excluding the single adult in that database.

We understand the request to re-run the BHM by adult and paediatric patients. However, we believe that doing so would not add meaningful insight and could actually reduce the robustness of the results. The BHM used was specifically designed to address heterogeneity across tumour types, which was identified as the main potential source of variation in response to larotrectinib. If we were to split the analysis further by age, the resulting subgroups - particularly for paediatric tumours - would become extremely small, leading to unstable and highly uncertain estimates. Although age was not an explicit factor in the hierarchical model, we believe the BHM adequately captures the relevant heterogeneity through tumour type. Additional stratification by age would add noise rather than enhance clarity.

We have adopted a more nuanced approach beyond examining heterogeneity; specifically, we have analysed the predicted response rate for an as-yet unevaluated tumour type based on the results of the BHM. The estimated distribution of the predicted response rate for this tumour type is presented in Figure 1. Notably, this distribution predicts that under larotrectinib treatment:

- Almost ■ out of ■ (■%) of all as-yet unevaluated tumour types (driven by NTRK gene fusions) would show response rates of 50% or higher.
- Approximately ■ out of ■ (■%) of these tumour types would show a response rate of 30% or higher.
- Almost ■ out of ■ (■%) of these tumour types would show a response rate of 10% or higher.

**Figure 1. Predicted density for response rate in a newly studied tumour type (ePAS9 BHM)**



The BHM also enables the reporting of a heterogeneity-corrected response rate distribution per tumour type. These results are summarised in Figure 2 and Table 5 which displays the 95% predicted intervals (PredI) and the predicted probabilities that the response rate is greater than 10%, 30% or 50%.



**Figure 2. Forest plot of predicted response rates (with 95% PredI), by tumour type**

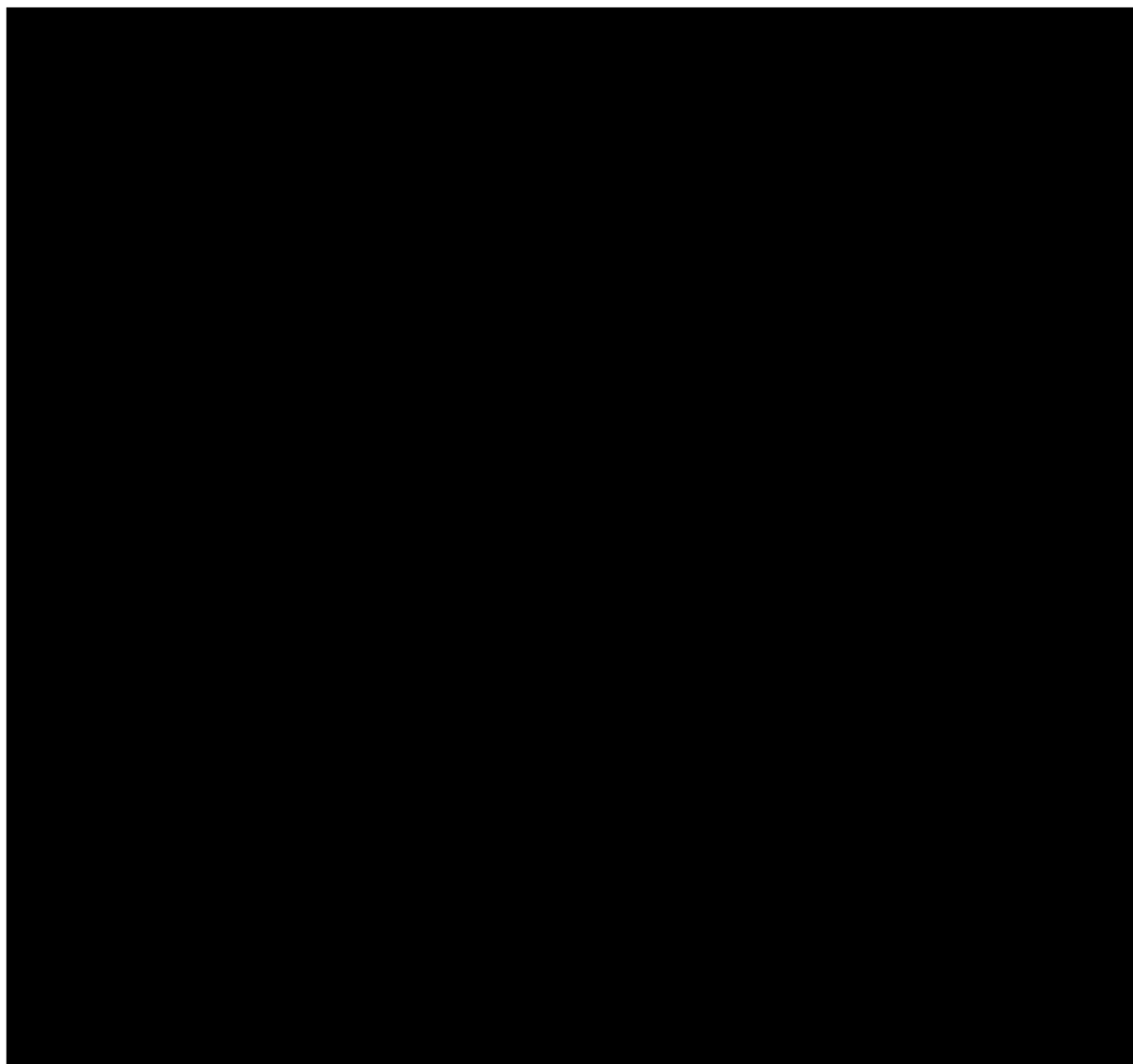


**Table 5. Estimates, 95% CI per tumour type, corr. for heterogeneity; prob. that response rate is higher than 50% / 30% / 10%**

| Tumour type         | Predicted response rate | 5% PredI Limit | 95% PredI Limit | Probability that response rate exceeds: |     |     |
|---------------------|-------------------------|----------------|-----------------|-----------------------------------------|-----|-----|
|                     |                         |                |                 | 50%                                     | 30% | 10% |
| Soft tissue sarcoma | ■                       | ■              | ■               | ■                                       | ■   | ■   |
| IFS                 | ■                       | ■              | ■               | ■                                       | ■   | ■   |

| Tumour type                     | Predicted response rate | 5% Predl Limit | 95% Predl Limit | Probability that response rate exceeds: |   |   |
|---------------------------------|-------------------------|----------------|-----------------|-----------------------------------------|---|---|
| Lung                            | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Thyroid                         | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Salivary gland                  | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Colorectal                      | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Melanoma                        | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Breast non-secretory            | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Pancreas                        | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Breast secretory                | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| GIST                            | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Cholangiocarcinoma              | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Bone sarcoma                    | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Gastric                         | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Cancer of unknown primary       | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Cervix                          | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Congenital mesoblastic nephroma | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Prostate                        | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Appendix                        | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Duodenal                        | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Esophageal                      | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| External auditory canal         | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Hepatic                         | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Lipofibromatosis                | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Testes                          | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Thymus                          | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Urothelial                      | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Uterus                          | ■                       | ■              | ■               | ■                                       | ■ | ■ |
| Total                           | ■                       | ■              | ■               | ■                                       | ■ | ■ |

Another sensitivity analysis was performed, exploring the BHM with ePAS9 and primary CNS combined.

In the July 2024 data, which formed the basis for the ePAS9 population, the separate primary CNS cohort included █ additional patients, of whom █ were classified as responders according to IRC-assessed RANO criteria.

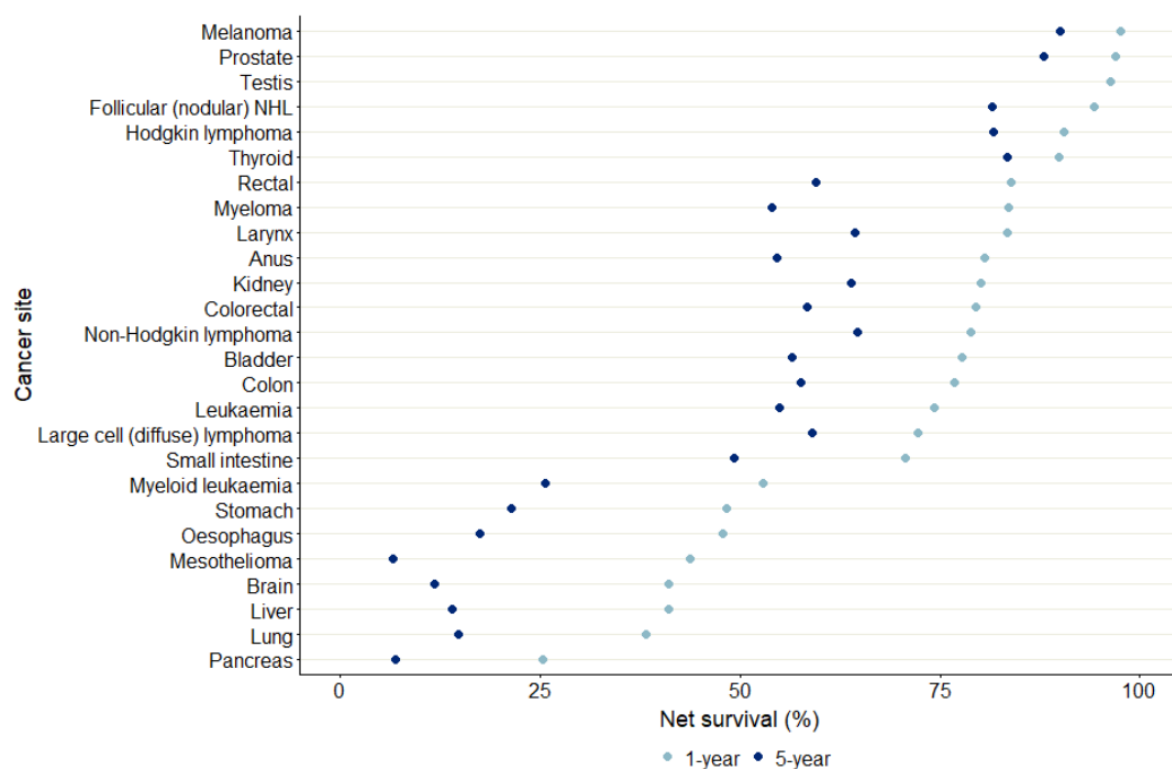
As a sensitivity analysis to the above BHM, a combined model incorporating the primary CNS data was performed. Both models had a similar quality of fit (with a residual deviance of █ for the original model and █ for the sensitivity analysis). Response rate for primary CNS was predicted as █% (95% Predl: █%-█%). The pooled mean response was estimated as █% (95% Predl: █%-█%). Predicted response rates per tumour type were in principle similar to the main model, showing negligible differences (█%) across all tumour types.

A14. ORR, PFS and OS outcomes █ between the ePAS9 and SAS3. Please discuss why, using the trial evidence and real-world evidence as appropriate.

There are several reasons that explain why outcomes █ between primary CNS patients and those with non-primary CNS tumours. Firstly, prognosis varies significantly between these two groups. Data from the UK indicate that patients with primary CNS tumours have substantially lower survival rates compared to most non-CNS solid tumours. For example, national cancer survival statistics for England (covering patients diagnosed with cancer from 2014 to 2018) report markedly lower 1-year and 5-year net survival rates for brain tumours compared to those for common extracranial cancers, for both males and females, see Figure 3 and Figure 4 below (22). This indicates that the primary CNS location is associated with an intrinsically poorer prognosis.

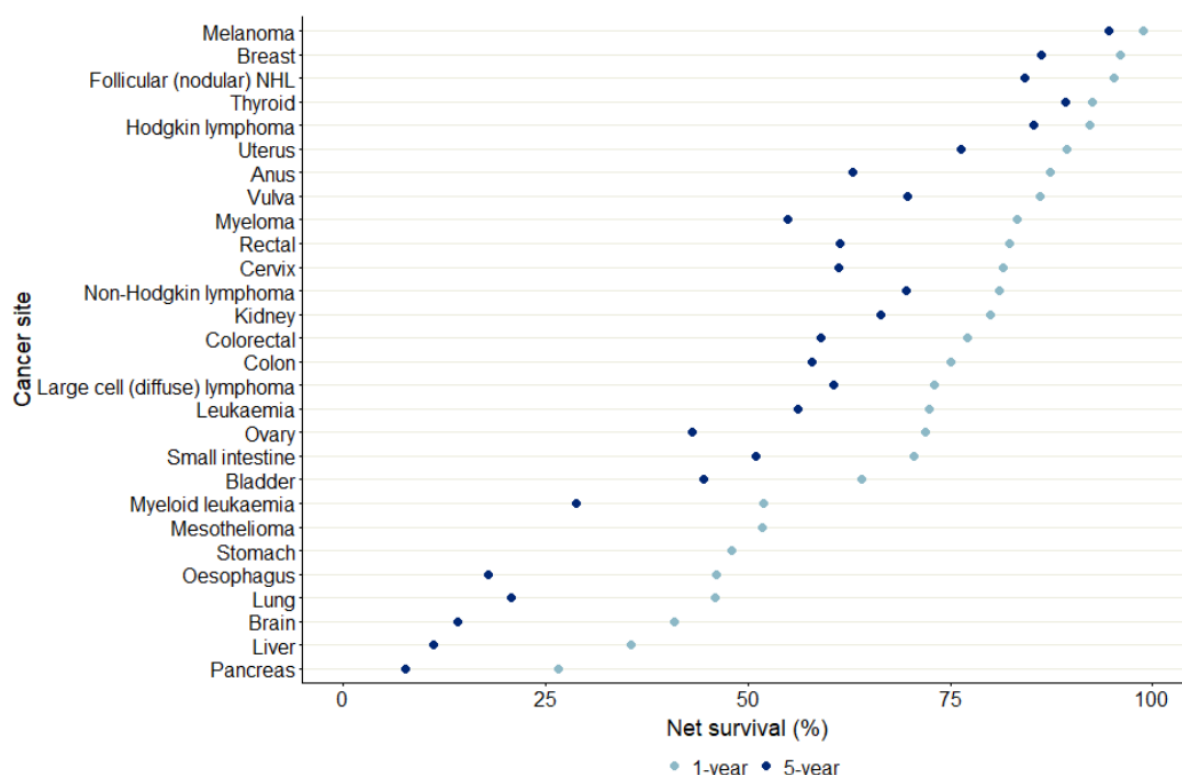
Additionally, this trend of numerically lower outcomes in primary CNS patients is also observed in the real-world study of larotrectinib, ON-TRK (please refer to section 2.13.1 of the CS). Patients with primary CNS tumours have a lower ORR (█% for primary CNS patients vs. █% for non-primary CNS patients), with most primary-CNS patients achieving stable disease (█%). Since this population is particularly hard to treat, it is important to emphasise that stable disease is a significant and positive outcome. This sentiment was echoed during the advisory board meeting, where UK clinicians mentioned that “the value of stable disease is generally underappreciated” and that “response and stable disease are both absolutely key” (1).

**Figure 3. Age-standardised 1-year and 5-year net survival for males (aged 15 to 99 years) diagnosed with cancer in 2014 to 2018**



Source: National Cancer Registration and Analysis Service, Public Health England, 2021 (22)

**Figure 4. Age-standardised 1-year and 5-year net survival for females (aged 15 to 99 years) diagnosed with cancer in 2014 to 2018**



Source: National Cancer Registration and Analysis Service, Public Health England, 2021 (22)

Additionally, patients with primary CNS tumours were evaluated by the IRC using the RANO criteria, whereas other solid tumours were evaluated by the IRC using RECIST v1.1. By investigator, primary CNS tumours were assessed by either RECIST v1.1 or RANO, while non-CNS tumours were assessed by RECIST v1.1.

The RANO criteria has more detailed requirements for identifying a PR in CNS tumours compared to RECIST. While the RECIST criteria mainly rely on changes in the longest diameter of the target lesion to define the response category, the RANO criteria include additional parameters, such as clinical stability and reliance on corticosteroids within the definition. This distinction can also explain the difference in classification of CR and PR. Nevertheless, the DCR, which combines CR, PR and SD, is ██████ for ePAS9 and SAS3, reported at █████% and █████%, respectively.

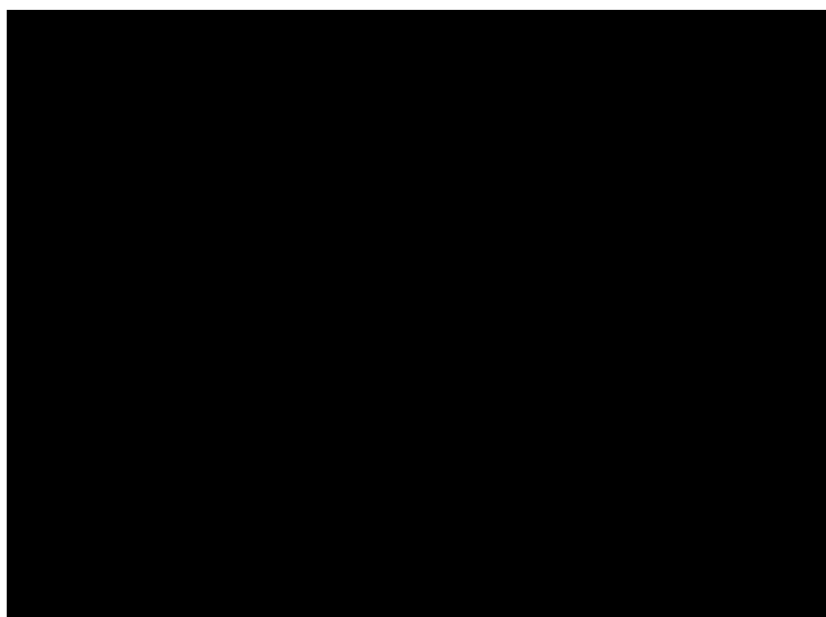
A15. Appendix C shows that ORR ██████ between the ██████ in ePAS9 and SAS3. Please provide separate PFS and OS

estimates and Kaplan-Meier curves for adult and paediatric patients for ePAS9 and SAS3, similarly to CS Figure 10.

Kaplan-Meier curves for progression-free survival and overall survival for adults and paediatrics are shown from Figure 5 to Figure 12.

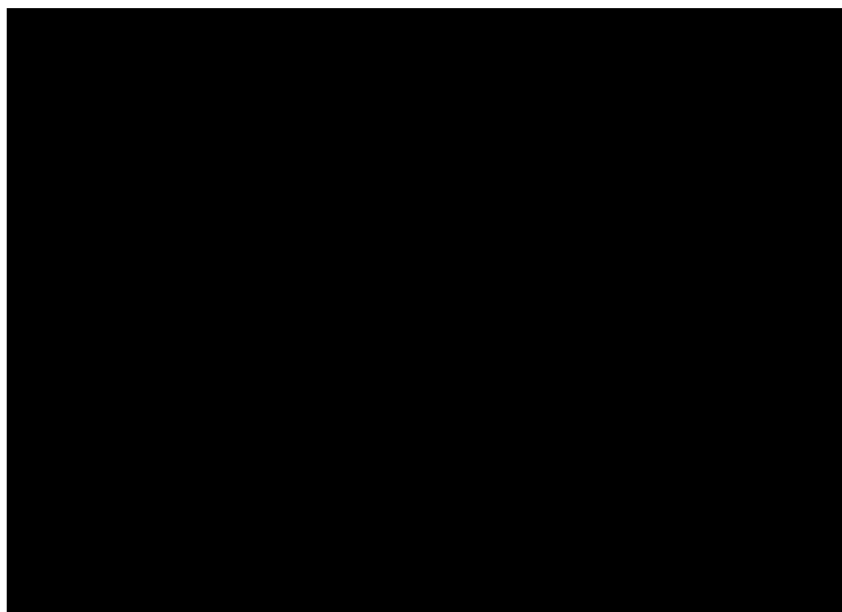
### **Progression-free survival**

**Figure 5. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessments for Adults (ePAS9, Visit Cut-off 20<sup>th</sup> July 2024)**



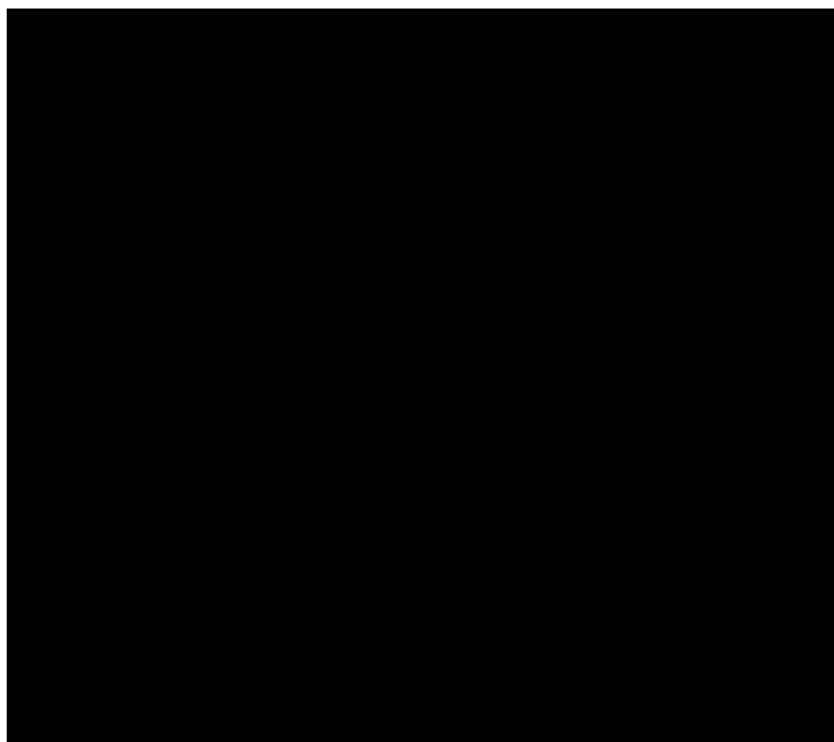
Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 6. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessments for Paediatrics (ePAS9, Visit Cut-off 20<sup>th</sup> July 2024)**



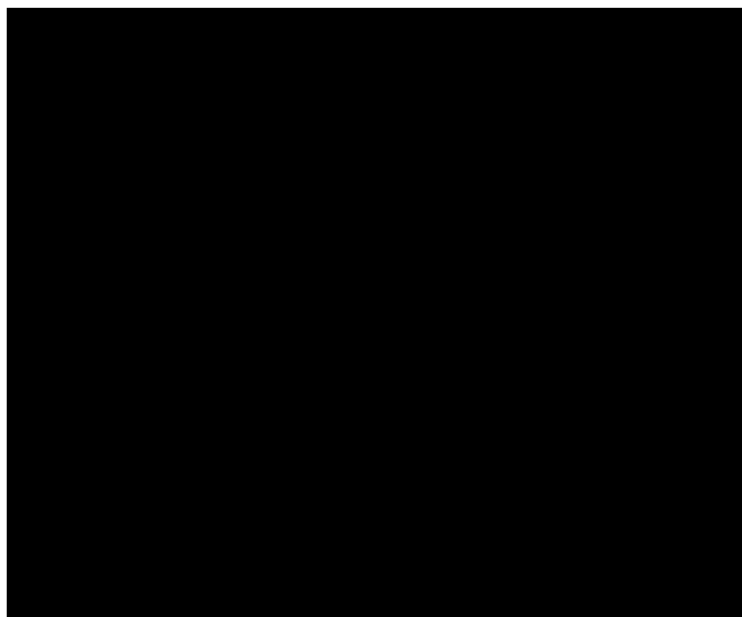
Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 7. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessments for Adults (SAS3, Visit Cut-off 20<sup>th</sup> July 2024)**



Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 8. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessments for Paediatrics (SAS3, Visit Cut-off 20<sup>th</sup> July 2024)**

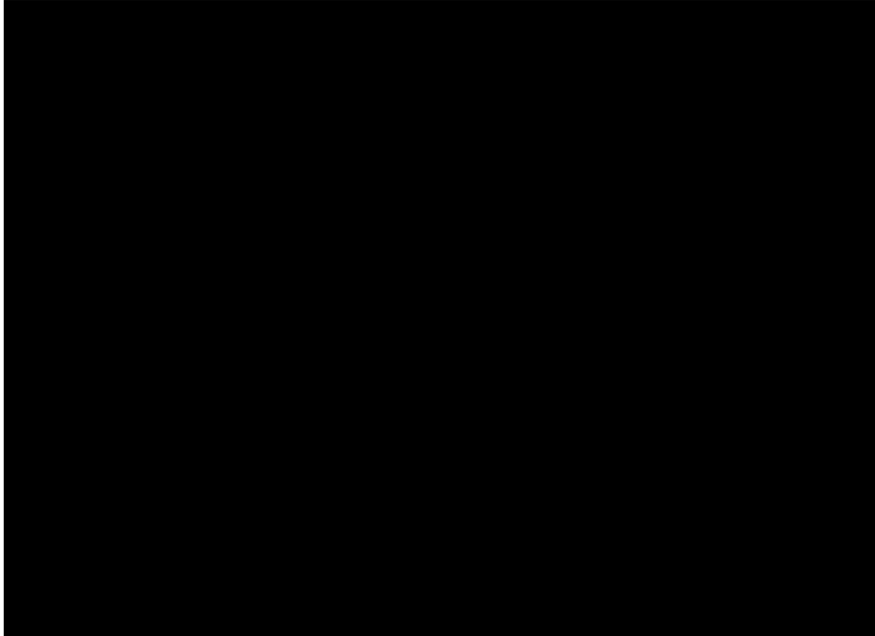


Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)



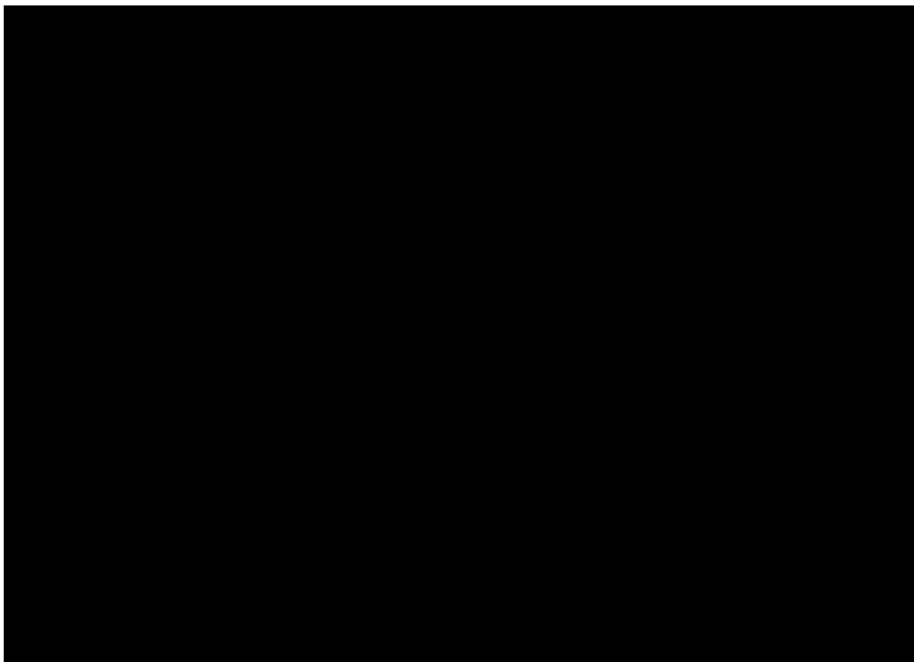
## Overall survival

**Figure 9. Kaplan-Meier Plot of Overall Survival for Adults (ePAS9, Visit Cut-off 20<sup>th</sup> July 2024)**



Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 10. Kaplan-Meier Plot of Overall Survival for Paediatrics (ePAS9, Visit Cut-off 20<sup>th</sup> July 2024)**



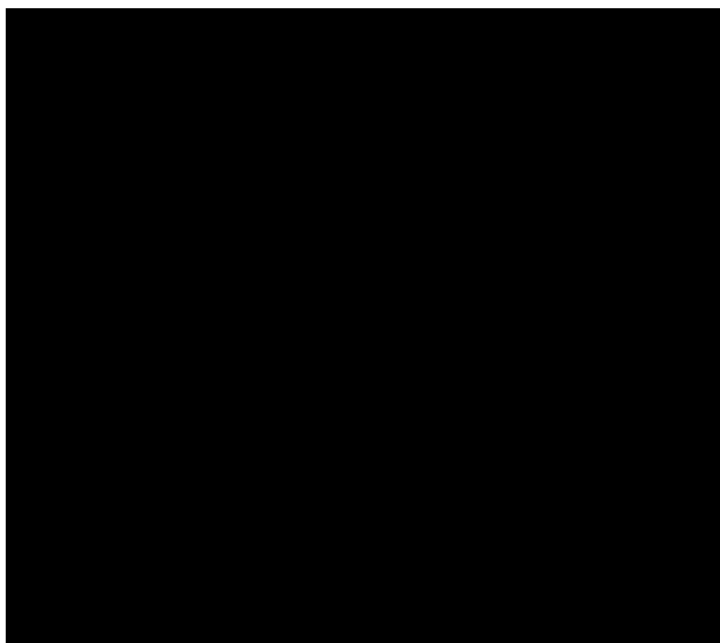
Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 11. Kaplan-Meier Plot of Overall Survival for Adults (SAS3, Visit Cut-off 20<sup>th</sup> July 2024)**



Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Figure 12. Kaplan-Meier Plot of Overall Survival for Paediatrics (SAS3, Visit Cut-off 20<sup>th</sup> July 2024)**



Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

## Estimates

PFS and OS estimates for ePAS9 and SAS3 population are presented in Table 6 to Table 13 for adults and paediatrics.

**Table 6. Progression-free Survival for Adults (ePAS9, data cut-off 20<sup>th</sup> July, 2024)**

| Status                                               | ePAS9<br>(N= [REDACTED]) |
|------------------------------------------------------|--------------------------|
| Progression Status [1,2,3]                           |                          |
| Progressed                                           | [REDACTED]               |
| Censored                                             | [REDACTED]               |
| Reason Progressed                                    |                          |
| Died without disease progression beforehand          | [REDACTED]               |
| Progressed                                           | [REDACTED]               |
| Reason Censored                                      |                          |
| Alive without documented disease progression         | [REDACTED]               |
| Surgical resection of tumor without pCR              | [REDACTED]               |
| Anti-cancer therapy date before death date           | [REDACTED]               |
| No evaluable postbaseline disease assessments        | [REDACTED]               |
| Duration of Progression-free Survival                |                          |
| 6 months or less                                     | [REDACTED]               |
| > 6 to 12 months                                     | [REDACTED]               |
| > 12 to 18 months                                    | [REDACTED]               |
| > 18 to 24 months                                    | [REDACTED]               |
| > 24 to 36 months                                    | [REDACTED]               |
| > 36 to 48 months                                    | [REDACTED]               |
| > 48 to 60 months                                    | [REDACTED]               |
| > 60 to 72 months                                    | [REDACTED]               |
| > 72 to 84 months                                    | [REDACTED]               |
| > 84 months                                          | [REDACTED]               |
| Duration of Progression-free Survival (months) [4,5] |                          |
| Median                                               | [REDACTED]               |
| 95% confidence interval for median                   | [REDACTED]               |
| Minimum, Maximum                                     | [REDACTED]               |
| Duration of Follow-up (months) [4]                   |                          |
| Median                                               | [REDACTED]               |
| 25th, 75th percentiles                               | [REDACTED]               |

| Status                                      | ePAS9<br>(N=■) |
|---------------------------------------------|----------------|
| Rate (%) of Progression-free Survival [4,5] |                |
| 6 months or more                            |                |
| 95% confidence interval                     |                |
| 12 months or more                           |                |
| 95% confidence interval                     |                |
| 18 months or more                           |                |
| 95% confidence interval                     |                |
| 24 months or more                           |                |
| 95% confidence interval                     |                |
| 36 months or more                           |                |
| 95% confidence interval                     |                |
| 48 months or more                           |                |
| 95% confidence interval                     |                |
| 60 months or more                           |                |
| 95% confidence interval                     |                |
| 72 months or more                           |                |
| 95% confidence interval                     |                |
| 84 months or more                           |                |
| 95% confidence interval                     |                |

Percentages are based on the number of patients in the analysis set.

A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.

The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.

Pathological complete response was previously referred to as surgical CR.

[1] Based on IRC assessments.

[2] Progression status based on radiologist and clinician assessments.

[3] Status as of the patient's last disease assessment on or before visit cutoff.

[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[5] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Table 7. Progression-free Survival for Paediatrics (ePAS9, data cut-off 20<sup>th</sup> July, 2024)**

| Status                                        | ePAS9<br>(N=■) |
|-----------------------------------------------|----------------|
| Progression Status [1,2,3]                    |                |
| Progressed                                    |                |
| Censored                                      |                |
| Reason Progressed                             |                |
| Died without disease progression beforehand   |                |
| Progressed                                    |                |
| Reason Censored                               |                |
| Alive without documented disease progression  |                |
| Surgical resection of tumor without pCR       |                |
| No evaluable postbaseline disease assessments |                |

| Status                                               | ePAS9<br>(N=■) |
|------------------------------------------------------|----------------|
| Duration of Progression-free Survival                |                |
| 6 months or less                                     |                |
| > 6 to 12 months                                     |                |
| > 12 to 18 months                                    |                |
| > 18 to 24 months                                    |                |
| > 24 to 36 months                                    |                |
| > 36 to 48 months                                    |                |
| > 48 to 60 months                                    |                |
| > 60 to 72 months                                    |                |
| > 72 to 84 months                                    |                |
| > 84 months                                          |                |
| Duration of Progression-free Survival (months) [4,5] |                |
| Median                                               |                |
| 95% confidence interval for median                   |                |
| Minimum, Maximum                                     |                |
| Duration of Follow-up (months) [4]                   |                |
| Median                                               |                |
| 25th,75th percentiles                                |                |
| Rate (%) of Progression-free Survival [4,5]          |                |
| 6 months or more                                     |                |
| 95% confidence interval                              |                |
| 12 months or more                                    |                |
| 95% confidence interval                              |                |
| 18 months or more                                    |                |
| 95% confidence interval                              |                |
| 24 months or more                                    |                |
| 95% confidence interval                              |                |
| 36 months or more                                    |                |
| 95% confidence interval                              |                |
| 48 months or more                                    |                |
| 95% confidence interval                              |                |
| 60 months or more                                    |                |
| 95% confidence interval                              |                |
| 72 months or more                                    |                |
| 95% confidence interval                              |                |
| 84 months or more                                    |                |
| 95% confidence interval                              |                |

Percentages are based on the number of patients in the analysis set.

A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.

The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.

Pathological complete response was previously referred to as surgical CR.

[1] Based on IRC assessments.

[2] Progression status based on radiologist and clinician assessments.

[3] Status as of the patient's last disease assessment on or before visit cutoff.

[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[5] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Table 8. Progression-free Survival for Adults (SAS3, data cut-off 20<sup>th</sup> July 2024)**

| Status                     | ePAS9<br>(N=■) |
|----------------------------|----------------|
| Progression Status [1,2,3] |                |
| Progressed                 |                |
| Censored                   |                |

| Status                                               | ePAS9<br>(N=■) |
|------------------------------------------------------|----------------|
| Reason Progressed                                    |                |
| Died without disease progression beforehand          | ■              |
| Progressed                                           | ■              |
| Reason Censored                                      |                |
| Alive without documented disease progression         | ■              |
| Duration of Progression-free Survival                |                |
| 6 months or less                                     | ■              |
| > 6 to 12 months                                     | ■              |
| > 12 to 18 months                                    | ■              |
| > 24 to 36 months                                    | ■              |
| Duration of Progression-free Survival (months) [4,5] |                |
| Median                                               | ■              |
| 95% confidence interval for median                   | ■              |
| Minimum, Maximum                                     | ■              |
| Duration of Follow-up (months) [4]                   |                |
| Median                                               | ■              |
| 25th,75th percentiles                                | ■              |
| Rate (%) of Progression-free Survival [4,5]          |                |
| 6 months or more                                     | ■              |
| 95% confidence interval                              | ■              |
| 12 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 18 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 24 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 36 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 48 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 60 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 72 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 84 months or more                                    | ■              |
| 95% confidence interval                              | ■              |

Percentages are based on the number of patients in the analysis set.

A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.

The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.

Pathological complete response was previously referred to as surgical CR.

[1] Based on IRC assessments.

[2] Progression status based on radiologist and clinician assessments.

[3] Status as of the patient's last disease assessment on or before visit cutoff.

[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[5] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005)  
(23)

**Table 9. Progression-free Survival for Paediatrics (SAS3, data cut-off 20<sup>th</sup> July 2024)**

| Status                                               | ePAS9<br>(N=■) |
|------------------------------------------------------|----------------|
| Progression Status [1,2,3]                           |                |
| Progressed                                           | ■              |
| Censored                                             | ■              |
| Reason Progressed                                    |                |
| Died without disease progression beforehand          | ■              |
| Progressed                                           | ■              |
| Reason Censored                                      |                |
| Alive without documented disease progression         | ■              |
| Surgical resection of tumor without pCR              | ■              |
| Duration of Progression-free Survival                |                |
| 6 months or less                                     | ■              |
| > 6 to 12 months                                     | ■              |
| > 12 to 18 months                                    | ■              |
| > 18 to 24 months                                    | ■              |
| > 24 to 36 months                                    | ■              |
| > 36 to 48 months                                    | ■              |
| > 48 to 60 months                                    | ■              |
| > 60 to 72 months                                    | ■              |
| > 72 to 84 months                                    | ■              |
| Duration of Progression-free Survival (months) [4,5] |                |
| Median                                               | ■              |
| 95% confidence interval for median                   | ■              |
| Minimum, Maximum                                     | ■              |
| Duration of Follow-up (months) [4]                   |                |
| Median                                               | ■              |
| 25th,75th percentiles                                | ■              |
| Rate (%) of Progression-free Survival [4,5]          |                |
| 6 months or more                                     | ■              |
| 95% confidence interval                              | ■              |
| 12 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 18 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 24 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 36 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 48 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 60 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 72 months or more                                    | ■              |
| 95% confidence interval                              | ■              |
| 84 months or more                                    | ■              |
| 95% confidence interval                              | ■              |

Percentages are based on the number of patients in the analysis set.

A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.

The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.

Pathological complete response was previously referred to as surgical CR.

[1] Based on IRC assessments.

[2] Progression status based on radiologist and clinician assessments.

[3] Status as of the patient's last disease assessment on or before visit cutoff.

[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.  
 [5] 95% confidence interval was calculated using Greenwood's formula.  
 Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005)  
 (23)

**Table 10. Overall Survival for Adults (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

| Status                                      | ePAS9<br>(N=██) |
|---------------------------------------------|-----------------|
| Vital Status [1]                            |                 |
| Dead                                        | ██              |
| Censored                                    | ██              |
| Reason Censored                             |                 |
| Alive                                       | ██              |
| Study discontinuation                       | ██              |
| Start taking a subsequent therapy           | ██              |
| Duration of Overall Survival (months) [2,3] |                 |
| Median                                      | ██              |
| 95% confidence interval for median          | ██              |
| Minimum, Maximum                            | ██              |
| Duration of Follow-up (months) [2]          |                 |
| Median                                      | ██              |
| 25th,75th percentiles                       | ██              |
| Rate (%) of Overall Survival [2,3]          |                 |
| 6 months or more                            | ██              |
| 95% confidence interval                     | ██              |
| 12 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 18 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 24 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 36 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 48 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 60 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 72 months or more                           | ██              |
| 95% confidence interval                     | ██              |
| 84 months or more                           | ██              |
| 95% confidence interval                     | ██              |

Percentages are based on the number of patients in the analysis set.

[1] Status as of the last contact on or before visit cutoff.

[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[3] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005)  
 (23)

**Table 11. Overall Survival for Paediatrics (ePAS9, data cut-off 20<sup>th</sup> July 2024)**

| Status           | ePAS9<br>(N=██) |
|------------------|-----------------|
| Vital Status [1] |                 |
| Dead             | ██              |
| Censored         |                 |



| Status                                      | ePAS9<br>(N=■) |
|---------------------------------------------|----------------|
| Reason Censored                             |                |
| Alive                                       |                |
| Study discontinuation                       |                |
| Start taking a subsequent therapy           |                |
| Duration of Overall Survival (months) [2,3] |                |
| Median                                      |                |
| 95% confidence interval for median          |                |
| Minimum, Maximum                            |                |
| Duration of Follow-up (months) [2]          |                |
| Median                                      |                |
| 25th,75th percentiles                       |                |
| Rate (%) of Overall Survival [2,3]          |                |
| 6 months or more                            |                |
| 95% confidence interval                     |                |
| 12 months or more                           |                |
| 95% confidence interval                     |                |
| 18 months or more                           |                |
| 95% confidence interval                     |                |
| 24 months or more                           |                |
| 95% confidence interval                     |                |
| 36 months or more                           |                |
| 95% confidence interval                     |                |
| 48 months or more                           |                |
| 95% confidence interval                     |                |
| 60 months or more                           |                |
| 95% confidence interval                     |                |
| 72 months or more                           |                |
| 95% confidence interval                     |                |
| 84 months or more                           |                |
| 95% confidence interval                     |                |

Percentages are based on the number of patients in the analysis set.

[1] Status as of the last contact on or before visit cutoff.

[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[3] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005)  
(23)

**Table 12. Overall Survival for Adults (SAS3, data cut-off 20<sup>th</sup> July 2024)**

| Status                                      | SAS3<br>(N=■) |
|---------------------------------------------|---------------|
| Vital Status [1]                            |               |
| Dead                                        |               |
| Censored                                    |               |
| Reason Censored                             |               |
| Alive                                       |               |
| Start taking a subsequent therapy           |               |
| Duration of Overall Survival (months) [2,3] |               |
| Median                                      |               |
| 95% confidence interval for median          |               |
| Minimum, Maximum                            |               |
| Duration of Follow-up (months) [2]          |               |
| Median                                      |               |
| 25th,75th percentiles                       |               |

| Status                             | SAS3<br>(N=■) |
|------------------------------------|---------------|
| Rate (%) of Overall Survival [2,3] |               |
| 6 months or more                   |               |
| 95% confidence interval            |               |
| 12 months or more                  |               |
| 95% confidence interval            |               |
| 18 months or more                  |               |
| 95% confidence interval            |               |
| 24 months or more                  |               |
| 95% confidence interval            |               |
| 36 months or more                  |               |
| 95% confidence interval            |               |
| 48 months or more                  |               |
| 95% confidence interval            |               |
| 60 months or more                  |               |
| 95% confidence interval            |               |
| 72 months or more                  |               |
| 95% confidence interval            |               |
| 84 months or more                  |               |
| 95% confidence interval            |               |

Percentages are based on the number of patients in the analysis set.

[1] Status as of the last contact on or before visit cutoff.

[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[3] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

**Table 13. Overall Survival for Paediatrics (SAS3, data cut-off 20<sup>th</sup> July 2024)**

| Status                                      | SAS3<br>(N=■) |
|---------------------------------------------|---------------|
| Vital Status [1]                            |               |
| Dead                                        |               |
| Censored                                    |               |
| Reason Censored                             |               |
| Alive                                       |               |
| Study discontinuation                       |               |
| Start taking a subsequent therapy           |               |
| Duration of Overall Survival (months) [2,3] |               |
| Median                                      |               |
| 95% confidence interval for median          |               |
| Minimum, Maximum                            |               |
| Duration of Follow-up (months) [2]          |               |
| Median                                      |               |
| 25th,75th percentiles                       |               |

| Status                             | SAS3<br>(N=■) |
|------------------------------------|---------------|
| Rate (%) of Overall Survival [2,3] |               |
| 6 months or more                   |               |
| 95% confidence interval            |               |
| 12 months or more                  |               |
| 95% confidence interval            |               |
| 18 months or more                  |               |
| 95% confidence interval            |               |
| 24 months or more                  |               |
| 95% confidence interval            |               |
| 36 months or more                  |               |
| 95% confidence interval            |               |
| 48 months or more                  |               |
| 95% confidence interval            |               |
| 60 months or more                  |               |
| 95% confidence interval            |               |
| 72 months or more                  |               |
| 95% confidence interval            |               |
| 84 months or more                  |               |
| 95% confidence interval            |               |

Percentages are based on the number of patients in the analysis set.

[1] Status as of the last contact on or before visit cutoff.

[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.

[3] 95% confidence interval was calculated using Greenwood's formula.

Source: Bayer. Data on file. Tables, figures and listings for NICE request. 2731953\_nice\_request\_tables\_20jul2024\_new (005) (23)

## Comparator evidence

A16. CS Table 49 lists comparators and trials for the tumour types included in the economic model. Please clarify the process by which these were identified and selected.

Comparators were selected following the process outlined in section 3.2.4 of the CS. Namely, tumour-specific ESMO guidelines were leveraged to identify the recommended second-line treatment, based on the assumption that most patients are treated in the second line within the SACT report (24). In cases where several treatments were available, UK clinical experts, who were part of an advisory board, selected the treatment they deemed most appropriate according to UK clinical practice. Additionally, when the guidelines were directly reporting NTRK inhibitors use at later lines of treatment, last-line therapies as specified in the guidelines were chosen.

Once the comparator had been chosen, the source of the data was determined based on clinician recommendation if no NICE TA was available. If a NICE TA was available,

it was leveraged to inform the selection. The detailed methodology for each tumour site is reported in question A1.

## ***Real-world evidence***

**A17. Priority question: Please provide the following additional data for the SACT data:**

- **Number of adults with primary CNS tumour**
- **Number of adults without primary CNS tumour**
- **Number of children with primary CNS tumour**
- **Number of children without primary CNS tumour**

Prior to the CS, the company already contacted the SACT team while reviewing the CDF SACT data report to request additional information, specifically regarding the breakdown between adult and paediatric patients. They responded with the following: *“NDRS have confirmed that unfortunately, as these were not outlined in the Data Collection Arrangement, they are unable to provide this additional data at this time”*. As a result, the requested data is not available.

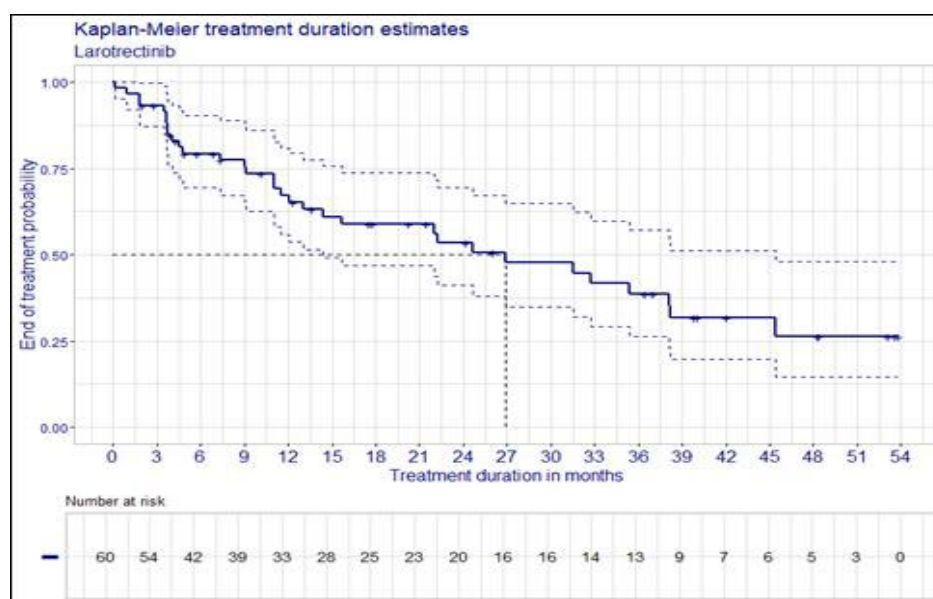
**A18. Priority question: For each of the subgroups listed in Question A18 above, please provide TTD and OS data, and corresponding Kaplan-Meier curves.**

As highlighted in question A17, this data is not available in the SACT report, and the company’s request for additional information was unfortunately rejected.

**A19. Priority question: CS Section 2.13.2.4.2 (SACT results) does not present a Kaplan-Meier curve for TTD. Please provide this.**

A Kaplan–Meier analysis of time to treatment discontinuation (TTD) is not available, as this analysis was not included in the SACT report. The report only provided summary data on treatment duration, together with the overall number of patients remaining on treatment at the data cut-off. Individual patient-level censoring information was not available; therefore, it is not possible to reproduce or generate a Kaplan–Meier analysis of TTD. For reference, the curve for duration on larotrectinib from SACT is displayed in Figure 13 (24).

**Figure 13. Kaplan–Meier analysis of treatment duration for larotrectinib, SACT report**



Source: SACT report (24)

### ***Matching adjusted indirect comparisons (MAICs)***

**A20. Priority question: The MAICs reported in CS Section 2.10 compare IPD from subsets of the clinical trial evidence against SOC cohorts from various data sources (e.g. FLATIRON). MAICs are normally performed where IPD is only available for some treatments, whilst aggregate outcomes and marginal covariate information is only available for other treatments. Please clarify whether IPD was available for some of the comparator evidence sources, and if so, why aggregate data was preferred.**

For the MAICs presented in Section 2.10 of the CS, the availability of IPD varied across analyses. Specifically, two of the MAICs (HMF and Bokemeyer) were conducted using only IPD from larotrectinib clinical trials and aggregate-level data from the comparator studies. In contrast, the remaining two MAICs (EPI VITRAKVI and VICTORIA) had access to IPD for both larotrectinib trials and the real-world comparator cohorts.

For the MAICs where IPD was available for both treatment and comparator populations, the analyses utilised both datasets directly to achieve the highest level of adjustment possible, allowing for more precise matching and weighting at the patient level. Conversely, for the MAICs where IPD was not available for the comparator

sources, only published aggregate outcomes and baseline characteristics could be used. In these cases, the tropomyosin receptor kinase inhibitor (TRKi) IPD (i.e., larotrectinib) was reweighted to match the aggregate-level characteristics of the comparator populations, in accordance with standard MAIC methodology.

Therefore, aggregate-level methods were employed only when IPD was not accessible for the comparator evidence sources. When IPD was available, it was fully utilised to enhance the robustness of the comparative analyses.

**A21. Priority question: Although VOYAGER 1 and 2 found numerically higher rates of death in patients with NTRK fusion positive tumours vs. NTRK negative patients, the difference was not statistically significant between cohorts. Bridgewater (2022) (25) noted that “in the absence of TRK inhibitors, the two studies did not find statistically different survival between patients with or without NTRK gene fusions, suggesting NTRK gene fusion is not a prognostic indicator itself”, whilst Bahzenova (2021) concluded that “based on current evidence, patients with NTRK gene fusions do not have a statistically worse or better prognosis than patients with NTRK wild-type”. Given this evidence, please justify the decision to only include NTRK fusion positive patients in the SOC cohorts of the MAICs.**

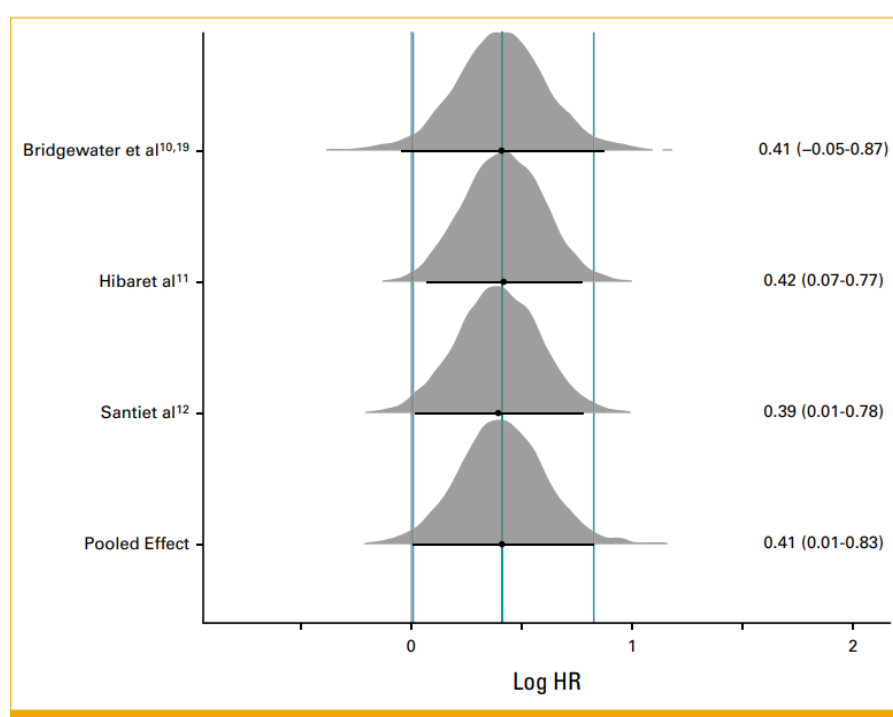
The decision to include only patients with NTRK fusion-positive tumours in the SOC cohorts of the MAICs was based on the mechanism of action and licensed indication of larotrectinib, rather than on the assumption of a prognostic difference between NTRK fusion positive and negative.

The common objective of the four MAICs is to evaluate the comparative effectiveness of larotrectinib versus standard-of-care (SoC) regimens in patients with TRK fusion-positive cancers, using matching-adjusted indirect comparison (MAIC) or other comparative methodologies to address the lack of direct, randomized data and facilitate understanding and comparability of larotrectinib’s clinical benefit across tumour types.

The majority of available evidence (e.g., Bridgewater 2022 (25); Bahzenova 2021(26)) could not conclude that there is a differential survival between NTRK-fusion positive and negative patients, as the observed differences were not statistically significant.

However, the meta-analysis by Lassen et al. (2023), which aggregates several evidence sources, concludes that the pooled HR estimate from this model was 1.51 (95% CI, 1.01 to 2.29) with a between-study heterogeneity parameter tau of 0.10 (95% CI, 0.00 to 0.52) (27). In summary, patients with NTRK gene fusions have a 51% increased risk of mortality compared to those without NTRK gene fusions. Furthermore, there is a 95% probability that the true HR lies between 1.01 and 2.29, based on the evidence provided by the observed pooled data. This additional evidence indicates that a prognostic difference cannot be excluded. Figure 14 displays the posterior mean log HR for the overall pooled and study-wise estimates with 95% CIs.

**Figure 14. Forest plot of log HRs (95% credible intervals) for overall survival from the best-fitting Bayesian random-effects model. Lassen et al. 2023**



Source: Lassen et al. 2023 (27)

Given this uncertainty and recognising that larotrectinib's benefit is restricted to tumours driven by NTRK fusions, restricting the SOC cohorts to NTRK fusion-positive patients was considered methodologically appropriate. This approach ensures that comparisons are conducted in a biologically and clinically relevant population, consistent with the licensed indication, and avoids potential bias from including molecularly distinct comparator populations.

A22. The systematic literature review did not identify the MAICs. Please clarify how the four MAICs (FLATIRON, VICTORIA, Hartwig Medical Foundation [HMF] and EPI VITRAKVI) were identified and selected. If this followed a systematic review process, please provide the results of the review, and any relevant exclusions.

All four studies were identified in the clinical SLR searches. However, they were excluded during screening based on study design, as observational studies were not within the scope of the original SLR. Consequently, they were also excluded in the SLR update for this CS in order to manage the scope of the search.

**A23. Priority question: The methods of all four MAICs are not reported in sufficient detail in the CS to assess their validity; most information is in separate publications. For each MAIC, please provide a structured report, including:**

**A. Variables:**

- **Process for identifying and selecting relevant prognostic factors and treatment effect modifiers.**
- **Availability of variables.**
- **Distribution of variables available and assessment of covariate overlap.**
- **Number (%) of individuals with zero weight.**
- **Evidence for effect modifier status: proposed size of interaction effect; potential size of bias reduction.**

**B. Weights**

- **Distribution of weights**
- **Effective sample size**

**C. Uncertainty**

- **Robust sandwich estimator/bootstrapping**

**D. Systematic error**



- **Present estimates of systematic error before and after adjustment**
- **If evidence is limited, discuss whether bias is likely to be substantial**

#### **E. Target population**

- **Discuss representativeness of the Larotrectinib population included vs. the NHS (SACT) population**
- **Discuss representativeness of the SOC population included vs. the NHS (SACT) population**
- **Discuss applicability of treatments in the SOC populations to NHS practice.**

#### **F. Standard ITC**

- **Present standard ITC to demonstrate impact of population adjustment.**
- **Assess sensitivity of results to different model specifications.**

#### **G. A discussion of strengths and limitations of each MAIC.**

Whilst we appreciate that some of this information is already reported in the CS and reference pack for some of the MAICs, this needs to be presented consistently in the CS (e.g. report effective sample size for FLATIRON, VICTORIA and EPI VITRAKVI, not just for HMF).

The requested details for each MAIC presented in the CS are provided below. It is important to note that the MAICs presented in the CS consistently showed benefits in favour of larotrectinib compared to real-world SoC cohorts. Furthermore, these MAICs provide the much-needed comparative clinical effectiveness of larotrectinib, complementing the evidence from the clinical trials and addressing a key uncertainty in TA630. While there are similarities in patient characteristics between the larotrectinib and SoC cohorts of the MAICs compared to the NHS (SACT) population (e.g., ECOG performance status, tumour type distribution), some differences do exist (e.g., age, rates of metastatic disease, line of therapy).

The representativeness of the MAIC cohorts compared to the NHS (SACT) population should be interpreted with caution due to the small number of patients in the SACT dataset (n=60) and the substantial missing data on key variables. In addition, as elaborated in the company's response to question A3, studies of tumour-agnostic and age-agnostic therapies like larotrectinib will inherently include heterogeneous patient populations, thereby making the assessment of representativeness challenging. Furthermore, given the highly restrictive nature of the CDF criteria for larotrectinib in NTRK fusion-positive solid tumours, the SACT population may not be fully representative of the NHS population who are likely to receive larotrectinib (refer to CS Section 2.13.2 for more details).

### **Flatiron MAIC**

#### **A. Variables:**

- **Process for identifying and selecting relevant prognostic factors and treatment effect modifiers.**
- **Availability of variables.**

In the Bokemeyer *et al.* (2023) study comparing larotrectinib with SoC using MAIC, the prognostic factors and treatment effect modifiers were selected based on clinical relevance and their availability in both datasets used in the study (i.e., individual patient level data from the larotrectinib trials and the aggregated data from Flatiron Health/Foundation Medicine real-world dataset), including NTRK fusion subtype, age, ECOG performance status, number of prior systemic therapies, disease stage at diagnosis, presence of brain metastases and tumour type. Where data were missing in the SoC group regarding the number of prior lines of therapy or the ECOG status, conservative assumptions were applied. For example, ECOG performance status was imputed to the more severe 2-4 category, or it was assumed that patients had  $\geq 3$  prior lines of therapy, to maintain analytical rigour. Sensitivity analyses were conducted to assess the impact of these imputations, ensuring the robustness of the comparison (28).

- **Distribution of variables available and assessment of covariate overlap.**

The distribution of the aforementioned variables was analysed to ensure that the patient populations were sufficiently comparable. Covariate overlap was assessed using statistical techniques, including inverse propensity score weighting and log-rank testing, to confirm that the matched populations had similar baseline characteristics. This validation step was crucial to minimise bias and ensure the reliability of the survival outcome comparisons between larotrectinib and SoC.

- **Number (%) of individuals with zero weight.**

The exact number of individuals with zero weight is not available; however, most weights were  $\leq 1$ , with few outliers with higher weights, as shown in .

- **Evidence for effect modifier status: proposed size of interaction effect; potential size of bias reduction.**

The larotrectinib trial population included 85 patients after applying eligibility criteria; however, after matching for baseline characteristics in the MAIC analysis, the effective sample size (ESS) reduced to 13.1 in the base case. While patient characteristics post-matching were comparable, only a small subset of patients were sufficiently similar for an unbiased comparison. Sensitivity analyses that relaxed matching assumptions increased the ESS up to 38.6, though overlap remained limited. Overall, while matching helps address bias, the results should be interpreted with caution given the small ESS.

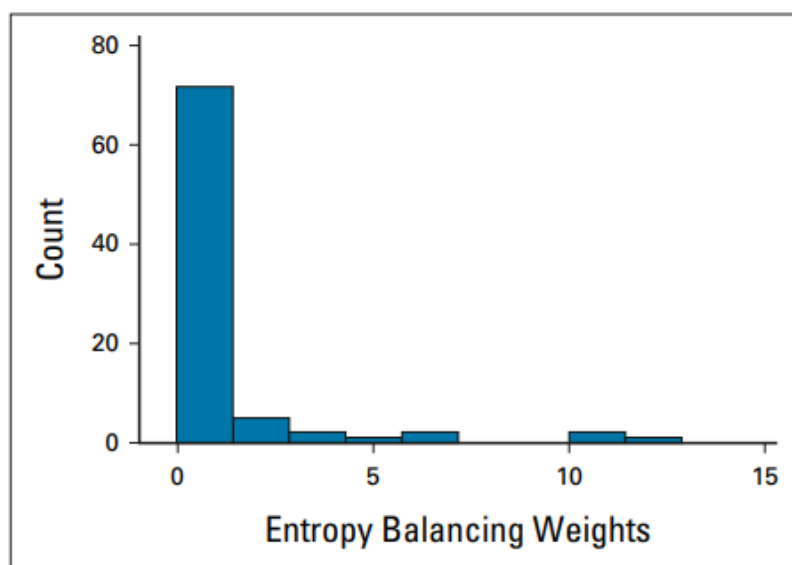
The size of the interaction effect was not explored, as subgroup analysis was not performed.

## **B. Weights**

- **Distribution of weights:**

The weight distribution is presented in Figure 15. Most weights were  $\leq 1$ , with some outliers with higher weights.

**Figure 15. Histogram of patient weights (Flatiron MAIC)**



Source: Bokemeyer *et al.* 2022 (28)

#### - **Effective sample size**

In the base case analysis, the ESS was 13.1. Sensitivity analyses that relaxed some matching assumptions increased the ESS to between 23.6 and 38.6, depending on which variables were included or excluded from the matching process. The HR and ESS using alternative variables for matching are presented in Table 15.

**Table 14. HR and effective sample sizes using alternative variables for matching (Flatiron MAIC).**

| Matching Variables                                | Effective sample size | HR (95% CI)         |
|---------------------------------------------------|-----------------------|---------------------|
| Base case                                         | 13.1                  | 0.22 (0.09 to 0.52) |
| Missing values in prior lines of therapy and ECOG | 23.6                  | 0.10 (0.04 to 0.22) |
| Plus removing CUP and breast cancer               | 26.4                  | 0.10 (0.05 to 0.21) |
| Plus removing CRC                                 | 37.9                  | 0.12 (0.05 to 0.26) |
| Plus removing salivary                            | 38.6                  | 0.12 (0.05 to 0.25) |

Abbreviations: CI, confidence interval; CRC, colorectal carcinoma; CUP, carcinoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio.

Source: Bokemeyer *et al.* 2022 (28)

#### **C. Uncertainty**

##### - **Robust sandwich estimator/bootstrapping**

To address uncertainty in the analysis, the study employed robust statistical techniques, specifically the robust sandwich estimator, to account for variability in the HR estimates. This approach helped to provide more reliable confidence intervals, especially in the context of a small effective sample size resulting from the matching process.

#### **D. Systematic error**

- **Present estimates of systematic error before and after adjustment**
- **If evidence is limited, discuss whether bias is likely to be substantial**

The study did not provide a direct numerical estimate of systematic error, either before or after adjustment. Instead, it addressed systematic error by comparing the treatment effect estimates (HRs) before and after matching on key baseline characteristics. The substantial change in the HR, from 0.09 before adjustment to 0.22 after adjustment, suggests that confounding and systematic differences between groups likely inflated the initial effect estimate. After adjustment, the estimate is considered less biased; however, the exact magnitude of systematic error is not quantified. Since the analysis relied on available variables for matching and could not account for unmeasured confounders, some residual bias remained. The study acknowledges these limitations, and given the small ESS and potential for unmeasured confounding, it is possible that bias could still be substantial.

#### **E. Target population**

- **Discuss representativeness of the Larotrectinib population included vs. the NHS (SACT) population**

The SACT population includes both adult and paediatric patients and features a broader distribution of tumour types, especially CNS/brain tumours, compared to the larotrectinib population in Bokemeyer *et al.*, which is restricted to adults. Importantly, both studies include comparable proportions of patients with certain tumour types, such as lung, sarcoma, and colorectal cancers. ECOG performance status is similar between groups for those with available data, but missing data is substantial in SACT. Both populations include patients with advanced/metastatic disease and a mix of lines

of therapy, with the majority of patients in both studies having received up to two lines of systemic therapy. Additionally, both studies report a high proportion of NTRK1 fusions; however, SACT also provides evidence for NTRK2 and NTRK3.

Overall, despite differences in age distribution and tumour type breadth, the two populations share key similarities in disease stage, treatment history, and molecular profile.

- **Discuss representativeness of the SOC population included vs. the NHS (SACT) population**

In terms of age, most patients were below 60 or 65 years in both datasets: 60.7% were aged below 65 years in Bokemeyer *et al.*, and 90% of the SACT cohort were below 60 years. In Bokemeyer *et al.*, 50% of patients had ECOG 0–1 and 50% had ECOG 2–4 (imputed), while in the SACT cohort, 41% had ECOG 0–1 and 5% had ECOG 2 (data missing for 53% of patients), suggesting a similar proportion of patients with good performance status across both groups. Regarding tumour origin, both datasets had a high proportion of NSCLC and sarcoma patients. However, the SACT data encompassed a broader range of tumour types, including CNS-related tumours, thyroid cancers, and other malignancies.

The highest proportion of patients had NTRK1 fusions in both studies: 82% of SoC patients in Bokemeyer *et al.* were NTRK1-positive, while in the SACT cohort, NTRK1 was also the most common fusion type, though the distribution was more balanced across NTRK1 (37%), NTRK2 (30%), and NTRK3 (32%). For prior lines of therapy, the majority of patients in both studies had received up to two lines of systemic therapy, with 71.4% of SoC patients in Bokemeyer *et al.* and 86% of patients in SACT.

Overall, while there are similarities between both cohorts in Bokemeyer *et al.* (e.g., ECOG performance status, prior lines of therapy) and the SACT population, there are notable differences in age, tumour type distribution and NTRK fusion types.

- **Discuss applicability of treatments in the SOC populations to NHS practice.**

The treatments used in the Bokemeyer *et al.* SoC cohort reflect real-world clinical practice in the United States prior to the widespread adoption of TRKi. While the study provides valuable comparative survival data, the specific treatment regimens administered to patients in the SoC cohort were not individually detailed. However, as detailed in Table 18, the study lists the types of treatment received in the comparator arm including chemotherapy, targeted therapies, immunotherapies, and hormonal treatments, reflecting standard treatments in NHS practice. Although individual regimens were not specified, the company does not anticipate substantial differences in the treatment pathways for solid tumours between the United States and NHS.

#### **F. Standard ITC**

- **Present standard ITC to demonstrate impact of population adjustment.**
- **Assess sensitivity of results to different model specifications.**

Bokemeyer *et al.* presented a standard ITC using a MAIC methodology to evaluate the overall survival benefit of larotrectinib versus SoC in patients with TRK fusion–positive cancers. The standard ITC is demonstrated by comparing unadjusted and adjusted HRs: before adjustment, the HR for overall survival was 0.09 (95% CI: 0.05 to 0.19), while after adjustment for baseline characteristics, the HR increased to 0.22 (95% CI: 0.09 to 0.52). This shift illustrates the impact of population adjustment, suggesting that the initial unadjusted estimate may have been influenced by confounding due to differences in patient characteristics.

To assess the sensitivity of results to different model specifications, the study conducted two sensitivity analyses. The first relaxed assumptions about missing data in ECOG performance status and prior lines of therapy, resulting in an increased effective sample size from 13.1 to 23.6 and a lower HR of 0.10 (95% CI: 0.04 to 0.22). Further sensitivity tests involved removing specific tumour types (e.g., CUP, breast, colorectal, salivary gland), which increased the effective sample size up to 38.6 and yielded HRs ranging from 0.10 to 0.12. These analyses confirmed the robustness of the treatment effect and demonstrated that the results were consistent across different matching specifications, reinforcing the validity of the adjusted comparison.

#### **G. A discussion of strengths and limitations of each MAIC.**

Bokemeyer *et al.* presents several strengths and limitations. A key strength is its ability to generate comparative effectiveness evidence in the absence of randomised controlled trials, which is particularly important for rare conditions like TRK fusion-positive cancers. The study adjusts for baseline differences between trial and real-world populations, thereby improving the validity of the comparison. It also includes sensitivity analyses that test the robustness of results under different matching specifications, which enhances confidence in the findings.

However, limitations include the lack of transparency around the specific treatments used in the SoC comparator arm, as the study assumes tumour-specific therapies without detailing them. Additionally, the small sample size and low effective sample size (ESS = 13.1) after matching may reduce statistical power and underestimate variability. The analysis was limited to variables reported in the comparator study, meaning some observed or unobserved prognostic factors may not have been accounted for. The use of conservative imputation for missing data and the potential impact of trial eligibility criteria on outcomes further constrain generalisability. Despite these limitations, the findings from Bokemeyer *et al.* offer important insights into the effectiveness of larotrectinib compared to real-world treatments for NTRK fusion-positive cancers, addressing an uncertainty highlighted in TA630. Facilitating access to this targeted therapy has the potential to improve outcomes for patients with these rare and challenging tumours.

## **VICTORIA**

### **A. Variables:**

- **Process for identifying and selecting relevant prognostic factors and treatment effect modifiers.**
- **Availability of variables.**

In the VICTORIA study, the prognostic factors and treatment effect modifiers were selected based on a literature-informed and clinically driven approach. The authors pre-specified five patient covariates (age, sex, race, ECOG performance status, and the presence of metastases at the start of therapy) as the relevant prognostic factors or potential effect modifiers to include. Variable selection was guided by both clinical



relevance and the requirement that these covariates be available in both datasets used in the study. Individual patient-level data were obtained from both datasets, from the larotrectinib clinical trials for the larotrectinib cohort and from four retrospective data sources for the real-world cohort. The selected variables were consistently available across both the larotrectinib clinical trial data and the real-world datasets, enabling robust matching and adjustment in the analysis (29).

- **Distribution of variables available and assessment of covariate overlap.**

Brose *et al.* evaluated the distribution of key baseline variables between the larotrectinib trial cohort and the real-world control group, focusing on age, sex, race, ECOG performance status, and presence of metastases. Prior to adjustment, the cohorts differed in several areas; for example, the real-world comparator cohort was older and had a higher proportion of white patients and ECOG 2–3 scores, while the larotrectinib group had more metastatic disease. After applying IPTW, these differences were minimised, and the groups showed similar distributions across all five covariates. The authors assessed balance using standardised differences, all of which fell below 10%, and confirmed overlap in propensity score distributions. These steps helped support the validity of the comparative effectiveness analysis by reducing potential bias from baseline differences.

- **Number (%) of individuals with zero weight.**

The study did not report the number or percentage of individuals with zero weight following IPTW.

- **Evidence for effect modifier status: proposed size of interaction effect; potential size of bias reduction.**

The study did not report subgroup analyses by key patient characteristics (e.g., age, sex, tumour type, performance status) that would allow for a formal assessment of effect modification or estimation of interaction effects. While the study applied matching and IPTW to balance cohorts on variables such as age, sex, race, ECOG performance status, and presence of metastases, these adjustments were used to control confounding rather than to explore heterogeneity of treatment effect.

The study offers reasonable support for bias reduction through adjustment for known effect modifiers, even though the ESS was not reported. The matching and weighting strategy incorporated key clinical variables (age, sex, ECOG performance status, and presence of metastases), which are widely recognised as effect modifiers in oncology and relevant to treatment outcomes (30). By aligning the adjustment model with these variables, the study achieved good covariate balance between the larotrectinib and real-world cohorts, with standardised differences <10%. This suggests that the risk of residual bias is likely limited. Overall, the methodological choices and consistency across sensitivity analyses lend confidence to the robustness of the findings.

## **B. Weights**

### **- Distribution of weights**

The distribution of weights generated through IPTW was reviewed to assess balance and overlap between the larotrectinib trial and real-world cohorts; however, the exact distribution statistics (e.g., mean, range, or histogram) were not available. The study also applied stabilised IPTW and conducted sensitivity analyses, including 5% trimming of extreme weights, to ensure the robustness of the comparative effectiveness results. These steps suggest that the weight distribution was considered acceptable and did not compromise the validity of the analysis.

### **- Effective sample size**

The effective sample size following IPTW was not explicitly reported in the publication. However, the study confirmed that all 82 patients in each cohort (larotrectinib and real-world control) were retained in the weighted analysis, and that stabilised IPTW was used to balance covariates.

## **C. Uncertainty**

### **- Robust sandwich estimator/bootstrapping**

The study did not explicitly report the use of robust sandwich estimators or bootstrapping methods to quantify uncertainty in the weighted analyses. Instead, it relied on Cox proportional hazards models to estimate HRs and confidence intervals for both unweighted and IPTW samples. Sensitivity analyses were performed, such as

left truncation and 5% trimming of extreme weights, to test the robustness of the findings.

#### **D. Systematic error**

- **Present estimates of systematic error before and after adjustment**
- **If evidence is limited, discuss whether bias is likely to be substantial**

The study did not present formal estimates of systematic error before and after adjustment. However, several steps were taken to reduce it. Matching was performed on tumour type and line of therapy, and IPTW was applied using five baseline covariates (age, sex, race, ECOG performance status, and presence of metastases). After adjustment, all standardised differences were <10%, and propensity score distributions showed good overlap.

Nevertheless, residual confounding from unmeasured variables could not be ruled out. For example, outcomes among patients treated in clinical trials may not generalise to the broader population of patients treated in the real-world. Additionally, the observational design and small sample sizes across tumour types limited the ability to explore subgroup effects or fully account for systematic error.

#### **E. Target population**

- **Discuss representativeness of the Larotrectinib population included vs. the NHS (SACT) population**

In both datasets, larotrectinib was used across multiple tumour types, and both reported a mix of metastatic and locally advanced disease. In terms of patient age, the VICTORIA dataset comprised exclusively adult patients, whereas the SACT dataset included both adults and paediatric patients; however, it is worth noting that adults represented the majority within the SACT cohort, accounting for 63% of the population. The VICTORIA dataset included five pre-specified tumour types (colorectal, NSCLC, salivary gland, soft tissue sarcoma, and thyroid cancer), all of which were represented in the SACT dataset, accounting for 47% of its patients (both adults and paediatrics). Larotrectinib was more commonly used as 2L therapy in the SACT dataset, whereas in VICTORIA, nearly half of patients received it as 1L treatment, potentially resulting

in a conservative estimate of the comparative clinical effectiveness of larotrectinib in this study and the model. Overall, while there are similarities between both cohorts in VICTORIA and the SACT population, there are notable differences in inclusion of paediatric patients and line of therapy.

**- Discuss representativeness of the SOC population included vs. the NHS (SACT) population**

The SoC group in the VICTORIA study consisted exclusively of adult patients, whereas the SACT dataset included both paediatric and adult patients, with adults comprising the majority of the population. ECOG performance status was thoroughly reported in the VICTORIA dataset, with 83% of patients having ECOG 0–1 after weighting, a proportion comparable to that observed in the SACT dataset (41%) among patients with available data (46%). The VICTORIA dataset included five pre-specified tumour types (colorectal, NSCLC, salivary gland, soft tissue sarcoma, and thyroid cancer) all of which were represented in the SACT dataset, accounting for 47% of its patients. In the VICTORIA real-world cohort patients were more often treated in 1L therapy (48%), whereas in SACT most patients were treated in 2L (78%). Overall, while both datasets offer valuable insights into real-world treatment, the SoC arm in VICTORIA was more narrowly defined to align with larotrectinib trial matching criteria, and the SACT population reflects broader clinical diversity.

**- Discuss applicability of treatments in the SOC populations to NHS practice.**

The SoC treatments used in VICTORIA are highly applicable to UK and NHS clinical practice, as they mirror the therapies NHS patients would typically receive in the absence of a TRKi. For instance, lenvatinib is an established NHS treatment for radioiodine-refractory thyroid cancer (approved by NICE in 2018), so its use in real-world thyroid cancer patients is directly relevant (31). Similarly, anthracycline (doxorubicin) chemotherapy is the standard 1L therapy for advanced soft tissue sarcoma in the UK, and gemcitabine ± docetaxel is a common 2L regimen – matching the study’s real-world sarcoma treatments. In metastatic colorectal cancer, the real-world patients who received ICIs likely had dMMR/MSI-high tumours; in the NHS these patients are now offered 1L pembrolizumab as well (per NICE TA709, 2021) (32).

Meanwhile, other colorectal cancer patients in the real-world arm would have received chemotherapy, which are standard NHS regimens. For TRK fusion lung cancer cases, standard chemotherapy or chemo-immunotherapy would be typically administered in the UK when no TRKi is given. In short, all the treatment categories in the real-world cohort (chemotherapy, targeted therapies such as multi-kinase inhibitors, immunotherapies, etc.) are available and routinely used in NHS practice for the corresponding cancers. Therefore, the effectiveness of larotrectinib was compared to a real-world benchmark that is highly relevant to oncology care in the UK, supporting the generalisability of the results to NHS patients.

## **F. Standard ITC**

### **- Present standard ITC to demonstrate impact of population adjustment.**

The study presented a robust ITC between larotrectinib and SoC therapies for patients with TRK fusion cancers, using real-world data. To adjust for population differences, patients were matched 1:1 based on tumour type and line of therapy, and applied IPTW using key variables such as age, sex, race, ECOG performance status, and presence of metastases. This adjustment ensured balanced cohorts and minimised confounding. The results showed that larotrectinib significantly improved outcomes across all measured endpoints: overall survival (OS), time to next treatment (TTNT), duration of therapy (DOT), and progression-free survival (PFS). For example, weighted median OS was not reached for larotrectinib versus 37.2 months for SoC, with a HR of 0.44 (95% CI, 0.23 to 0.83). These findings underscore the value of population adjustment in ITC studies, especially in rare cancer settings where randomised trials are impractical. They also demonstrate that larotrectinib is more effective than non-TRKi therapies.

### **- Assess sensitivity of results to different model specifications.**

The sensitivity of the results in the larotrectinib versus SoC comparison was thoroughly assessed using multiple model specifications. The study applied several sensitivity analyses to test the robustness of the OS findings. These included:

- Left truncation adjustment, which corrected for bias due to delayed entry into the study (e.g., patients only entering the risk set at the time of genomic

sequencing). This yielded a HR of 0.27 (95% CI: 0.14–0.51) in the weighted sample, showing a consistent survival benefit.

- 5% trimming of propensity scores, which excluded patients with extreme scores to reduce the influence of outliers. This analysis produced an HR of 0.46 (95% CI: 0.24–0.89), again supporting the main findings.
- Restricted mean survival time (RMST) estimates at 12, 24, and 36 months also consistently favoured larotrectinib, with statistically significant differences at each time point.

These alternative model specifications confirmed that the observed treatment effect was not driven by a single analytic approach, demonstrating strong internal validity and robustness of the comparative effectiveness results.

#### **A. A discussion of strengths and limitations of each MAIC.**

The study has several notable strengths. It used a rigorous ITC framework, combining exact matching on tumour type and line of therapy with IPTW to adjust for key baseline characteristics such as age, sex, race, ECOG performance status, and presence of metastases. This dual approach enhances the validity of the comparative effectiveness analysis and minimises confounding. The inclusion of multiple real-world data sources - spanning both US and international academic centres - adds diversity and generalisability to the findings. Moreover, sensitivity analyses, including left truncation and propensity score trimming, consistently confirmed the robustness of the results.

Nevertheless, the study has some limitations. Differences in outcome definitions between clinical trials and real-world data (e.g., RECIST-based vs. chart-reviewed progression) could have introduced measurement bias. Imaging data availability and assessment frequency in real-world settings can vary, potentially affecting PFS estimates. Residual confounding is also possible due to unmeasured variables not captured in the propensity model. Despite these limitations, the study provides compelling real-world comparative evidence supporting larotrectinib's benefit over SoC in TRK fusion cancers.

## **HMF**

### **A. Variables:**

- **Process for identifying and selecting relevant prognostic factors and treatment effect modifiers.**
- **Availability of variables.**

In the Bokemeyer *et al.* (2025) study, the selection of prognostic factors and treatment effect modifiers was guided by both clinical relevance and the availability of baseline characteristics in the datasets used. Individual adult patient-level data from three larotrectinib clinical trials were matched to aggregate real-world data from the Hartwig Medical Foundation (HMF) database. The matching process focused on variables present in both datasets and regarded as clinically important for outcomes in TRK fusion–positive cancers. The factors chosen for matching were age group, number of previous lines of systemic therapy, NTRK1 fusion status, and year of biopsy or treatment initiation. Patient sex and primary tumour location were not included in the main matching analysis due to concerns about overadjustment and insufficient numbers in each tumour category for stable analysis. However, these variables were incorporated in sensitivity analyses to assess their impact on the results. The selection process was constrained by the limited set of baseline characteristics reported in the HMF dataset and the need to ensure sufficient overlap between the larotrectinib and SoC populations (33).

- **Distribution of variables available and assessment of covariate overlap.**

The distribution of the selected variables was carefully examined to ensure comparability between the larotrectinib and SoC populations. Covariate overlap was assessed using inverse propensity score weighting, which balanced the baseline characteristics of the two groups. After matching, the ESS was reduced, indicating that only patients with sufficient overlap in these key variables contributed to the final analysis. This approach was essential to minimise bias and enhance the reliability of the survival outcome comparisons between the two groups. Sensitivity analyses further confirmed that the matched populations were similar in their baseline characteristics, supporting the validity of the results.

- **Number (%) of individuals with zero weight.**

The number and percentage of individuals with zero weight after matching are not explicitly reported in the Bokemeyer *et al.* (2025) publication. However, the study provided information about the distribution of weights following the MAIC, stating that over 80% of patients had weights  $\leq 1$ , and around 20% had weights  $>1$ , with no concerns about outliers or excessive weighting (Figure 16).

Evidence for effect modifier status: proposed size of interaction effect; potential size of bias reduction.

After applying the eligibility criteria, the larotrectinib trial population consisted of 120 patients, but following matching for baseline characteristics in the MAIC analysis, the ESS was reduced to 36 in the base case. Sensitivity analyses that included additional matching factors, further decreased the ESS to 12, indicating even more limited overlap. Overall, although matching helps address bias, the results should be interpreted with caution given the small ESS.

The study did not explore the size of the interaction effect, as subgroup analyses were not performed.

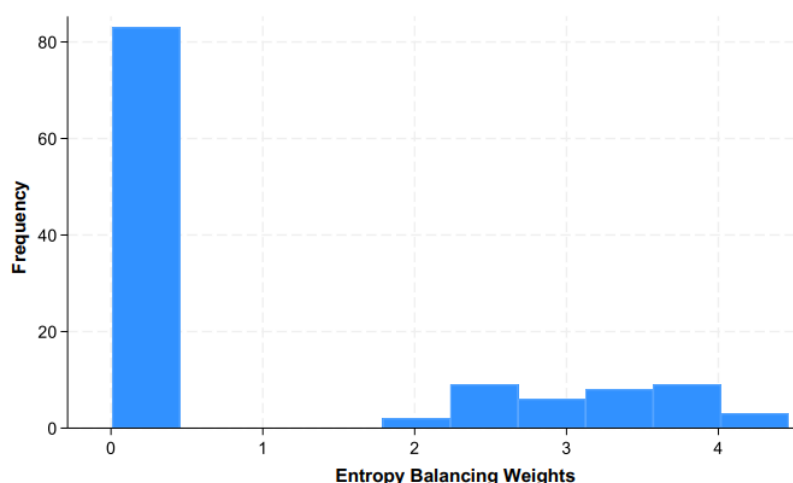
## **B. Weights**

- **Distribution of weights**

The weight distribution is presented in Figure 13. Most weights were  $\leq 1$ , with some outliers with higher weights.



**Figure 16. Histogram of patient weights (HMF MAIC; N=82)**



Source: Bokemeyer *et al.*, 2025 (33)

### - Effective sample size

In the base case analysis, the ESS was 36. Sensitivity analyses did not impact or further reduce the ESS to 12, depending on which variables were included in the matching process. The HR and ESS using alternative variables for matching are presented in Table 16.

**Table 15. HR and effective sample sizes using alternative variables for matching (HMF MAIC).**

| Matching Factors            | ESS | HR (95% CI)         | RMST Mean Difference, Months (95% CI) |
|-----------------------------|-----|---------------------|---------------------------------------|
| Base case (weighted)        | 36  | 0.16 (0.07 to 0.36) | 9.8 (5.6 to 14.0)                     |
| Base case 1 patient sex     | 36  | 0.16 (0.07 to 0.37) | 9.7 (5.5 to 13.9)                     |
| Base case 1 tumour location | 12  | 0.29 (0.12 to 0.69) | 7.0 (2.8 to 11.2)                     |

Note: Assumed to follow the same distribution as observed data.

CI= confidence interval; ESS= effective sample size; HR= hazard ratio; RMST= restricted mean survival time

Source: Bokemeyer *et al.*, 2025 (33)

## C. Uncertainty

### - Robust sandwich estimator/bootstrapping

Bokemeyer *et al.* (2025) do not explicitly mention the use of robust sandwich estimators or bootstrapping methods to address uncertainty in the analysis.

#### **D. Systematic error**

- **Present estimates of systematic error before and after adjustment**
- **If evidence is limited, discuss whether bias is likely to be substantial**

The study did not provide direct numerical estimates of systematic error either before or after adjustment. Instead, systematic error was addressed by comparing HR estimates before and after matching on key baseline characteristics. For example, the HR for OS in the unadjusted analysis was 0.18 (95% CI, 0.10 to 0.34), while after matching, the HR was 0.16 (95% CI, 0.07 to 0.36). This modest change suggests that confounding and systematic differences between groups may have influenced the initial effect estimate, and that adjustment reduced some bias, although the exact magnitude of systematic error is not quantified.

Since the analysis relied on a limited set of available variables for matching and could not account for unmeasured confounders, some residual bias likely remains. The study acknowledges these limitations, noting the small ESS and the potential for unmeasured confounding.

#### **E. Target population**

- **Discuss representativeness of the Larotrectinib population included vs. the NHS (SACT) population**

In the Bokemeyer *et al.* (2025) study, the larotrectinib population consisted of patients aged  $\geq 18$  years, and thus no paediatric population was included, whereas the SACT population included both paediatric and adult patients. Both studies enrolled a comparable proportion of male and female participants, ensuring a balanced representation of genders across the study populations. While the Bokemeyer *et al.* (2025) study excluded patients with certain tumour types, such as those with primary CNS tumours, the SACT population included a high proportion of these cases (35%). Nevertheless, both studies featured a high proportion of patients with other tumour types, including lung and bone/soft tissue cancers, resulting in broadly similar representation across certain tumour types. In both studies, larotrectinib was generally introduced in earlier lines of treatment, as the majority of patients had received two or fewer prior lines of therapy (68.3% in the Bokemeyer *et al.* 2025 vs. 86% in SACT).

Overall, despite some differences in eligibility and tumour types, both studies were similar in that they mainly included adults, had a balanced gender distribution, featured comparable representation of certain tumour types, and introduced larotrectinib in earlier lines of therapy.

- **Discuss representativeness of the SOC population included vs. the NHS (SACT) population**

As outlined above, in the Bokemeyer *et al.* (2025) study, the larotrectinib population consisted of adults, whereas the SACT population included both paediatric and adult patients. Both studies enrolled a comparable proportion of male and female participants, ensuring a balanced representation of genders across the study populations. While the Bokemeyer *et al.* (2025) study excluded patients with certain tumour types, such as those with primary CNS tumours, the SACT population included a high proportion of these cases (35%). Nevertheless, both studies featured a comparable proportion of patients with other tumour types, including lung, head and neck, and colorectal cancers, resulting in broadly similar representation across certain cancer groups. In both studies, treatment was generally introduced in earlier lines as the majority of patients had received two or fewer prior lines of therapy (66.7% in Bokemeyer *et al.* 2025 vs. 86% in SACT).

Overall, despite some differences in eligibility and tumour types, both studies were similar in that they mainly included adults, had a balanced gender distribution, featured comparable representation of certain cancer groups, and introduced larotrectinib in earlier lines of therapy.

- **Discuss applicability of treatments in the SOC populations to NHS practice.**

The treatments used in the SoC cohort in Bokemeyer *et al.* (2025), as sourced from the Santi *et al.* (2024) study, reflect real-world clinical practice in the Netherlands prior to the adoption of TRKis (34). While the analysis provides valuable comparative survival data, the specific systemic therapies administered to patients in the SoC cohort were not individually detailed in the publication. Instead, the study assumed that patients received tumour-specific therapies appropriate for their cancer type, which may have included chemotherapy, targeted therapies (excluding TRKi),

immunotherapies, or hormonal treatments. This approach introduces some uncertainty when considering direct applicability to NHS practice, where treatment pathways are guided by national protocols and funding mechanisms such as NICE and the CDF. However, the company does not anticipate substantial differences between the treatment pathways for solid tumours in the Netherlands and those in the NHS, as both systems follow international standards and evidence-based guidelines for systemic anticancer therapy. Notably, the Netherlands, as a European country, follows the European Society for Medical Oncology (ESMO) recommendations, which are widely recognised across Europe and closely aligned with the NHS protocols. Thus, the SoC arm in the Bokemeyer *et al.* (2025) analysis is considered broadly relevant to NHS clinical practice.

#### **F. Standard ITC**

- **Present standard ITC to demonstrate impact of population adjustment**
- **Assess sensitivity of results to different model specifications.**

Bokemeyer *et al.* presented a standard ITC using a MAIC methodology to evaluate the overall survival benefit of larotrectinib versus SoC in patients with TRK fusion-positive cancers. The standard ITC is demonstrated by comparing unadjusted and adjusted HRs for overall survival: before adjustment, the HR for overall survival was 0.18 (95% CI: 0.10 to 0.34), while after adjustment for baseline characteristics the HR was 0.16 (95% CI: 0.07 to 0.36). This was quite a small shift and illustrates the impact of population adjustment, suggesting that the initial unadjusted estimate may have been modestly influenced by confounding due to differences in patient characteristics between the larotrectinib and SoC cohorts.

To further assess the sensitivity of results to different model specifications, the study conducted additional analyses. For example, adding patient sex as a matching factor did not change the ESS and had little impact on the weighted results, while including tumour location as a matching variable decreased the ESS and slightly reduced the estimated difference between groups, though results remained statistically significant. These analyses confirmed the robustness of the treatment effect and demonstrated that the results were consistent across different matching specifications, reinforcing the validity of the adjusted comparison.

## **G. A discussion of strengths and limitations of each MAIC.**

Bokemeyer *et al.* presents some strengths and limitations. A key strength of the study is the inclusion of sensitivity analyses, such as matching on additional variables like patient sex and tumour location, which tests the robustness of the results under different specifications and enhance confidence in the findings. However, limitations include the lack of transparency around the specific treatments used in the SoC comparator arm, as the study assumes tumour-specific therapies without detailing them. Additionally, the small sample size and low ESS after matching may reduce statistical power and underestimate variability. The analysis is restricted to variables reported in the comparator study; therefore, some observed or unobserved prognostic factors may not have been accounted for, potentially introducing bias. Nonetheless, the study provides meaningful comparative data for larotrectinib in TRK fusion cancers and, despite methodological limitations, employs approaches that help address confounding and strengthen the validity of the observed survival benefit.

### **EPI VITRAKVI**

#### **A. Variables:**

- **Process for identifying and selecting relevant prognostic factors and treatment effect modifiers**
- **Availability of variables**

The Orbach *et al.* (2024) study compared patients with advanced or metastatic infantile fibrosarcoma (IFS) who received larotrectinib with an external control. The selection of prognostic factors and treatment effect modifiers was guided by both clinical relevance and data availability across the study datasets. Key covariates were identified through a systematic literature review (SLR) and expert medical opinion, focusing on factors known to influence outcomes in IFS. The key covariates included IRS group classification, age at index, and time from locally advanced/metastatic disease diagnosis to treatment initiation were identified. Additional covariates were considered, such as sex, disease history, and treatment-related information. The availability of variables was determined by the data sources used: IPD from the larotrectinib SCOUT trial, and IPD data from external historical control cohorts (Institut

Curie and CWS databases). Baseline demographic, clinical, and treatment characteristics were well documented for both groups, with minor exceptions. Where direct data were unavailable (e.g., IRS classification in the SCOUT trial), derivations were made using disease status and expert opinion (35).

- **Distribution of variables available and assessment of covariate overlap**

The distribution of key baseline variables was analysed to ensure comparability between the larotrectinib and historical SoC chemotherapy groups. Covariate overlap was assessed primarily using the IPTW method based on a propensity score model. The propensity score was obtained from a logistic regression including Intergroup Rhabdomyosarcoma Study (IRS) group, age at index, and time from diagnosis to treatment initiation as covariates. Each patient was weighted by the reciprocal of the probability of receiving the treatment they received, thereby balancing the distribution of these key variables across groups.

- **Number (%) of individuals with zero weight**

The study does not report information regarding individuals with zero weight.

- **Evidence for effect modifier status: proposed size of interaction effect; potential size of bias reduction**

The study did not provide a direct calculation of ESS post-weighting; however, sensitivity analyses were performed, including 5% trimming and truncation of large weights, to assess the robustness of the weighted models. In the absence of explicit reporting on ESS or overlap, the potential size of bias reduction cannot be precisely quantified from the available data. Additionally, the size of the interaction effect was not explored, as subgroup analyses focused on the line of therapy rather than formal interaction testing. Overall, matching and weighting approaches in the study aimed to address bias due to effect modifiers, but the lack of detailed ESS reporting and interaction effect analysis suggests that residual bias may remain.

## **B. Weights**

- **Distribution of weights**

Each patient was weighted by the reciprocal of the probability of receiving the treatment that the patient actually received. The distribution of weights was assessed through sensitivity analyses, including 5% trimming (excluding patients with weights in the lowest and highest 2.5% of the propensity score distribution) and truncation of large weights. Overall, while the study describes the use of weighting and some steps to manage extreme values, the precise distribution of weights is not reported in detail.

- **Effective sample size**

The effective sample size is not calculated in the study. However, the analysis included 51 patients with IFS in the SCOUT study and 42 patients in the pooled external historical control cohorts, pooled from the Institut Curie database (N=18) and the CWS database (N=24).

### C. Uncertainty

- **Robust sandwich estimator/bootstrapping**

Orbach *et al.* (2024) does not explicitly report the use of robust sandwich estimators or bootstrapping methods to quantify uncertainty in the weighted analyses. HRs were reported using unweighted Cox proportional hazards models with treatment status as indicator variable, and weighted models that were stratified by IRS groups. Further, sensitivity analyses were conducted, where robustness of the weighted models was assessed by 5% trimming of IPTW weights and truncating large weights.

### D. Systematic error

- **Present estimates of systematic error before and after adjustment**
- **If evidence is limited, discuss whether bias is likely to be substantial**

The study did not present formal estimates of systematic error before and after adjustment. However, several steps were taken to reduce it. Matching and IPTW were applied to reduce the gap between treatment groups. The use of a historical control group has inherent drawbacks of non-randomisation and non-blinding, possibly resulting in selection, confounding, and detection bias. Therefore, a robust methodological approach was followed to account for the different risks of bias,

ensuring the validity of the inferences drawn from this external historically controlled study (36).

To reduce risk of selection bias, the external historical control group was carefully selected by using strict selection criteria and by performing an SLR to identify databases with IFS cohorts. The inclusion of multiple databases not only allowed to increase the sample size but also improved generalisability of the results. Patients with IFS are treated according to the same general approach in Europe, which ensures a relatively homogeneous external historical control group. The selection of the external historical cohorts was based on strict objective criteria, such as prospective enrolment and data collection since the year 2000, as the historical SoC (chemotherapy), the use of biomolecular diagnostics, and the classification of the disease have largely remained unchanged when compared with the current clinical context since then.

Confounding bias was addressed using IPTW to reduce the potential bias introduced by comparing the results of a single-arm (non-randomised, non-controlled) study with an external control. This statistical method allows to adjust the treatment effect for measured confounding variables.

Further, the risk of detection bias was mitigated by choosing a composite primary endpoint (time to medical treatment failure) that is objective and consists of events selected for their clinical relevance and reliable measurement methods.

#### **E. Target population.**

- **Discuss representativeness of the Larotrectinib population included vs. the NHS (SACT) population**

Direct comparison between IPDof EPI VITRAKVI and aggregated dataset of SACT poses challenges, since SACT is an aggregated dataset and the company does not have data separated by adults and children. Therefore, the comparisons presented below are based on the entire cohort of SACT and should be interpreted with caution.

EPI VITRAKVI included patients aged  $\leq 21$  years, while the SACT population included a broader age range with a predominance of adults (63%  $\geq 20$  years; direct split of adults and paediatrics not mentioned). Both studies included patients with locally advanced and metastatic disease, but most of the patients on larotrectinib in EPI VITRAKVI had locally advanced disease (80%), with fewer having metastatic disease



(20%) whereas in SACT population around 40% patients had metastatic disease. EPI VITRAKVI included only patients with advanced or metastatic IFS, while the SACT population included patients with diverse tumour types; notably, the SACT data also included a meaningful proportion of IFS patients (7%). Larotrectinib is used in EPI VITRAKVI in mostly 1L, whereas most of the SACT population was treated as 2L (78%), which is expected given that EPI VITRAKVI included only paediatric patients with IFS. All patients in EPI VITRAKVI had documented NTRK fusion (i.e., NTRK3 in most IFS cases), whereas the SACT population had balanced distribution of NTRK genes (NTRK1 [37%], NTRK2 [30%], NTRK3 [32%]).

- **Discuss representativeness of the SOC population included vs. the NHS (SACT) population**

The representativeness of the SoC population included in EPI VITRAKVI compared to the SACT population is broadly similar to that of the larotrectinib population as discussed above. In addition, all patients in the SoC group received chemotherapy as 1L systemic therapy, whereas most patients in the SACT population received larotrectinib as 2L therapy (78%).

- **Discuss applicability of treatments in the SOC populations to NHS practice**

All patients in the SoC population of EPI VITRAKVI received prior radiotherapy, with some (21.4%) who underwent surgery. The use of chemotherapy as initial treatment aligns with approaches commonly used in paediatric oncology across Europe, including the UK. Therefore, the effectiveness of larotrectinib was compared to a real-world benchmark that is relevant to oncology care in the UK, supporting the generalisability of the results to NHS patients.

#### **F. Standard ITC**

- **Present standard ITC to demonstrate impact of population adjustment**
- **Assess sensitivity of results to different model specifications**

The study presented a robust ITC between larotrectinib and external control group for patients with IFS, using real-world data. To adjust for population differences, patients

were matched and IPTW was applied to ensure balanced cohorts and minimised confounding. Several sensitivity analyses were conducted, as presented in Table 17. Robustness of the weighted models was assessed by 5% trimming of IPTW weights and truncating large weights. The robustness of the primary endpoint regarding line of treatment was assessed through matching on line of therapy (first line/second or later lines), with the index date set at start of matched line of therapy. For subgroup analyses by line of prior systemic treatment only unweighted analyses were planned, as the weights were calculated per patient overall and not by subgroups.

**Table 16. Sensitivity and subgroup analyses of time to medical treatment failure**

|                                    | Events, n/N (%) |                        | Unweighted            |         | Weighted                      |         |
|------------------------------------|-----------------|------------------------|-----------------------|---------|-------------------------------|---------|
|                                    | Larotrectinib   | External Control Group | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI)         | P value |
| <b>Sensitivity analysis</b>        |                 |                        |                       |         |                               |         |
| 5% IPTW trimming <sup>a</sup>      | 4/51 (7.8)      | 14/39 (35.9)           | NA                    | NA      | 0.20 (0.06-0.64) <sup>b</sup> | 0.0067  |
| IPTW truncating <sup>c</sup>       | 4/51 (7.8)      | 15/42 (35.7)           | NA                    | NA      | 0.20 (0.06-0.62) <sup>b</sup> | 0.0055  |
| Matching by line of therapy        | 2/27 (7.4)      | 10/27 (37.0)           | 0.16 (0.03-0.73)      | 0.0180  | 0.08 (0.01-0.71) <sup>d</sup> | 0.0230  |
| <b>Subgroup analysis</b>           |                 |                        |                       |         |                               |         |
| First line of treatment            | 1/19 (5.3)      | 15/42 (35.7)           | 0.14 (0.02-1.06)      | 0.0571  | NA                            | NA      |
| Second or higher line of treatment | 3/32 (9.4)      | 6/8 (75.0)             | 0.05 (0.01-0.20)      | <0.0001 | NA                            | NA      |

A hazard ratio <1 favours the larotrectinib group.

CI= confidence interval; IPTW= inverse probability of treatment weighting; IRS= Intergroup Rhabdomyosarcoma Study, n= number of patients presenting an event; N= total number of patients; NA= not applicable.

<sup>a</sup>Included patients within 2.5%-97.5% percentile of propensity scores.

<sup>b</sup>Weighted by stabilized IPTW and stratified by IRS groups.

<sup>c</sup>Truncating large weights changed only one patient's stabilized IPTW to 10.

<sup>d</sup>Weighted and stratified by line of therapy (first line and second line or higher) and IRS groups.

Source: Orbach *et al.* 2024; Figure 1 (35)

## G. A discussion of strengths and limitations of each MAIC.

The strengths of the MAIC approach in the EPI VITRAKVI study include its use of IPTW to balance key prognostic factors between the larotrectinib and historical control groups, systematic selection of external controls, and the application of sensitivity analyses to test the robustness of findings. These methodological choices help reduce confounding and enhance the reliability of comparative effectiveness estimates in a rare disease setting where randomised trials are not feasible.

The main limitation of this study was the limited number of included patients, the rarity of events of clinical interest, and consequently, the lack of statistical power. The risk of measurement bias was also present in this study. Notably, the SCOUT study was a well-monitored clinical trial that used validated response evaluation criteria, while the external historical control cohorts regrouped real-world data without strong pre-established protocol, regularly scheduled tumour assessments, or centralised reading. Furthermore, the imbalance in follow-up time and the rate of censoring (10%) may have affected the results, as well as potential unmeasured confounders.

Despite these limitations, the study demonstrates the feasibility and value of using robust comparative effectiveness methodologies in rare disease settings. Through systematic matching, propensity score weighting, and sensitivity analyses, it provides important real-world evidence supporting the clinical benefit of larotrectinib.

**A24. Priority question: We understand that the comparator arms in the four MAIC SOC cohorts were eligible if they had a positive test for an NTRK fusion but had not received larotrectinib. For each of the MAICs, please clarify why these patients received chemotherapy instead of an NTRK fusion inhibitor, despite being NTRK fusion test positive, providing numbers (%) with reasons (or stating where this is not available).**

The introduction of TRKis is relatively recent. The first clinical trial enrolling patients with NTRK-positive tumours (Phase I – LOXO-TRK-14001) began in May 2014. Prior to this, there was no access to TRKis, and even after 2014, access to TRKis remained limited to clinical trials. Real-world availability of TRKis only began much later – in November 2018 in the United States and in October 2019 across European countries (37, 38).

As a result, no patients were treated with TRKis in real-world settings before these dates. Consequently, most patients who tested positive for NTRK fusions did not receive a TRKi, despite being eligible based on their molecular profile. In addition, even after TRKi approval, factors such as limited awareness of NTRK fusions, evolving testing practices, and label restrictions contributed to delayed adoption. These factors often led to TRKis being used in later lines of therapy rather than as early-line treatment options.

For each of the specific MAICs, there is no explicit explanation regarding why patients received the standard of care (SoC) instead of a TRKi. However, based on the respective study periods, it can be reasonably inferred that TRKis was not yet routinely available during those times, and that early use was further hindered by gradual clinical adoption and regulatory labelling.

#### Study Periods:

- HMF: 2012 to 2020
- Bokemeyer: The study notes that patients in the comparator arm were recruited “before widespread acceptance of NTRK testing”. The study period spans from January 2011 to December 2019.
- EPI VITRAKVI: 2000 to June 2022
- VICTORIA: Data collection occurred between January 2011 and June 2023, with timelines varying by real-world data (RWD) source. For example, Flatiron data collection began in 2011, while GENIE data collection started in 2013.

A25. The publications for the FLATIRON, HARTWIG and VITRAKVI MAICs do not provide details of the comparator arm SoC treatments. Please provide details, similarly to that provided for the VICTORIA MAIC in Brose (2025), Table S4.

We do not have access to this information for HMF because the details of the comparator arm standard-of-care (SoC) treatments were not reported in the publications. Since aggregated data were leveraged, the data was restricted and therefore not available for disclosure.

For EPI VITRAKVI, the publication specifies that patients were treated with a chemotherapy-based regimen, but it does not provide details on the specific regimen. Similarly, for FLATIRON, although there is no detail on the specific treatment regimen, Table 18 below shows the type of treatments received in the comparator arm.

**Table 17. Type of treatment received by NTRK+ patients**

| Treatment type                         | Total     | Line 1    | Line 2   | Line 3   | Line 4  |
|----------------------------------------|-----------|-----------|----------|----------|---------|
| Number of patient-lines*, n            | 44        | 22        | 12       | 3        | 1       |
| Chemotherapy, n (%)                    | 21 (47.7) | 16 (72.7) | 4 (33.3) | 1 (33.3) | 0 (0.0) |
| Chemotherapy + hormone therapy, n (%)  | 2 (4.5)   | 2 (9.1)   | 0 (0.0)  | 0 (0.0)  | 0 (0.0) |
| Chemotherapy + targeted therapy, n (%) | 10 (22.7) | 4 (18.2)  | 6 (50.0) | 0 (0.0)  | 0 (0.0) |

|                                           |         |         |         |          |           |
|-------------------------------------------|---------|---------|---------|----------|-----------|
| Hormone therapy, n (%)                    | 2 (4.5) | 0 (0.0) | 1 (8.3) | 0 (0.0)  | 1 (100.0) |
| Immunotherapy, n (%)                      | 1 (2.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0)   |
| Targeted therapy, n (%)                   | 1 (2.3) | 0 (0.0) | 1 (8.3) | 0 (0.0)  | 0 (0.0)   |
| Targeted therapy + hormone therapy, n (%) | 1 (2.3) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0)   |

Source: Supplementary analysis. Hibar *et al.*, 2022 (39)

## Section B: Clarification on cost-effectiveness data

### *Population*

B1. Please justify the grouping of adults and paediatric patients in the cost-effectiveness results, given the high level of heterogeneity in terms of baseline characteristics, tumour type, potential outcomes, and overall cost-effectiveness estimates in these two populations.

The decision to group adult and paediatric subgroups into a single cost-effectiveness estimate is justified by the limited evidence available for NTRK fusion-positive cancers, a rare condition that inherently restricts sample sizes and increases heterogeneity. Given the small patient populations, any clinically defined subgroup would lack sufficient data to draw meaningful conclusions.

While the adult and paediatric subgroups were analysed separately due to this heterogeneity, the final result aims to present the whole target population of larotrectinib regardless of age. The pooled ePAS9 analysis shows that larotrectinib has demonstrated a durable response in NTRK fusion-positive solid tumours across multiple tumour types, irrespective of age, histology type, or specific NTRK gene fusion (40).

### **B2. Priority question: Please present cost-effectiveness results separately across all analyses for adult and paediatric patients.**

The cost-effectiveness results for adults and paediatric patients are presented separately across all scenario analyses in Table 19. ICERs for adults range from £[REDACTED] to £[REDACTED] per QALY, with the intra-patient analysis generating an outlier however the intra-patient analysis has additional uncertainty due to the assumptions required for OS and degree of GMI adjustment. The paediatric ICERs range from £[REDACTED] to £[REDACTED] per QALY, reflecting differences in baseline prognosis and treatment

benefit. ICERs for adults are generally higher because adults have shorter life expectancy and lower absolute QALY gains compared to paediatric patients, who experience longer survival and greater quality-of-life improvements. These results should not be summed to produce a single ICER, as the final estimate is based on the overall population distribution used in the model, which determines the weighted ICER in the base case.

**Table 18. Scenario analyses results (deterministic)**

| No.  | Scenario                                                                                                                              | ICER (£/ QALY)* |            |
|------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------|
|      |                                                                                                                                       | Adults          | Paediatric |
|      | Base case (deterministic)                                                                                                             | ████            | ████       |
| 1.1  | MAIC source: VICTORIA for paediatric patients                                                                                         | ████            | ████       |
| 1.2  | MAIC source: HMF (Bokemeyer 2024)                                                                                                     | ████            | ████       |
| 1.3  | MAIC source: Flatiron (Bokemeyer 2023)                                                                                                | ████            | ████       |
| 2.1  | Modelling approach (responder/non-responder; 100% responders in larotrectinib)                                                        | ████            | ████       |
| 2.2  | Modelling approach (responder/non-responder BHM ORR excluding tumour locations with < 5 patients; 65.2% responders in larotrectinib)  | ████            | ████       |
| 2.3  | Modelling approach (responder/non-responder; BHM ORR excluding tumour locations with < 2 patients; 55.2% responders in larotrectinib) | ████            | ████       |
| 2.4  | Modelling approach (responder/non-responder; BHM ORR all ePAS9+SAS3; 47.0% responders in larotrectinib)                               | ████            | ████       |
| 3    | Modelling approach (Intra-patient comparison)                                                                                         | ████            | ████       |
| 4.1  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: No)                                              | ████            | ████       |
| 4.2  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: Yes, using VOYAGER 1)                            | ████            | ████       |
| 4.3  | Modelling approach (naïve-literature based comparator; adjustment for NTRK+ fusions: Yes, using VOYAGER 2)                            | ████            | ████       |
| 5.1  | Modelling approach (mixture cure modelling with no restriction on treatment duration)                                                 | ████            | ████       |
| 5.2  | Modelling approach (mixture cure modelling with a stopping rule for cured patients)                                                   | ████            | ████       |
| 6.1  | Treatment waning (Immediate treatment waning)                                                                                         | ████            | ████       |
| 6.2  | Treatment waning (Waning over entire time horizon)                                                                                    | ████            | ████       |
| 7    | PD utility (weighted average of literature utility)                                                                                   | ████            | ████       |
| 8    | NTRK testing costs (included)                                                                                                         | ████            | ████       |
| 10   | Trial cohort dataset (ePAS2 + SAS3)                                                                                                   | ████            | ████       |
| 11.1 | Discount rates (0% discount rate)                                                                                                     | ████            | ████       |
| 11.2 | Discount rates (6% discount rate)                                                                                                     | ████            | ████       |
| 12.1 | Time horizon (20-year horizon)                                                                                                        | ████            | ████       |
| 12.2 | Time horizon (40-year horizon)                                                                                                        | ████            | ████       |

BHM = Bayesian Hierarchical Model; HMF = Hartwig Medical Foundation; ICER = incremental cost-effectiveness ratio; MAIC = Matching-Adjusted Indirect Comparison; NTRK = Neurotrophic Tyrosine Receptor Kinase; ORR = Objective Response Rate; PD = Progressive Disease; QALYs = quality-adjusted life years; SOC = standard of care  
 \* The QALYs and ICER include the severity modifier adjustment

## ***Intervention and comparators***

**B3. Please comment on how has been larotrectinib used in NHS practice (by tumour site) compared to the proposed positioning in the TA630 economic model? For example, has it been used earlier in the pathway than anticipated?**

In the original submission, larotrectinib was positioned as a last-line treatment, primarily due to its novelty and the literal interpretation of the label. The label includes that larotrectinib is intended for patients who have “no satisfactory treatment options”. This phrasing can be subjective and may be interpreted differently by various healthcare professionals, potentially leading to the understanding that patients with an NTRK gene fusion should only receive larotrectinib after exhausting all other treatment lines.

However, clinical practice, as observed in the CDF and real-world study (e.g., ON-TRK), shows that larotrectinib is predominantly used earlier in the treatment pathway, usually as a second-line treatment in the UK. Clinicians have found larotrectinib to be more appropriate than alternative treatments based on their experience and the expected outcomes relative to those alternatives. Confidence in its use has also been strengthened by the consistency of clinical trial data readouts and the durability of responses observed over extended follow-up periods. Additionally, the treatment’s favourable toxicity profile and alignment with patient needs are key factors in clinicians’ decision-making. The additional clinical evidence since TA630 is summarised in Table 20.

Unfortunately, the SACT data lacks the level of detail needed to determine when larotrectinib has been used at the tumour level. Nonetheless, discussions with UK clinicians during the advisory board reinforce the positioning of larotrectinib as a second-line treatment option. For example, during the advisory board, when reviewing the appropriate comparator for cholangiocarcinoma, a clinician mentioned that “if patients are fit and do not have EGFR or IDH1 mutations, they would receive the combination gemcitabine, cisplatin and durvalumab as a first-line treatment. Larotrectinib would not be displacing this treatment and should be used as a second-line treatment” (1).

**Table 19. Prior lines of therapy in larotrectinib clinical trials (studies 20288, 20289 and 20290) and real-world studies**

| Tumour location       | ePAS9+ SAS3                                                                         | ON-TRK (N = 120)                                                                    | Flatiron MAIC (N = 102) | VICTORIA (N = 82) | SACT 2025 (N = 60) | Weighted Average                                                                      | NICE TA630 |
|-----------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------|-------------------|--------------------|---------------------------------------------------------------------------------------|------------|
| STS adults (non-GIST) |  |  | 1.57                    | 1.65              |                    |  | 3L         |



| Tumour location       | ePAS9+ SAS3 | ON-TRK (N = 120) | Flatiron MAIC (N = 102) | VICTORI A (N = 82) | SACT 2025 (N = 60) | Weighted Average | NICE TA630        |
|-----------------------|-------------|------------------|-------------------------|--------------------|--------------------|------------------|-------------------|
| Salivary gland cancer |             |                  | 1.57                    | 1.46               | 1.27               |                  | 2L                |
| IFS                   |             |                  |                         |                    | 1.27               |                  | Proxy (last line) |
| Thyroid cancer        |             |                  |                         | 1.16               | 1.27               |                  | 2L+               |
| Melanoma              |             |                  |                         |                    |                    |                  | 3L                |
| Lung - NSCLC          |             |                  | 1.57                    | 2.46               | 1.27               |                  | 2/3L              |
| Colorectal cancer     |             |                  | 1.57                    | 2.41               | 1.27               |                  | 3L                |
| STS adults (GIST)     |             |                  |                         |                    |                    |                  | 4L                |
| Cholangiocarcinoma    |             |                  |                         |                    |                    |                  | 2L+               |
| Breast cancer         |             |                  | 1.57                    |                    |                    |                  | 3L                |
| Pancreas              |             |                  |                         |                    |                    |                  | 2L                |
| Appendix              |             |                  |                         |                    |                    |                  | Proxy (3L)        |
| CNS                   |             |                  |                         |                    | 1.27               |                  | 1L+               |
| STS paediatrics       |             |                  |                         |                    |                    |                  | Last line         |
| Bone sarcoma          |             |                  |                         |                    |                    |                  | 2L                |

1L= first-line; 2L= second-line; 3L= third-line; CNS= Central nervous system; ePAS9= Extended primary analysis set 9; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; N/R= Not reported; SACT= Systemic anti-cancer therapy; SAS3= Supplemental analysis set 3; STS= Soft tissue sarcoma.

Note: In cases where the number of prior lines of therapy was reported as a range, the lower bound estimate was used.

## Model structure

B4. Please add functionality to the model to easily change the weighting of paediatric and adult patients in the model results.

Total outcomes for larotrectinib are generated by combining the adult starting cohort and paediatric starting cohort outcomes using the ratio of adult to paediatric tumour locations (% for paediatric tumour locations). This is an input in the model which

can be adjusted in the 'Characteristics' tab within the population weighting section (cell H21) by adjusting the user input for the STS paediatrics population.

## ***Treatment effectiveness***

**B5. Priority question: In TA630 the Committee concluded that the assumption of equal response across histologies is inappropriate and expressed a preference for a response-based model based on BHM.**

**a) Please provide further justification for the rejection of a response-based model structure.**

As outlined in the CS, to inform the responder/non-responder analysis originally submitted, a Bayesian hierarchical model (BHM) was used to adjust for heterogeneity in objective response rate (ORR) that may arise from differences in tumour location. However, the ORR estimates generated by the BHM proved highly sensitive to the inclusion criteria for tumour locations, resulting in substantial variability and instability. For example, when all tumour locations were included, the ORR was █%; excluding locations with fewer than two patients █ the ORR to █% and applying a threshold of at least five patients per tumour type █ the ORR further to █%. This wide range of results demonstrates that the BHM is highly sensitive to its underlying assumptions and sample composition, undermining its reliability for informing a responder/non-responder analysis.

Nevertheless, a response-based scenario analysis was conducted within the model to explore the impact of response heterogeneity, ensuring that this aspect was adequately addressed. Given the instability and sensitivity of the BHM approach, a response-based model structure is not justified for this analysis.

Further, additional studies have been conducted since the original submission which provide a comparator arm to estimate relative effects. This is the preferred modelling approach since there is no need to assume treatment effect was received based on responder status. Furthermore, larotrectinib efficacy is skewed by assumptions regarding responders. If treatment with larotrectinib is assumed to be represented by responders, then this ignores the benefits of stable disease, which are attributed to non-responders, hence overestimating SOC. Clinical feedback from the advisory

board reported that stable disease holds strong value, especially in patients with a primary CNS tumour (1).

**b) Please clarify whether (and how many) patients with stable disease continued treatment in the ePAS9 and SAS3 trials. Do patients achieving stable disease as a highest level of response continue treatment with larotrectinib in NHS practice?**

■ patients from the combined ePAS9 and SAS3 datasets achieved a best response of stable disease (or non-CR/ non-PD). These patients had similar PFS and TTD as shown by Figure 17, which indicates ongoing treatment until progression.

Achieving stable disease signifies that the tumour is not progressing, which is a positive indication that the treatment is having an effect. In the context of NTRK fusion-positive tumours, where options are limited, maintaining disease stability can be a critical marker of treatment success.

Stable disease allows for ongoing management of the disease, providing patients with the opportunity to remain on effective therapy.

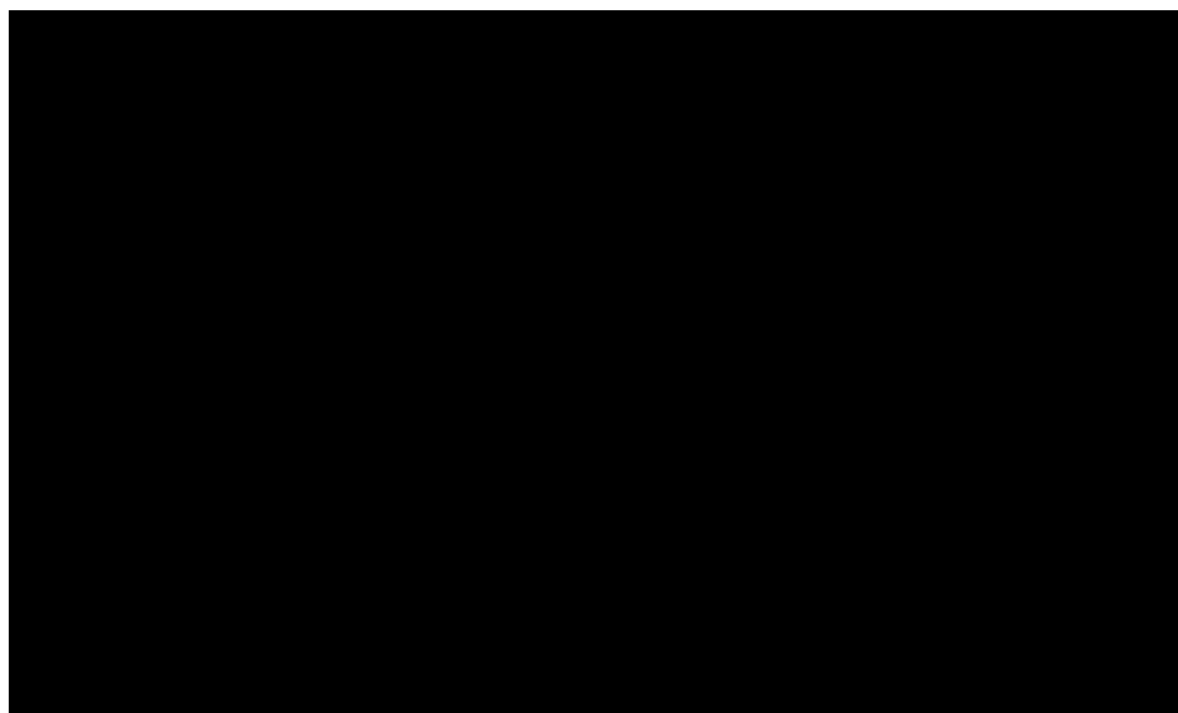
Maintaining stability in disease can have a positive impact on patients' quality of life. When a tumour is stable, patients may experience fewer symptoms, and a better overall sense of well-being compared to those whose disease is progressing. This stability can allow patients to maintain their daily activities and enjoy a better quality of life during treatment.

In NHS clinical practice, stable disease can inform treatment decisions. It may lead to continued treatment rather than switching to a different therapy, especially if the patient is tolerating the treatment well and showing no signs of progression. This can be particularly beneficial in the context of NTRK fusion-positive tumours, where treatment options are limited and the disease can be challenging to manage.

Clinical advisors confirmed during the advisory board that, in NHS practice, patients with stable disease can continue treatment if they are deriving clinical benefit. Advisors also noted that some patients may remain on treatment for extended periods, and in rare cases, may achieve long-term remission. Further, clinicians highlighted examples

of durable benefit reinforcing that treatment continuation for stable disease is clinically appropriate.

**Figure 17. PFS and TTD for ePAS9+SAS3 that had a best response of stable disease** [REDACTED]



**B6. Priority question: Please present an updated response-based model which uses BHM analyses accounting for the different levels of response in adults and children separately as discussed in Question A13a.**

See response to question A13.

**B7. Priority question: Please explore a scenario in which individual histology response rates produced by the BHM are individually applied in the model (per Question A13a). A single ICER may then be generated as a weighted average according to the distribution of tumour types in the NHS population. QALY severity weighting should be applied histology-specific outcomes.**

As per the response to A13 and explained in CS Section 3.15, the BHM has shown instability and tumour specific responses are uncertain given the small sample size.

Therefore disaggregating by tumour types would add considerable uncertainty and so this option was not pursued in the model.

**B8. Priority question: Please justify the modelling of an average post-progression survival of [REDACTED] years in paediatric patients in the company base case. Given that no subsequent treatments are modelled, long-term PPS seems implausible and inconsistent with the experience of the EAG's clinical experts.**

**a) Please make specific reference to clinical expert opinion and provide a clinical and biological rationale supporting post-progression outcomes of this magnitude.**

The clinical experts at the advisory board were presented with the KM survival curves and survival estimates at the 10- and 40-year landmarks. They recommended using Exponential or Gamma as acceptable options for OS extrapolation. Weibull was selected because it produces survival estimates very similar to Gamma at key landmarks (10 years: 68.4% vs. 67.9%; 40 years: 30.2% vs. 26.7%) and is compatible with proportional hazards assumptions, which was necessary for applying MAIC-derived hazard ratios in scenario analyses.

Paediatric soft tissue sarcomas, particularly IFS, are often associated with a favourable prognosis (41, 42). A 5-year OS rate of 96% has been reported for locally advanced IFS; however, this figure includes patients who have undergone disfiguring surgery. This aligns with feedback from the advisory board, where clinicians stated that for some patients, their disease is and stays under control for an indefinite period of time and there is a proportion of patients who are possibly cured (1).

Patients treated with larotrectinib often demonstrate durable disease control, suggesting a prolonged survival benefit. According to Yeh *et al.* (2020), 5-year survivors of childhood cancer have a conditional life expectancy ranging from 48.5 to 57.1 years, depending on the year of diagnosis (43). Although a life expectancy gap remains compared with the general population, these patients still live more than 20 years on average. This supports the plausibility of long-term survival following an initial response to effective targeted therapy such as larotrectinib, even without explicitly modelling post-progression treatments.

As stated in question B9, this model represents a simplification of real-world conditions in which post-progression treatments may occur, albeit at a reportedly low rate in the CDF. Since these therapies would likely be received in both treatment arms, their impact can reasonably be assumed to cancel out without the need for complex model structures. Notably, modelling subsequent treatments for each individual tumour type would be highly impractical.

**b) The Committee in TA630 stated that they considered post-progression survival of this magnitude implausible. Please comment on why the model structure as presented in the current appraisal was taken further without adjustment, e.g. alternative OS data used, inclusion of effect waning, etc.**

No alternative OS data for paediatric TRK fusion cancers are available, however multiple MAIC OS HRs were explored for the larotrectinib vs SOC incremental OS, generating similar or better ICERs (range: £[REDACTED] to £[REDACTED]). The model structure was retained to reflect the best available evidence. Further we have included two scenario analyses to explore the impact of treatment waning:

- Immediate waning after the end of the KM data to a treatment effect of 0. This increased the base case paediatric ICER by £[REDACTED] ().
- Gradual waning of the treatment effect based on the MAIC-derived hazard ratio. This increased the base case paediatric ICER by £[REDACTED] (Table 19).

**B9. Priority question: Section 2.7 of the Company Submission appears to refer only to subsequent NTRK inhibitors when considering subsequent treatments.**

**a) Please present evidence from ePAS9 and SAS3 on the use of any subsequent non-palliative treatments given (i.e. non-BSC), including surgical resection, in adult and paediatric patients following progression. Please comment on whether any such treatments are representative of NHS practice.**

**b) As appropriate per B9a above, please account for the costs of subsequent treatments in the model, or if not relevant to NHS practice,**

**undertake crossover adjustment to remove the impact of these treatments on modelled OS.**

Table 21 summarises the subsequent treatments received by patients in ePAS9. Corresponding data for SAS3 are presented in Question A10.

Across both datasets, [REDACTED] patients did not receive any subsequent treatment following larotrectinib. This aligns with NHS practice, where the SACT report indicates that only 13% of patients received a subsequent therapy, with 25% of those entering a clinical trial.

Among those who did receive further treatment after larotrectinib, the most common category was “other (unknown) systemic therapy” ([REDACTED]% in ePAS9 and [REDACTED]% in SAS3). Since the specific regimens are not identified, it is difficult to assess how representative these treatments are of NHS practice or to estimate associated costs.

The second most common subsequent treatment was another NTRK inhibitor ([REDACTED]% in ePAS9 and [REDACTED]% in SAS3). However, this is unlikely to reflect NHS clinical practice, as entrectinib is the only other TRKi available in the UK (via the Cancer Drugs Fund). The CDF criteria restrict patients from receiving another TRKi prior to entrectinib, making subsequent TRKi use after larotrectinib highly improbable.

In summary, while some patients in clinical trials received subsequent therapy after larotrectinib, this does not appear to occur frequently among NHS patients.

**Table 20. Summary of subsequent therapies (ePAS9)**

| Subsequent Therapy         | Pediatrics (Age < 18 years)<br>N=99 (100%) | Adults (Age >= 18 years)<br>N=205 (100%) | Total<br>N=304 (100%) |
|----------------------------|--------------------------------------------|------------------------------------------|-----------------------|
| Other systemic therapies   | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |
| NTRK inhibitor therapies   | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |
| Radiotherapy               | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |
| Surgery                    | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |
| Cryoablation of tumor      | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |
| Radioactive iodine therapy | [REDACTED]                                 | [REDACTED]                               | [REDACTED]            |

**B10. Priority question: Please justify the application of a substantially larger effect size for PFS (0.21 [0.02 – 2.84]) than for OS (0.8 [0.41 – 1.58]) in**

**paediatric patients, given that the magnitude of uncertainty in the PFS HR renders this analysis and the point estimate essentially meaningless. Please provide a clinical rationale for a difference of this magnitude in the effect of larotrectinib relative to SoC on OS compared to PFS.**

The HR (larotrectinib vs. SoC) effect size from the EPI-VITRAKVI study for PFS is 0.8 (0.41 – 1.58) and for OS it is 0.21 (0.02 – 2.84). This indicates that the uncertainty is greater in the OS estimate compared to what was stated in the question. This uncertainty is linked to the low number of deaths reported in the analysis (n=11).

To address this, multiple treatment effect sources were explored. The VICTORIA MAIC effect size for PFS is 0.29 (0.18 – 0.46), and for OS, it is 0.44 (0.23 – 0.83) (29). These estimates have less uncertainty and are more similar to each other; this scenario generated similar results to EPI-VITRAKVI HRs. In addition, the HMF (33) OS HR of 0.16 (0.07 – 0.36) and Flatiron OS HR of 0.22 (0.09 – 0.52) are comparable to the OS HR point estimate from EPI-VITRAKVI (28).

**B11. Priority question: Please present a scenario analysis in which SACT KM data (ideally by adult and paediatric patients) is used to directly model PFS and OS on larotrectinib, with a HR derived from the SACT MAIC described in Question A3 used to generate SoC curves.**

See response to question A3.

### ***Health-related quality of life***

**B12. Priority question: In TA630 the committee considered it implausible that post-progression utility would be significantly higher in the larotrectinib arm than for the comparator arm across the entire population.**

- a) Please provide further justification for this assumption in the present model given the position expressed by the Committee.
- b) Please provide descriptive data on the distribution of EQ-5D responses collected following disease progression in ePAS9 and SAS3, including the timing of each assessment relative to the date of progression.



- c) **Please explore alternative approaches for estimating post-progression utility values from ePAS9 and SAS3 which place greater weight on data collected later after progression, e.g. excluding questionnaires administered immediately following progression.**
  - d) **Please provide information on the extent of missing EQ-5D data in the post-progression health state in ePAS9 and SAS3, including the number and proportion of patients with available data at each assessment point following progression.**
  - e) **Please provide clarity on whether the company has investigated whether missing EQ-5D data post-progression is systematically related to patient or disease characteristics, e.g. sicker patients, those hospitalised with complications, those with shorter survival, were not completing questionnaires. If so, please summarise the findings and describe any adjustments made to account for differential attrition/missing data.**
- a) This assumption is supported by a large number of post-progression assessments (████ in the current dataset vs. 74 in TA630), increasing reliability. In addition, the updated pooled analysis included █████ patients (vs. 93 in TA630), with extended follow-up and broader tumour type representation, providing a more robust and generalisable estimate of health-related quality of life in both pre- and post-progression states.
  - b) The descriptive data per study are presented in Table 22. The median time from date of progression to the last post-progression HRQoL assessment was █████ (range █████) days in Study 20289 and █████ (range █████) days in Study 20290. Descriptive data further broken down by assessment number are provided in Table 23. Finally, the number of assessments per post-progression time window (≤1 week, 1-4 weeks, 1-3 months, 3-6 months, 6-12 months, >12 months) are summarised in Table 24. Among the post-progression assessments, █████% (Study 20289) and █████% (Study 20290) were collected at least 6 months after the date of progression.

**Table 21. Descriptive data – post-progression HRQoL assessments per study, relative to timing of progression**

| Study | N assessments | N patients | Mean (days) | SD (days) | Median (days) | Q1 (days) | Q3 (days) | Min (days) | Max (days) | Median (weeks) | Median (months) |
|-------|---------------|------------|-------------|-----------|---------------|-----------|-----------|------------|------------|----------------|-----------------|
| 20289 |               |            |             |           |               |           |           |            |            |                |                 |
| 20290 |               |            |             |           |               |           |           |            |            |                |                 |

**Table 22. Post-progression HRQoL assessments per study grouped by assessment number, relative to timing of progression**

| Assessment # | Study 20289 |             |               |           |           |                | Study 20290 |             |               |           |           |                |
|--------------|-------------|-------------|---------------|-----------|-----------|----------------|-------------|-------------|---------------|-----------|-----------|----------------|
|              | N           | Mean (days) | Median (days) | Q1 (days) | Q3 (days) | Median (weeks) | N           | Mean (days) | Median (days) | Q1 (days) | Q3 (days) | Median (weeks) |
| 1            |             |             |               |           |           |                |             |             |               |           |           |                |
| 2            |             |             |               |           |           |                |             |             |               |           |           |                |
| 3            |             |             |               |           |           |                |             |             |               |           |           |                |
| 4            |             |             |               |           |           |                |             |             |               |           |           |                |
| 5            |             |             |               |           |           |                |             |             |               |           |           |                |
| 6            |             |             |               |           |           |                |             |             |               |           |           |                |
| 7            |             |             |               |           |           |                |             |             |               |           |           |                |
| 8            |             |             |               |           |           |                |             |             |               |           |           |                |
| 9            |             |             |               |           |           |                |             |             |               |           |           |                |
| 10           |             |             |               |           |           |                |             |             |               |           |           |                |
| 11           |             |             |               |           |           |                |             |             |               |           |           |                |
| 12           |             |             |               |           |           |                |             |             |               |           |           |                |
| 13           |             |             |               |           |           |                |             |             |               |           |           |                |
| 14           |             |             |               |           |           |                |             |             |               |           |           |                |
| 15           |             |             |               |           |           |                |             |             |               |           |           |                |
| 16           |             |             |               |           |           |                |             |             |               |           |           |                |
| 17           |             |             |               |           |           |                |             |             |               |           |           |                |
| 18           |             |             |               |           |           |                |             |             |               |           |           |                |
| 19           |             |             |               |           |           |                |             |             |               |           |           |                |
| 20           |             |             |               |           |           |                |             |             |               |           |           |                |
| 21           |             |             |               |           |           |                |             |             |               |           |           |                |

| Assessment # | Study 20289 |             |               |           |           |                | Study 20290 |             |               |           |           |                |
|--------------|-------------|-------------|---------------|-----------|-----------|----------------|-------------|-------------|---------------|-----------|-----------|----------------|
|              | N           | Mean (days) | Median (days) | Q1 (days) | Q3 (days) | Median (weeks) | N           | Mean (days) | Median (days) | Q1 (days) | Q3 (days) | Median (weeks) |
| 22           |             |             |               |           |           |                |             |             |               |           |           |                |
| 23           |             |             |               |           |           |                |             |             |               |           |           |                |
| 24           |             |             |               |           |           |                |             |             |               |           |           |                |
| 25           |             |             |               |           |           |                |             |             |               |           |           |                |
| 26           |             |             |               |           |           |                |             |             |               |           |           |                |
| 27           |             |             |               |           |           |                |             |             |               |           |           |                |
| 28           |             |             |               |           |           |                |             |             |               |           |           |                |
| 29           |             |             |               |           |           |                |             |             |               |           |           |                |
| 30           |             |             |               |           |           |                |             |             |               |           |           |                |
| 31           |             |             |               |           |           |                |             |             |               |           |           |                |
| 32           |             |             |               |           |           |                |             |             |               |           |           |                |
| 33           |             |             |               |           |           |                |             |             |               |           |           |                |
| 34           |             |             |               |           |           |                |             |             |               |           |           |                |
| 35           |             |             |               |           |           |                |             |             |               |           |           |                |
| 36           |             |             |               |           |           |                |             |             |               |           |           |                |
| 37           |             |             |               |           |           |                |             |             |               |           |           |                |
| 38           |             |             |               |           |           |                |             |             |               |           |           |                |

**Table 23. Timing distribution of post-progression HRQoL assessments per study, relative to timing of progression**

| Time window | 20289<br>n (%) | 20290<br>n (%) |
|-------------|----------------|----------------|
| ≤1 week     |                |                |
| 1-4 weeks   |                |                |
| 1-3 months  |                |                |
| 3-6 months  |                |                |
| 6-12 months |                |                |
| >12 months  |                |                |

- c) The requested scenario is presented in Table 25, and the base case results are also presented for comparison. For each patient, the first assessment after progression was excluded, resulting in [REDACTED] and [REDACTED] assessments excluded in Study 20289 and Study 20290, respectively. Overall, the results are similar to the base case, and no significant differences were observed. The MMRM results for the progressed disease health state resulted in a mean utility of [REDACTED] (95 CI: [REDACTED]), compared to [REDACTED] (95% CI [REDACTED]) in the base case.

**Table 24. Scenario results – excluding assessments immediately following progression**

|                                                      |                    | Mean Values                  | OLS Regression           |    | MMRM                |    |
|------------------------------------------------------|--------------------|------------------------------|--------------------------|----|---------------------|----|
|                                                      | Assessments<br>(N) | Mean Utility<br>(SD/ 95% CI) | Mean Utility<br>(95% CI) | SE | LS Mean<br>(95% CI) | SE |
| Base case: all assessments post-progression included |                    |                              |                          |    |                     |    |
| Progression-Free                                     | ■                  | ■                            | ■                        | ■  | ■                   | ■  |
| Progressed Disease                                   | ■                  | ■                            | ■                        | ■  | ■                   | ■  |
| P Value                                              |                    |                              | ■                        |    | ■                   |    |
| Scenario: First assessment post-progression excluded |                    |                              |                          |    |                     |    |
| Progression-Free                                     | ■                  | ■                            | ■                        | ■  | ■                   | ■  |
| Progressed Disease                                   | ■                  | ■                            | ■                        | ■  | ■                   | ■  |
| P Value                                              |                    |                              | ■                        |    | ■                   |    |

(\*) denotes significance at 0.05; Note: AR model assumed for correlation

CI= confidence interval; LS= least squares; MMRM= mixed models for repeated measures; OLS= ordinary least squares; SE= standard error.

- d) The available data per patient per cycle following progression are presented in Table 26. Overall, HRQoL assessments were available for most patients in the first cycles following progression, with less frequent assessments in the later cycles.

**Table 25. HRQoL data availability per cycle post-progression**

| Post-progression cycle | Study 20289          |                               |                 |                        | Study 20290          |                               |                 |                        |
|------------------------|----------------------|-------------------------------|-----------------|------------------------|----------------------|-------------------------------|-----------------|------------------------|
|                        | Patients at risk (n) | Patients with assessments (n) | Assessments (n) | Patients with data (%) | Patients at risk (n) | Patients with assessments (n) | Assessments (n) | Patients with data (%) |
| 1                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 2                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 3                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 4                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 5                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 6                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 7                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 8                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 9                      |                      |                               |                 |                        |                      |                               |                 |                        |
| 10                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 11                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 12                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 13                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 14                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 15                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 16                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 17                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 18                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 19                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 20                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 21                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 22                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 23                     |                      |                               |                 |                        |                      |                               |                 |                        |
| 24                     |                      |                               |                 |                        |                      |                               |                 |                        |

| Post-<br>progression<br>cycle | Study 20289             |                                     |                     |                           | Study 20290             |                                     |                     |                           |
|-------------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|
|                               | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) |
| 25                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 26                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 27                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 28                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 29                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 30                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 31                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 32                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 33                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 34                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 35                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 36                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 37                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 38                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 39                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 40                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 41                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 42                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 43                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 44                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 45                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 46                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 47                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 48                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 49                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 50                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 51                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 52                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 53                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 54                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 55                            |                         |                                     |                     |                           |                         |                                     |                     |                           |

| Post-<br>progression<br>cycle | Study 20289             |                                     |                     |                           | Study 20290             |                                     |                     |                           |
|-------------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|
|                               | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) |
| 56                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 57                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 58                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 59                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 60                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 61                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 62                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 63                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 64                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 65                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 66                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 67                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 68                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 69                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 70                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 71                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 72                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 73                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 74                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 75                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 76                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 77                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 78                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 79                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 80                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 81                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 82                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 83                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 84                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 85                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 86                            |                         |                                     |                     |                           |                         |                                     |                     |                           |

| Post-<br>progression<br>cycle | Study 20289             |                                     |                     |                           | Study 20290             |                                     |                     |                           |
|-------------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|-------------------------|-------------------------------------|---------------------|---------------------------|
|                               | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) | Patients at<br>risk (n) | Patients with<br>assessments<br>(n) | Assessment<br>s (n) | Patients with<br>data (%) |
| 87                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 88                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 89                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 90                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 91                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 92                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 93                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 94                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 95                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 96                            |                         |                                     |                     |                           |                         |                                     |                     |                           |
| 97                            |                         |                                     |                     |                           |                         |                                     |                     |                           |



- e) To estimate the HRQoL completeness rate following progression, OS data were used to calculate the "expected number of cycles" per patient (i.e., the expected maximum number of assessments post-progression). The number of assessments for which the patient had data was then divided by the expected number of cycles. Patient baseline characteristics, mean survival outcomes, and number of observations stratified by <50% vs. ≥50% completion are presented in Table 27.

Overall, patients with higher completion rates had shorter OS. This is expected given how the completion rates were defined, and considering that patients with longer survival post-progression had higher tendency to miss HRQoL assessments as they are being followed up for a longer period of time. Additionally, patients with a higher completion rate had notably lower baseline utility.

To further explore potential differences between patients with a low number versus those with a high number of assessments post-progression, similar tables were produced, stratifying patients based on the median number of post-progression HRQoL assessments (1 in Study 20289; 2 in Study 20290). These results are presented in Table 28 and Table 29. Patients with a higher number of assessments had higher mean overall survival and post-progression survival; however, no notable differences were observed in baseline utility, mean age, gender, ECOG performance status or extent of disease.

Overall, no systematic differences were identified based on high/low completion rates or the number of complete assessments. The MMRM analysis presented in the CS utilised all available data, regardless of survival or disease severity at baseline. Furthermore, the majority of patients had a low number of assessments post-progression, regardless of survival. Therefore, it is unlikely that patients with short survival are underrepresented in the analysis.

**Table 26. Characteristics of patients stratified by completeness rate post-progression**

| Study       | Characteristic                 | Completeness<br>≥50% | Completeness<br><50% | All patients |
|-------------|--------------------------------|----------------------|----------------------|--------------|
| Study 20289 | N                              | 100                  | 100                  | 200          |
|             | Age, years - mean (SD)         | 65 (10)              | 65 (10)              | 65 (10)      |
|             | Female - n (%)                 | 100 (50)             | 100 (50)             | 200 (50)     |
|             | Paediatric (<18 years) - n (%) | 0 (0)                | 0 (0)                | 0 (0)        |
|             | Baseline utility - mean (SD)   | 0.75 (0.10)          | 0.75 (0.10)          | 0.75 (0.10)  |
|             | ECOG, n (%)                    | 100 (50)             | 100 (50)             | 200 (50)     |
|             | 0                              | 100 (50)             | 100 (50)             | 200 (50)     |

| Study       | Characteristic                                | Completeness<br>≥50% | Completeness<br><50% | All patients |
|-------------|-----------------------------------------------|----------------------|----------------------|--------------|
|             | 1                                             |                      |                      |              |
|             | 2                                             |                      |                      |              |
|             | 3                                             |                      |                      |              |
|             | Missing                                       |                      |                      |              |
|             | Disease extent, n (%)                         |                      |                      |              |
|             | Metastatic                                    |                      |                      |              |
|             | Primary CNS                                   |                      |                      |              |
|             | Missing                                       |                      |                      |              |
|             | Time on treatment, months – mean (SD)         |                      |                      |              |
|             | Overall survival, months - mean (SD)          |                      |                      |              |
|             | Progression-free survival, months - mean (SD) |                      |                      |              |
|             | Post-progression survival, months - mean (SD) |                      |                      |              |
|             | No. of observations - median (IQR)            |                      |                      |              |
| Study 20290 | N                                             |                      |                      |              |
|             | Age, years - mean (SD)                        |                      |                      |              |
|             | Female - n (%)                                |                      |                      |              |
|             | Paediatric (<18 years) - n (%)                |                      |                      |              |
|             | Baseline utility - mean (SD)                  |                      |                      |              |
|             | ECOG, n (%)                                   |                      |                      |              |
|             | 0                                             |                      |                      |              |
|             | 1                                             |                      |                      |              |
|             | 2                                             |                      |                      |              |
|             | 3                                             |                      |                      |              |
|             | Missing                                       |                      |                      |              |
|             | Disease extent, n (%)                         |                      |                      |              |
|             | Metastatic                                    |                      |                      |              |
|             | Primary CNS                                   |                      |                      |              |
|             | Missing                                       |                      |                      |              |
|             | Time on treatment, months – mean (SD)         |                      |                      |              |
|             | Overall survival, months - mean (SD)          |                      |                      |              |
|             | Progression-free survival, months - mean (SD) |                      |                      |              |
|             | Post-progression survival, months - mean (SD) |                      |                      |              |
|             | No. of observations - median (IQR)            |                      |                      |              |

**Table 27. Characteristics of patients in Study 20289 stratified by number of assessments post-progression**

| Study       | Characteristic                 | 1 | >1 |
|-------------|--------------------------------|---|----|
| Study 20289 | N                              |   |    |
|             | Age, years - mean (SD)         |   |    |
|             | Female - n (%)                 |   |    |
|             | Paediatric (<18 years) - n (%) |   |    |
|             | Baseline utility - mean (SD)   |   |    |
|             | ECOG performance status, n (%) |   |    |
|             | 0                              |   |    |

| Study | Characteristic                                | 1                                                                                  | >1                                                                                  |
|-------|-----------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|       | 1                                             |  |  |
|       | 2                                             |  |  |
|       | 3                                             |  |  |
|       | Missing                                       |  |  |
|       | Disease extent, n (%)                         |                                                                                    |                                                                                     |
|       | Metastatic                                    |  |  |
|       | Primary CNS                                   |  |  |
|       | Missing                                       |  |  |
|       | Time on treatment, months – mean (SD)         |  |  |
|       | Overall survival, months - mean (SD)          |  |  |
|       | Progression-free survival, months - mean (SD) |  |  |
|       | Post-progression survival, months - mean (SD) |  |  |
|       | No. of observations - median (IQR)            |  |  |

**Table 28. Characteristics of patients in Study 20290 stratified by number of assessments post-progression**

| Study       | Characteristic                                | 1-5                                                                                  | >5                                                                                    |
|-------------|-----------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Study 20290 | N                                             |   |    |
|             | Age, years - mean (SD)                        |   |   |
|             | Female - n (%)                                |  |  |
|             | Paediatric (<18 years) - n (%)                |  |  |
|             | Baseline utility - mean (SD)                  |  |  |
|             | ECOG performance status, n (%)                |                                                                                      |                                                                                       |
|             | 0                                             |  |  |
|             | 1                                             |  |  |
|             | 2                                             |  |  |
|             | 3                                             |  |  |
|             | Missing                                       |  |  |
|             | Disease extent, n (%)                         |                                                                                      |                                                                                       |
|             | Metastatic                                    |  |  |
|             | Primary CNS                                   |  |  |
|             | Missing                                       |  |  |
|             | Time on treatment, months – mean (SD)         |  |  |
|             | Overall survival, months - mean (SD)          |  |  |
|             | Progression-free survival, months - mean (SD) |  |  |
|             | Post-progression survival, months - mean (SD) |  |  |
|             | No. of observations - median (IQR)            |  |  |

B13. Please provide further justification for the generally substantially higher utility applied in the pre-progression health state on larotrectinib relative to the SoC arm, given the Committee's position that this generated bias in favour of larotrectinib, and

that lower pre-progression utilities would be more generalisable to NHS clinical practice.

See response to question B12a.

**B14. Priority question: Many of the selected sources of health state utility listed in CS Table 53 (Page 166) are old and may be unlikely to represent quality of life in current practice.**

**a) Please present the alternative utilities for each tumour site identified in the literature searches described in Section 3.4.1.**

The health-related quality of life systematic literature review identified four studies reporting utility data for specific tumour sites (Table 30).

**Table 29. Alternative comparator utility data**

| Tumour site | Utility                                                                                                                                                                                                                                                                                                  | Reference                                    |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| NSCLC       | <ul style="list-style-type: none"> <li>Pre-progression utility (95% CI): 0.653 (0.61-0.70)</li> <li>Responsive utility increment: 0.019</li> <li>Progressive utility (95% CI): 0.473 (0.41-0.51)</li> </ul>                                                                                              | Roth 2020 (44); Suh 2024 (45); Suh 2025 (46) |
| Colorectal  | <ul style="list-style-type: none"> <li>Pre-progression utility (95% CI): 0.82 (0.78-0.86) <ul style="list-style-type: none"> <li>Larotrectinib on-treatment utility: 0.83</li> <li>Entrectinib on-treatment utility: 0.83</li> </ul> </li> <li>Progressive utility (95% CI): 0.64 (0.55-0.75)</li> </ul> | Suh 2022 (47); Suh 2025 (46)                 |
| STS adults  | <ul style="list-style-type: none"> <li>Pre-progression utility (95% CI): 0.43 (0.39-0.47)</li> <li>Responsive utility increment: 0.125</li> <li>Progressive utility (95% CI): 0.3 (0.26-0.34)</li> </ul>                                                                                                 | Suh 2022 (47); Suh 2025 (46)                 |
| Thyroid     | <ul style="list-style-type: none"> <li>Pre-progression utility (95% CI): 0.80 (0.77-0.84)</li> <li>Responsive utility increment: 0.06</li> <li>Progressive utility (95% CI): 0.50 (0.45-0.56)</li> </ul>                                                                                                 | Suh 2024 (45); Suh 2025 (46)                 |

CI = Confidence interval; NSCLC = non-small cell lung cancer; STS = soft tissue sarcoma.

**b) Please provide a reference for the Thyroid utility.**

Thyroid utility was sourced from the Bayer model for radioiodine-refractory differentiated thyroid cancer in TA535. The values were derived from EQ-5D data collected during the DECISION trial (31).

**c) Please provide references for the cholangiocarcinoma utility.**

Due to the lack of data, cholangiocarcinoma utility was derived from a weighted average of health state utilities for other tumour sites. The references for these can be found in B14d below.

**d) Please provide a description of the original source of each comparator utility, e.g. EQ-5D data from affected patients, vignettes/TTO, etc.**

The description of the original source for each comparator utility is presented in Table 31.

**Table 30. Comparator utility sources**

| Tumour locations      | Description of source                                                                                                                                                                                                                                                                                 | Reference                                                |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| NSCLC                 | EQ-5D data from NSCLC patients.                                                                                                                                                                                                                                                                       | Chouaid 2013 (48)                                        |
| Salivary              | Utilities obtained from a cost-utility analysis for head and neck cancer. PFS utility derived from standard gamble responses on advanced breast cancer by oncology nurses, adjusted using expert opinion. PD utility derived from TTO responses on advanced head and neck cancer by resident doctors. | Liberto 2012 (49); Brown 2012 (50); Hollenbeak 2001 (51) |
| Melanoma              | EQ-5D utility values from melanoma patients.                                                                                                                                                                                                                                                          | KEYNOTE-002 trial (52)                                   |
| Colorectal            | EQ-5D data from metastatic colorectal cancer patients.                                                                                                                                                                                                                                                | Grothey 2013 (53)                                        |
| STS adults (GIST)     | EQ-5D assessment in patients with metastatic and/or unresectable GIST.                                                                                                                                                                                                                                | TA488 GRID study (54)                                    |
| STS adults (non-GIST) | In the absence of STS-specific data, TA185 implemented standard gamble utility values from NSCLC patients.                                                                                                                                                                                            | TA185 (55); Nafees 2008 (56)                             |
| STS paediatric        | Combined EQ-5D and mapped QLQ-C30 utility data from adult patients with advanced STS for PFS. For PD, post-progression utilities from this dataset were combined with an estimate of utility in the terminal phase of the disease from a vignette study in the UK general public, employing TTO.      | Delea 2014 (57); Shingler 2012 (58)                      |
| Breast                | PFS utility derived from QLQ-C30 data in patients with locally advanced or metastatic breast cancer, mapped to EQ-5D values. PD utility values obtained from the UK general public using the standard gamble method and descriptions of metastatic breast cancer.                                     | Kaufman 2015 (59); Lloyd 2006 (60)                       |
| Cholangiocarcinoma    | Weighted average of health state utilities for other tumour sites.                                                                                                                                                                                                                                    |                                                          |
| CNS/Glioma            | EORTC QLQ-C30 utility data from patients with malignant gliomas.                                                                                                                                                                                                                                      | Osoba 2000 (61); Osoba 2000 <sup>b</sup> (62)            |
| Pancreas              | PFS utility derived from EQ-5D data in patients with advanced pancreas cancer. For PD utility, EQ-5D index scores were elicited using the TTO method derived from patients with locally advanced or metastatic gastric cancer.                                                                        | TA440; Romanus 2012 (63); Al-Batran 2016 (64)            |
| Thyroid               | EQ-5D data from patients with locally advanced or metastatic thyroid cancer.                                                                                                                                                                                                                          | TA535 (31); DECISION trial                               |

CNS= central nervous system; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5= EuroQol 5 dimension; GIST= gastrointestinal stromal tumours; NSCLC= non-small-cell lung cancer; PFS= progression-free survival; PD= progressive disease; STS= soft tissue sarcoma; TTO= time-trade-off.

**e) Do the company consider all SoC utilities to have been derived in alignment with the NICE reference case?**

The majority of utility values (NSCLC, melanoma, colorectal cancer, STS GIST, breast cancer, pancreatic cancer and thyroid cancer utilities) are considered consistent with the NICE reference case, which specifies measuring health-related quality of life in the relevant patient population, preferably using the EQ-5D instrument for adults, or where necessary, applying mapping from other measures. The health state utility values for STS paediatric patients could not be identified and were therefore set equivalent to EQ-5D results from the general STS population, in line with the approach in TA630.

Utility values for salivary, STS (non-GIST) and CNS/Glioma indications were applied in TA630 and were sourced from previously published NICE technology appraisals (TA185 and TA23, respectively). However, the methodologies used in the original utility sources do not fully align with the NICE reference case because the EQ-5D instrument was not used. No subsequent NICE technology appraisals providing utility inputs for these indications have been identified. Consequently, there are no alternative sources or preferred utility values available to replace those currently applied. Consistent with TA630, cholangiocarcinoma patients were assigned the weighted average of health state utilities for other tumour sites. While this approach does not strictly conform to the NICE reference case, it represents a pragmatic solution given the absence of published utility data for this indication.

***Resource use***

**B15. Priority question: In TA630, the Committee concluded that post-progression treatment costs for larotrectinib should be included in the model, preferably aligned with modelled survival benefits. The model appears to assume that all patients can only receive BSC beyond the point of progression. Please include the costs of all subsequent therapies (or NHS-relevant alternatives) as described in your response to Question B9.**

As per question B9, the cost of subsequent treatment has not been modelled for either larotrectinib or the comparator treatments. Any potential costs associated with subsequent therapies are assumed to cancel out, as they would apply equally to both

treatment arms or may even be greater in the comparator arm, given that discounting would be less when receiving subsequent treatment earlier.

Furthermore, subsequent treatments following larotrectinib are not routinely observed in NHS practice, as evidenced by SACT data showing that only a small proportion of patients (13%) receive further therapy after progression. If anything, patients in the comparator arm would be more likely to receive a TRK inhibitor as a subsequent treatment, which would increase costs in that arm. As such, the exclusion of subsequent treatment costs is considered a conservative assumption.

Given the limited evidence on subsequent treatment patterns and their likely minimal impact on incremental cost-effectiveness results, this simplification is considered appropriate and unlikely to bias model outcomes.

B16. If larotrectinib has been used in the NHS earlier than the last line of systemic therapy in some tumour types, please comment on whether the company considers it appropriate to model further lines of therapy after larotrectinib in these histologies. See response to question B15.

B17. Please comment further on the company's position that diagnostic testing costs should no longer be included in the economic model. Please clarify whether NHS England has indicated to the company that their position on this issue has changed since TA630.

The company considers that, given that NTRK testing is already embedded within the NHS Genomic Medicine Service and funded centrally through the National Genomic Test Directory, it does not represent an additional cost specific to the introduction of targeted therapies such as larotrectinib. Therefore, including testing within the model would not reflect a real incremental cost or decision point from the NHS perspective.

Indeed, the treatment is already available in England via the Cancer Drugs Fund (CDF), and the NHS infrastructure and clinical pathways have been adapted to support access, including established testing and referral mechanisms through the NHS Genomic Laboratory Hubs. Therefore, no additional implementation burden or cost related to testing is expected upon routine commissioning, supporting the exclusion of testing from the economic model.

Incorporating testing into the model would also introduce unnecessary complexity and uncertainty, as testing pathways vary by tumour type, clinical indication, and local genomic infrastructure. These variations do not alter the treatment's relative clinical or economic value once an NTRK fusion has been identified. As such, excluding testing from the model aligns with NICE's reference case, which recommends focusing on costs and benefits directly associated with the intervention being appraised, rather than broader system-level diagnostic processes that are already commissioned and operational.

NHS England has indicated in the BIA of larotrectinib that “

**B18. Priority question: CS Tables 60 and 61 indicate that the unit costs applied to calculate testing costs were drawn directly from those used by the EAG in TA630. Please update unit costs based on current NHS NGS fusion panel tariffs. Please provide live testing cost calculations in the model and amend to reflect current testing pathways.**

At this time, we have not updated the testing unit costs as we do not have access to the NHS NGS fusion panel tariffs. During the clarification meeting on 3<sup>rd</sup> November 2025, the EAG noted that testing costs vary across regions, and that no single region is representative of national practice. Given this regional variability, and in the absence of a national tariff, we have retained the original unit costs drawn from the EAG model in TA630. However, the model has been programmed to allow for live updates to testing costs.

**B19. Priority question: Please adopt a more granular approach to the inclusion of genomic testing costs. Testing costs should reflect the appropriate counterfactual in each tumour type. For example:**

- a) **Where NTRK fusions are the only actionable gene fusion in a given tumour type, the full cost of the NGS fusion panel should be attributed to the use of TRK inhibitors, as testing would not occur in the absence of larotrectinib and entrectinib in NHS practice.**



- b) Where there are multiple actionable fusion targets, please apportion the NGS testing cost across all relevant actionable fusions, i.e. costs should be divided according to the number of potential target fusions in that tumour type.**
- c) If there is an actionable fusion target at an earlier line of therapy, it may therefore be appropriate to assume fusion status is already known, and thus testing costs may be excluded.**

NTRK fusion testing strategies vary by tumour site, depending on the NTRK fusion rate and whether the current diagnostic pathway for that tumour site already involves NGS testing. When a tumour histology has a high NTRK fusion rate, patients should be tested with an RNA-based NGS panel for the three NTRK fusion types. For tumour histologies with lower fusion rates, a cheaper screening test, IHC, can be used, with a confirmatory RNA-based NGS offered only to those who screen positive. However, if the current diagnostic pathway for a particular tumour site with low NTRK fusion rates already includes an RNA-NGS panel, the existing panel can be expanded to also detect the NTRK fusions (at a negligible additional costs) and screening with IHC is not necessary.

In TA630, the ERG assumed as a starting point that NTRK fusion testing will be performed with:

- RNA-based NGS for tumour sites with high NTRK fusion rates
- IHC followed by RNA-based NGS (henceforth referred to as NGS) testing for tumour sites with low NTRK fusion rates

WGS is currently recommended in the National Genomic Test Directory for sarcomas, melanomas, and paediatric cancers. However, the accuracy of WGS to detect NTRK fusion types is not perfect, and confirmatory NGS of patients who screen positive would still be required before patients are offered larotrectinib (65). Therefore, for these tumour sites, if NTRK fusion rates are low, screening with WGS (instead of IHC) is conducted in all patients, followed by NGS testing for those who screen positive with WGS (65). WGS is assumed to impose no incremental cost, as it would be offered to

the full tumour site population (i.e., patients in the comparator treatment would also have received WGS) (65).

Screening with WGS is assumed not to be necessary for IFS patients, given the high NTRK fusion rate for this tumour site. All IFS patients are, therefore, assumed to be tested with NGS (65). NICE guidance for glioma, NSCLC, colorectal cancer and breast cancer recommends testing with an RNA-based NGS panel at earlier lines of therapy, which can be expanded to include all NTRK fusion types at a negligible incremental cost (66). Therefore, an assumption is made that fusion status is already known, and thus testing costs may be excluded.

For STS, IFS and cholangiocarcinoma there are multiple actionable fusion targets, and the NGS testing cost is divided across all relevant actionable fusions. Finally, salivary cancer patients are already routinely tested for NTRK fusion in the NHS, so no testing costs are attributed to these tumour sites (65).

The type of testing costs per tumour type are presented in below. As per response to B18, the model is programmed to allow for live unit costs per test type to be applied in the absence of an estimate for the NHS NGS fusion tariff:

**Table 31. Testing costs per tumour type**

| <b>Tumour locations</b> | <b>Testing cost</b>                                                       | <b>Source</b>                                                                                   |
|-------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| NSCLC                   | No cost (testing in previous lines)                                       | NG122 (66)                                                                                      |
| Salivary                | No cost (already routinely tested)                                        | Management of Salivary Gland Tumours: United Kingdom National Multidisciplinary Guidelines (67) |
| Melanoma                | WGS + NGS (full NGS cost)                                                 | NG14 (68)                                                                                       |
| Colorectal              | No cost (NGS testing in previous lines)                                   | NG151, DG27 (69, 70)                                                                            |
| STS adults (GIST)       | IHC + NGS (full cost)                                                     | TA488 (71)                                                                                      |
| STS adults (non-GIST)   | IHC + NGS (1/3 price of NGS cost; 2 other targets [EWSR1-NR4A3 and EZH2]) | ESMO–EURACAN–GENTURIS (7)                                                                       |
| STS paediatric          | WGS + NGS (1/3 price of NGS cost; 2 other targets [EWSR1-NR4A3 and EZH2]) | UK guidelines for the management of soft tissue sarcomas (72)                                   |
| Breast                  | No cost (testing in previous lines)                                       | TA1040 (73)                                                                                     |
| Cholangiocarcinoma      | IHC + NGS (1/2 price of NGS cost; 1 other target [FGR2])                  | British Society of Gastroenterology guidelines (74)                                             |
| CNS/Glioma              | No cost (NGS testing in previous lines)                                   | NG99 (75)                                                                                       |
| Pancreas                | IHC + NGS (full cost)                                                     | NG85 (76)                                                                                       |
| Thyroid                 | IHC + NGS (full cost)                                                     | NG230 (77)                                                                                      |

B20. In TA630, the Committee considered that paediatric dosing should be adjusted to reflect the lower doses in the trial and that a 4-week wastage scenario was appropriate. Please update the current submission to align with the Committee's preferred approach.

The cost-effectiveness model has been revised to include a scenario with adjusted paediatric dosing, consistent with the calculations performed by the ERG in TA630. The paediatric dose was derived by applying a proportional adjustment to the recommended paediatric dose, reflecting the ratio of actual to recommended adult dosing observed in the trials. This functionality has been added into the 'Treatment cost' sheet of the updated cost-effectiveness model.

Additionally, a scenario applying a four-weekly prescribing pattern has been introduced, in which larotrectinib is prescribed every fourth model cycle, rather than a weekly supply every cycle. The option to select this scenario has been incorporated into the 'Controls' sheet of the model. The results of the two scenarios are presented separately, as well as combined, in Table 33.

**Table 32. Scenario results for alternative larotrectinib dosing and prescribing patterns**

| Scenario                           | Larotrectinib |       | SOC    |       | ICER (£/QALY) | Adult ICER (£/QALY) | Paediatric ICER (£/QALY) |
|------------------------------------|---------------|-------|--------|-------|---------------|---------------------|--------------------------|
|                                    | Costs         | QALYs | Costs  | QALYs |               |                     |                          |
| Base case results                  | ██████        | 8.936 | ██████ | 2.612 | ██████        | ██████              | ██████                   |
| 1) Adjusted paediatric dosing      | ██████        | 8.936 | ██████ | 2.612 | ██████        | ██████              | ██████                   |
| 2) Four-weekly prescribing pattern | ██████        | 8.936 | ██████ | 2.612 | ██████        | ██████              | ██████                   |
| 1) and 2)                          | ██████        | 8.936 | ██████ | 2.612 | ██████        | ██████              | ██████                   |

ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life years; SOC= standard of care

B21. In TA630, the Committee concluded that oral-administration costs should be included in the model. The SB11Z oral chemotherapy tariff is typically applied to reflect monitoring of patients receiving oral chemotherapy. Please update the current model to apply the SB11Z oral chemotherapy tariff to the larotrectinib arm at an interval appropriate to monitoring on larotrectinib.

Larotrectinib is classified as a targeted therapy specifically for NTRK fusion-positive solid tumours, distinguishing it from traditional oral chemotherapy agents. The SB11Z tariff is designed for conventional chemotherapy treatments, which have different monitoring and management requirements. The monitoring protocols for larotrectinib significantly differ from those associated with standard oral chemotherapy; while all therapies require patient monitoring, the assessments and follow-up procedures for targeted therapies like larotrectinib are tailored to their specific side effects and efficacy profiles. As an oral medication, larotrectinib comes as a capsule or oral solution that should be taken twice daily, according to the prescribed dose. This offers greater flexibility and convenience in administration, allowing it to be taken by patients or administered by caregivers at home. This characteristic aligns more closely with the management of targeted therapies rather than traditional chemotherapy, which often necessitates more intensive monitoring and administration protocols, typically involving administration at the hospital, prolonged administration times, and close supervision by healthcare professionals to manage potential side effects and complications. The ability for patients or caregivers to administer larotrectinib at home emphasises a patient-centric approach to treatment, reducing the burden on healthcare facilities and related costs.

For these reasons, we believe the SB11Z oral chemotherapy tariff should not be included in the analysis. However, we have added functionality to the 'Controls' sheet to allow users to select its inclusion if required.

**B22. Priority question: Many unit costs appear to have been sourced from older NICE appraisals. Where these costs are based on NHS National Cost Collection data, please update the unit costs to reflect current NCC 2023/24 or PSSRU 2024 values.**

Most unit costs are taken from NCC 2023/24 or PSSRU 2024; where not available, costs are adjusted using the inflation rate. For health state costs (Appendix M Table 6), NICE appraisals are used as sources only for frequency data, while NCC 2023/24 and PSSRU 2024 remain the sources for the costs.

B23. The SoC drug costs reported in Table 55 do not match the values applied in the model. Please clarify which values the company considers correct and amend either Table 55 or the model as appropriate.

The correct costs are those applied in the model. We have amended Table 55 of the CS to reflect these values (see Table 32 below).

**Table 33. Treatments to be included in the active comparator arm of the economic model (updated Table 55 from CS)**

| Tumour location       | Included comparators   | Dose                                                                                                                    | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source                     |
|-----------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|-------------|------------|---------------------------------|
| NSCLC                 | Nintedanib             | 200 mg twice daily on days 2 to 21 of a standard 21-day docetaxel treatment cycle                                       | Oral        | 8,000.00                     | 12,000      | £2,151.10  | TA347 (78)                      |
|                       | Docetaxel              | 75 mg/m <sup>2</sup> once per 21-day cycle                                                                              | IV          | 139.10                       | 80          | £9.48      |                                 |
| Salivary              | Cisplatin              | 80 mg/m <sup>2</sup> on day 1                                                                                           | IV          | 142.20                       | 10          | £3.68      | Airoldi <i>et al.</i> 2017 (79) |
|                       | Vinorelbine            | 25 mg/m <sup>2</sup> on days 1 and 8                                                                                    | IV          | 88.88                        | 500         | £175.52    |                                 |
| Melanoma              | Pembrolizumab          | 2 mg/kg once every 3 weeks                                                                                              | IV          | 140.00                       | 100         | £2,630.00  | NICE TA357 (80)                 |
| Colorectal            | Trifluridine-tipiracil | 35 mg/m <sup>2</sup> twice a day on days 1-5 and days 8-12 of 28-day cycle                                              | Oral        | 1,190.00                     | 400         | £666.67    | Mayer <i>et al.</i> 2015 (81)   |
| STS adults (GIST)     | Regorafenib            | 160 mg taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle. | Oral        | 3,360.00                     | 3,360       | £3,744.00  | NICE TA488 (54)                 |
| STS adults (non-GIST) | Trabectedin (1mg)      | 1.22 mg/m <sup>2</sup> body surface area, administered as IV over 24 hours with a 3-week interval between cycles.       | IV          | 2.07                         | 1           | £1,229.40  | TA185 (55)                      |

| Tumour location | Included comparators | Dose                                                                                                                                                                                                | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source         |
|-----------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|-------------|------------|---------------------|
| STS paediatrics | Irinotecan           | 50 mg/m <sup>2</sup> per day for 5 days at weeks 1, 4, 13, 25, 34, 46, 49;                                                                                                                          | IV          | 1,385.81                     | 500         | £16.59     | VIT-0910 trial (82) |
|                 | Vincristine          | 1.5 mg/m <sup>2</sup> on day 1 of weeks 1, 2, 4, 5, 13, 14, 25, 26, 34, 35, 46, 47, 49, 50.                                                                                                         | IV          | 16.63                        | 10          | £63.72     |                     |
|                 | Temozolomide         | 125 mg/m <sup>2</sup> /day<br>Dose will be escalated to 150 mg/m <sup>2</sup> /day at cycle 2<br>TMZ will be given orally, prior to vincristine and irinotecan, on days 1-5 repeated every 3-weeks. | Oral        | 600.00                       | 1,250       | £20.15     |                     |
| Breast          | Vinorelbine (IV)     | 30 mg/m <sup>2</sup> weekly for 6 months;                                                                                                                                                           | IV          | 52.20                        | 500         | £175.52    | NICE TA423 (83)     |
|                 | Vinorelbine (oral)   | 60 mg/m <sup>2</sup> weekly for first 3 administrations and 80mg/m <sup>2</sup> weekly for subsequent administrations for 6 months                                                                  | Oral        | 139.20                       | 80          | £95.70     |                     |
|                 | Gemcitabine          | 1250 mg/m <sup>2</sup> two times per 21-day cycle for 6 months                                                                                                                                      | IV          | 4,350.00                     | 2,000       | £19.74     |                     |

| Tumour location    | Included comparators | Dose                                                                                                                                                                            | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source                       |
|--------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------|-------------|------------|-----------------------------------|
|                    | Docetaxel            | 100 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                        | IV          | 174.00                       | 80          | £9.48      |                                   |
|                    | Paclitaxel           | 175 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                        | IV          | 304.50                       | 300         | £18.75     |                                   |
|                    | Doxorubicin          | 75 mg/m <sup>2</sup> once per 21-day cycle for 6 months                                                                                                                         | IV          | 130.50                       | 200         | £19.01     |                                   |
| Cholangiocarcinoma | 5-fluorouracil       | 400 mg/m <sup>2</sup> (5–10 min bolus) completed on day 1, and fluorouracil 2400 mg/m <sup>2</sup> as continuous intravenous infusion starting on day 1 and finishing on day 2. | IV          | 4977.03                      | 5,000       | £6.13      | ABC-06 trial (84)                 |
|                    | Oxaliplatin          | 85 mg/m <sup>2</sup> (2-h intravenous infusion)                                                                                                                                 | IV          | 151.09                       | 200         | £28.24     |                                   |
|                    | Folinic acid         | 350 mg; 2-h intravenous infusion concurrently with oxaliplatin infusion                                                                                                         | IV          | 350.00                       | 3500        | £62.62     |                                   |
| CNS/Glioma         | Lomustine            | 110 mg/m <sup>2</sup> day on 1 every 6 weeks                                                                                                                                    | Oral        | 187                          | 800         | £780.82    | Batchelor <i>et al.</i> 2013 (85) |
| Pancreas           | Gemcitabine          | 2000 mg/m <sup>2</sup> administered 4                                                                                                                                           | IV          | 5,332.53                     | 2,000       | £19.74     | Conroy <i>et al.</i> 2022 (86)    |



| Tumour location | Included comparators | Dose                     | Admin route | Dose per treatment cycle, mg | mg per pack | Pack cost* | Dose source            |
|-----------------|----------------------|--------------------------|-------------|------------------------------|-------------|------------|------------------------|
|                 |                      | times every 6-week cycle |             |                              |             |            |                        |
| Thyroid         | Lenvatinib (10mg)    | 24 mg once daily         | Oral        | 600                          | 300         | £1,437.00  | SELECT trial 2015 (87) |
|                 | Lenvatinib (4mg)     |                          | Oral        | 120                          | 120         | £1,437.00  |                        |

AUC= area under the curve; GIST= gastrointestinal stromal tumour; IFS= infantile fibrosarcoma; IV= intravenous; STS= soft tissue sarcoma

Source: British national formulary 2021 (88).

B24. The health state costs by tumour location presented in Table 57 in the CS do not fully correspond to the health state cost inputs used in the model. Please clarify which health state costs are correct and amend either Table 57 or the model as appropriate.

The correct costs are those applied in the model. We have amended Table 57 to reflect these values below (Table 33).

**Table 34. Health state costs by tumour location (updated Table 57)**

| Tumour locations              | Progression-free, start-up | Progression-free, per cycle | Progressed, start-up | Progressed, per cycle | Death/End-of-life |
|-------------------------------|----------------------------|-----------------------------|----------------------|-----------------------|-------------------|
| Larotrectinib tumour agnostic | ██████                     | ██████                      | ██████               | ██████                | ██████            |
| NSCLC                         | £0.00                      | £106.07                     | £0.00                | £223.50               | £8,575.58         |
| Salivary                      | £2.67                      | £107.82                     | £335.00              | £82.55                | £7,802.79         |
| Colorectal/Appendix           | £0.00                      | £52.55                      | £1,877.10            | £65.63                | £8,722.76         |
| Melanoma                      | £516.11                    | £114.71                     | £856.27              | £114.71               | £9,814.31         |
| STS (GIST)                    | £34.75                     | £36.09                      | £728.55              | £38.51                | £10,920.87        |
| Non-GIST/Bone sarcoma         | £0.00                      | £27.48                      | £0.00                | £54.97                | £7,775.11         |
| Breast                        | £0.00                      | £65.51                      | £0.00                | £65.51                | £7,208.03         |
| Glioma                        | £516.21                    | £0.00                       | £0.00                | £0.00                 | £7,775.11         |
| Pancreas                      | £358.75                    | £96.72                      | £0.00                | £94.10                | £5,073.34         |
| STS paediatric/IFS            | £0.00                      | £27.19                      | £0.00                | £54.38                | £7,775.11         |
| Cholangiocarcinoma            | £0.00                      | £356.65                     | £0.00                | £192.35               | £7,775.11         |
| Thyroid                       | £0.00                      | £79.04                      | £0.00                | £79.04                | £9,872.17         |

NSCLC= non-small-cell lung cancer; GIST= gastrointestinal stromal tumours; STS= soft tissue sarcoma; IFS= infantile fibrosarcoma.

Health state costs are based on the source NICE TA or literature.

Start-up cost is the one-time cost of health resources required for assessment and/or treatment initiation when patients enter a health state. Start-up cost is assumed £0 if the source does not mention any HRU details or aggregate health state cost.

Glioma TA reported monitoring cost over the treatment period by a fixed schedule that did not fit a per cycle calculation. Thus, the total costs were applied as a one-off cost to glioma health states. Round 2015 was used to inform end-of-life cost for tumour locations that did not have this data in the TA or literature sources.

## Severity modifier

**B25. Priority question: The model appears to weight QALY gains according to the prevalence of each tumour type, rather than by the distribution of QALY gain across tumour types. This assumes QALYs are generated equally across all tumour types (i.e. no heterogeneity in outcome). Please apply severity**

**weights to QALY gains within each respective tumour type, based on the estimated QALY contribution from each, rather than weighting by prevalence.**

Applying QALY severity weights in proportion to the QALYs in each tumour type would require disentangling the survival curves for each tumour location to generate a tumour specific QALY estimate. This is not feasible within the current modelling approach, which uses pooled survival curves across tumour types. Disaggregating the survival curves by tumour types would add considerable uncertainty given the small sample sizes, and using a BHM approach would also result in significant uncertainty given the instability of the BHM (CS Section 3.15). Therefore, weighting by prevalence best reflects the aggregated curves, as the total QALY calculated will limit the potential extra QALY contributions from some tumour locations, such as those for paediatric patients.

B26. Please clarify whether QALY shortfall calculations included any consideration of the potential prognostic value of NTRK fusions.

The QALY shortfall calculations did not include consideration of the potential prognostic value of NTRK fusions.

**B27. Priority question: The company states that starting ages and sex distributions used to calculate QALY shortfall were based on the larotrectinib trial, whilst QALY gain was based on the naïve literature-based comparator scenario. As the trial population is likely to skew younger, this may lead to an overestimation of QALY shortfall. Please present recalculated QALY shortfall using age and sex distributions from the respective literature source for each tumour type.**

In the base-case analysis, the QALY shortfall was calculated using starting ages and sex distributions from the larotrectinib trial to align with the characteristics of the target population. However, we have recalculated the shortfall using patient starting ages and sex distributions reported in the literature (see Table 34). In the alternative analysis (Table 35), the severity modifiers were revised as follows: STS adults (non-GIST) decreased from ■ to ■, CNS/Glioma from ■ to ■, and Thyroid from ■ to ■, relative to the base-case estimates. Functionality was added to the 'Controls' sheet to select this scenario.

**Table 35. Summary starting ages and sex distributions reported in the literature**

| Tumour location                                        | Starting age (years) | Percentage female (%) | Source                            |
|--------------------------------------------------------|----------------------|-----------------------|-----------------------------------|
| NSCLC                                                  | 60                   | 27%                   | NICE TA347 (78)                   |
| Salivary                                               | 58                   | 38%                   | Airoldi <i>et al.</i> 2017 (79)   |
| Melanoma                                               | 62                   | Unknown*              | NICE TA357 (80)                   |
| Colorectal (used as proxy for appendix)                | 63                   | 39%                   | Mayer <i>et al.</i> 2015 (81)     |
| STS adults (GIST)                                      | 60                   | 36%                   | NICE TA488 (54)                   |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | 57                   | 69%                   | Demetri <i>et al.</i> 2016 (89)   |
| STS paediatrics (used as proxy for IFS)                | 12                   | 30%                   | VIT-0910 trial (82)               |
| Breast                                                 | 55                   | 100%                  | NICE TA423 (83)                   |
| Cholangiocarcinoma                                     | 65                   | 47%                   | ABC-06 trial (84)                 |
| CNS/Glioma                                             | 54                   | Unknown*              | Batchelor <i>et al.</i> 2013 (85) |
| Pancreas                                               | 64                   | 45%                   | Conroy <i>et al.</i> 2022 (86)    |
| Thyroid                                                | 64                   | 52%                   | SELECT trial 2015 (87)            |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma

\*Gender distributions not reported in the literature. Assumed that 50% of population are female for the purposes of the calculation, however the QALY weight was consistent across 0-100% female populations.

**Table 36. Summary of QALY shortfall analysis using literature-based starting ages and sex distributions**

| Tumour location                                        | Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | Absolute QALY shortfall | Proportional QALY shortfall | QALY weight |
|--------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------|-----------------------------|-------------|
| NSCLC                                                  | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Salivary                                               | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Melanoma                                               | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Colorectal (used as proxy for appendix)                | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| STS adults (GIST)                                      | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| STS paediatrics (used as proxy for IFS)                | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Breast                                                 | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Cholangiocarcinoma                                     | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| CNS/Glioma                                             | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Pancreas                                               | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |
| Thyroid                                                | ■                                               | ■                                                                                                | ■                       | ■                           | ■           |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma

QALY shortfalls and modifiers calculated using the QALY shortfall calculator recommended by the NICE DSU (90).

**B28. Priority question: Please present a recalculation of QALY shortfall using utilities based on the company scenario which adopts a non-treatment specific PFS utility based on the larotrectinib trials, and a weighted average literature utility.**

The QALY shortfall was recalculated using a non-treatment specific PFS and PD utility based on the larotrectinib trials and a weighted average of literature-reported values, respectively (Table 36). Functionality was added to the 'Utilities' sheet to enable selection of this scenario.

**Table 37. Summary of QALY shortfall analysis adopting non-treatment specific utilities**

| Tumour location                                        | Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | Absolute QALY shortfall | Proportional QALY shortfall | QALY weight |
|--------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------|-----------------------------|-------------|
| NSCLC                                                  | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Salivary                                               | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Melanoma                                               | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Colorectal (used as proxy for appendix)                | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| STS adults (GIST)                                      | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| STS paediatrics (used as proxy for IFS)                | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Breast                                                 | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Cholangiocarcinoma                                     | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| CNS/Glioma                                             | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Pancreas                                               | ████                                            | ████                                                                                             | ████                    | ████                        | █           |
| Thyroid                                                | ████                                            | ████                                                                                             | ████                    | ████                        | █           |

CNS= Central Nervous System; GIST= Gastrointestinal stromal tumour; IFS= Infantile fibrosarcoma; NSCLC= Non-small cell lung cancer; QALY= Quality-adjusted life year; STS= Soft tissue sarcoma  
QALY shortfalls and modifiers calculated using the QALY shortfall calculator recommended by the NICE DSU (90).

B29. Please incorporate QALY shortfall calculations into the model to allow QALY gain multipliers to reflect the selected parameter values.

The QALY shortfall calculations have been added into the model in the 'QALY shortfall' sheet. Controls for selecting the relevant recalculations are provided in the 'Controls' and 'Utilities' sheets.

## Section C: Textual clarification and additional points

### *Systematic literature review searches – Appendix C*

C1. Please clarify how non-randomised studies and pooled analyses were identified. The search strategies presented in CS Appendix B, Tables 2 and 3 contain several search lines designed to limit retrieval to RCTs so would not have identified all non-randomised studies or all pooled analyses.

The study design terms used in Appendix B of the CS for Embase and MEDLINE were broad, which helped in capturing all types of trials (RCTs, non-RCTs, single-arm or pooled studies), as detailed in Table 37.

**Table 38. Study design filters used in clinical SLR (reproduced from Appendix B of CS)**

|                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Broad common search terms in Embase</b>                                                                                                         |
| Clinical Trial/                                                                                                                                    |
| multicenter study/                                                                                                                                 |
| Phase 2 clinical trial/                                                                                                                            |
| Prospective Study/                                                                                                                                 |
| <b>Broad search terms in MEDLINE</b>                                                                                                               |
| Clinical Trial/                                                                                                                                    |
| multicenter study/                                                                                                                                 |
| (nonrandom\$ or non random\$ or non-random\$ or quasi-random\$ or quasirandom\$).ti,ab.                                                            |
| parallel group\$.ti,ab.                                                                                                                            |
| (trial or single arm or uncontrolled study or uncontrolled clinical study or randomised or randomized or noncomparative or non-comparative).ti,ab. |

However, adding more non-randomised and single-arm study design terms in Embase (as detailed in Table 38) increased the search hits from 745 to 1,602. After deduplication and the removal of references published after 6<sup>th</sup> May 2025 (the date of the CS search), it resulted in an additional 651 references. Upon screening these new references, no relevant non-randomised, single-arm or pooled studies were identified, confirming that no studies were missed based on the earlier search strategy. Additionally, a comprehensive hand search was conducted to ensure no relevant articles were overlooked.

**Table 39. Additional study design filters used in Embase**

|                                                                                                               |
|---------------------------------------------------------------------------------------------------------------|
| <b>Additional search terms in Embase</b>                                                                      |
| (nonrandom\$ or non random\$ or non-random\$ or quasi-random\$ or quasirandom\$).ti,ab.                       |
| (trial or single arm or uncontrolled study or uncontrolled clinical study or randomised or randomized).ti,ab. |
| parallel group\$.ti,ab.                                                                                       |

C2. Please confirm if the searches in CS Appendix B, Tables 2, 3 and 4 were designed to identify comparator studies as well as studies of larotrectinib.

Yes, the searches were designed to capture all comparator studies. No search terms for interventions or comparators were applied in the strategy, ensuring the inclusion of all treatment studies. The term “larotrectinib” was combined with population-related terms using the “OR” operator, allowing for the retrieval of studies both with and without larotrectinib. This approach ensured that relevant comparator studies were captured alongside those involving larotrectinib.

C3. Several mistakes with search syntax have been found in the search strategies in CS Appendix B, Tables 2, 3, and 4 (e.g. left-hand truncation is included which is not supported in Ovid, incorrect search commands, incorrect truncation). Please clarify whether any relevant studies may have been missed as a result.

The search syntax was reassessed to check for left-hand truncation issues. After re-running the searches across all databases (Embase®, MEDLINE®, and CENTRAL®), no errors were found when the original terms (1a, 2a, 3a) were repeated, and no changes in results (1b, 2b, 3b) occurred when truncation was modified, as detailed in Table 39, Table 40 and Table 41 confirming that no relevant studies were missed in the earlier search strategy.

**Table 40. Database: Embase® 1974 to October 29, 2025**

| #  | Searches                                                                                                                                                                                                                                             | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | (\$cancer* or \$sarcoma* or \$carcinoma* or malign* or melanoma* or nephroma* or \$cytoma* or \$glioma* or \$blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp. | 7853610 |
| 1b | (cancer* or sarcoma* or carcinoma* or malign* or melanoma* or nephroma* or cytoma* or glioma* or blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp.             | 7853610 |
| 2a | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab.                                                                                          | 824274  |
| 2b | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.                                                                                            | 824274  |
| 3a | (larotrectinib' or 'loxo 101' or 'loxo101' or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                   | 2000    |
| 3b | (larotrectinib or loxo 101 or loxo101 or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                        | 2000    |



**Table 41. Database: Ovid MEDLINE(R)® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to October 31, 2025**

| #  | Searches                                                                                                                                                                                                                                             | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab.                                                                                          | 611317  |
| 1b | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.                                                                                            | 611317  |
| 2a | (larotrectinib' or 'loxo 101' or 'loxo101' or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                   | 512     |
| 2b | (larotrectinib or loxo 101 or loxo101 or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                        | 512     |
| 3a | (\$cancer* or \$sarcoma* or \$carcinoma* or malign* or melanoma* or nephroma* or \$cytoma* or \$glioma* or \$blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp. | 5689622 |
| 3b | (cancer* or sarcoma* or carcinoma* or malign* or melanoma* or nephroma* or cytoma* or glioma* or blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp.             | 5689622 |

**Table 42. Database: EBM Reviews - Cochrane® Central Register of Controlled Trials September 2025, EBM Reviews - Cochrane® Database of Systematic**

| #  | Searches                                                                                                                                                                                                                                             | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab.                                                                                          | 5755    |
| 1b | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.                                                                                            | 5755    |
| 2a | (larotrectinib' or 'loxo 101' or 'loxo101' or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                   | 18      |
| 2b | (larotrectinib or loxo 101 or loxo101 or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                        | 18      |
| 3a | (\$cancer* or \$sarcoma* or \$carcinoma* or malign* or melanoma* or nephroma* or \$cytoma* or \$glioma* or \$blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp. | 312709  |
| 3b | (cancer* or sarcoma* or carcinoma* or malign* or melanoma* or nephroma* or cytoma* or glioma* or blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp.             | 312709  |

C4. Please clarify if a study design search filter was used in the strategies presented in CS Appendix B, Tables 2 and 3. If yes, please provide references for any search filters used.

Yes, study design search filters were applied and adapted from established sources, CDA and SIGN. Below are the links for reference:

- CDA: [https://searchfilters.cda-amc.ca/list?q=&ps=20&p=1&topic\\_facet=economic%20evaluations%20%20models%20000000%7CEconomic%20evaluations%20%26%20models](https://searchfilters.cda-amc.ca/list?q=&ps=20&p=1&topic_facet=economic%20evaluations%20%20models%20000000%7CEconomic%20evaluations%20%26%20models)
- SIGN: <https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts?authuser=0>

## Cost-effectiveness – Appendix E

C5. Please confirm if the searches in Tables 3, 4 and 5 were designed to identify economic evaluations, economic models and cost and resource use studies of comparator treatments as well as studies of larotrectinib.

As noted in the company's response to C2, no restrictions were applied regarding interventions or comparators in the search strategy. The term "larotrectinib" was combined with population terms using the "OR" operator, allowing for the retrieval of studies that did not specifically mention larotrectinib. This approach ensured that studies reporting on relevant comparator treatments were also captured.

C6. There are some mistakes with search syntax in Table 3, Table 4 and Table 5 involving incorrect truncation and incorrect search commands. Please clarify how these mistakes would have affected the retrieval of relevant studies?

As outlined in our response to C3, we modified the truncation and command syntax and re-ran the search terms. The number of hits remained consistent; therefore, no relevant studies were missed as a result. Below, Table 42, Table 43 and Table 44 provide the search terms and outputs from each database—Embase®, MEDLINE®, and EconLit®, respectively.

**Table 43. Database: Embase® 1974 to October 29, 2025**

| #  | Searches                                                                                                                                                                                                                                             | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | (\$cancer* or \$sarcoma* or \$carcinoma* or malign* or melanoma* or nephroma* or \$cytoma* or \$glioma* or \$blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp. | 7853610 |
| 1b | (cancer* or sarcoma* or carcinoma* or malign* or melanoma* or nephroma* or cytoma* or glioma* or blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp.             | 7853610 |
| 2a | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab.                                                                                          | 824274  |
| 2b | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.                                                                                            | 824274  |
| 3a | (larotrectinib' or 'loxo 101' or 'loxo101' or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                   | 2000    |
| 3b | (larotrectinib or loxo 101 or loxo101 or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                        | 2000    |

**Table 44. Database: Ovid MEDLINE(R)® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to October 31, 2025**

| #  | Searches                                                                                                                                                    | Results |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab. | 611317  |

| #  | Searches                                                                                                                                                                                                                                             | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1b | exp gene fusion/ or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.                                                                                            | 611317  |
| 2a | (larotrectinib' or 'loxo 101' or 'loxo101' or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                   | 512     |
| 2b | (larotrectinib or loxo 101 or loxo101 or Vitrakvi or arry 470 or arry470).mp.                                                                                                                                                                        | 512     |
| 3a | (\$cancer* or \$sarcoma* or \$carcinoma* or malign* or melanoma* or nephroma* or \$cytoma* or \$glioma* or \$blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp. | 5689622 |
| 3b | (cancer* or sarcoma* or carcinoma* or malign* or melanoma* or nephroma* or cytoma* or glioma* or blastoma* or tumor* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*).mp.             | 5689622 |

**Table 45. Database: EconLit® 1886 to October 23, 2025**

| #  | Searches                                                                                                                                                   | Results |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1a | gene fusion.mp. or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (\$TRK* and genomic and translocation*).ti,ab. | 51      |
| 1b | gene fusion.mp. or (gene and (fusion* or alterations* or mutation* or rearrangement* or hybrid*)).ti,ab. or (TRK* and genomic and translocation*).ti,ab.   | 51      |

C7. On page 9 there is mention of a search of the NICE HTA database, please provide the URL of this database.

Please find below the NICE guidance URLs used for the searches:

- NTRK- <https://www.nice.org.uk/guidance/published?q=NTRK&from=2023-01-01&to=2025-06-06>
- TRK- <https://www.nice.org.uk/guidance/published?q=TRK&from=2023-01-01&to=2025-06-06>

C8. The HTA database and NHS EED databases are listed as sources searched for the original 2019 SLR. However, these sources were not available via Wiley in 2019. Please clarify if these databases were searched for the 2019 review or the 2025 update review and if yes, please provide the interface used to search them along with the search strategies.

The original SLR search strategy conducted in the Cochrane (Wiley) library in 2019 is shown in Table 45, includes CENTRAL, CDSR, NHS EED and HTA database as per CS. However, we acknowledge that by August 2018, NHS EED and HTA were no longer part of the Cochrane library. Therefore, the 2019 searches, conducted via the Cochrane Wiley interface, inadvertently referenced the inclusion of NHS EED and HTA in the CS documentation. Nevertheless, the supplementary hand searches were carried out to ensure the inclusion of all relevant studies. For the 2025 SLR update,

the HTA and NHS EED databases were excluded because they stopped updating after March 2015.

**Table 46. Search strategy for cost-effectiveness models for treatment of NTRK fusion-positive solid tumours (Cochrane® Library) – (reproduced from Appendix EG of CS)**

| Set# | Searched for                                               | Results |
|------|------------------------------------------------------------|---------|
| S1   | cost benefit analys*                                       | 14524   |
| S2   | eq5d or eq 5d or euroqol                                   | 7821    |
| S3   | hui or hui2 or hui 2 or hui3 or hui 3                      | 1720    |
| S4   | cost or costs or costly or costing*                        | 66509   |
| S5   | economic* or price* or pricing or pharmacoeconomic*        | 34158   |
| S6   | MeSH descriptor: [Cost-Benefit Analysis] explode all trees | 6420    |
| S7   | MeSH descriptor: [Economics, Medical] explode all trees    | 61      |
| S8   | decision analytic model*                                   | 975     |
| S9   | decision model*                                            | 8743    |
| S10  | simulation model*                                          | 4129    |
| S11  | markov model*                                              | 1266    |
| S12  | state transition model*                                    | 485     |
| S13  | markov cohort model*                                       | 283     |
| S14  | (discrete event simulation or DES model)                   | 592     |
| S15  | MeSH descriptor: [Models, Economic] explode all trees      | 317     |
| S16  | (OR #1-#15)                                                | 93519   |
| S17  | *trk*                                                      | 201     |
| S18  | #17 AND #16                                                | 24      |

C9. Please clarify if any search filters were used in the strategies presented in Tables 3 and 4 of Appendix E. If yes, please provide references for any search filters used.

Yes, the study design search filters were adapted from established sources, CDA and SIGN. Below are the links for reference:

- CDA: [https://searchfilters.cda-amc.ca/list?q=&ps=20&p=1&topic\\_facet=economic%20evaluations%20%20models%20000000%7CEconomic%20evaluations%20%26%20models](https://searchfilters.cda-amc.ca/list?q=&ps=20&p=1&topic_facet=economic%20evaluations%20%20models%20000000%7CEconomic%20evaluations%20%26%20models)
- SIGN: <https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts?authuser=0>

## ***Health-related quality of life – Appendix F***

C10. There are some mistakes with search syntax in Table 4, Table 5 and Table 6 involving incorrect truncation and incorrect search commands. Please clarify how these mistakes would have affected the retrieval of relevant health-related quality of life studies?

As noted in the company's response to C3, the truncation and command syntax were modified, and the search was re-ran. The number of hits remained consistent; therefore, no relevant health-related quality of life studies was missed.

C11. Please clarify if any search filters were used in the strategies presented in Tables 4 and 5 of Appendix F. If yes, please provide references for any search filters used.

As noted in the company's responses to C4 and C9, study design search filters were applied and adapted from established sources, including CDA and SIGN. Links to the relevant resources are provided in the responses to questions C4 and C9.

C12. In Section 3.4.1 - Tumour location specific utilities (page 158 of the CS report) targeted literature searches are mentioned. Please provide the search strategies and the search results.

This was a wording error in the CS. Instead of targeted literature searches, pragmatic desk research was performed without formal search strategies and documented results.

C13. In Section 3.4.3 - Mapping (page 161 of the CS report) a targeted literature review is mentioned. Please provide the search strategies and the search results used for this review.

See response to question C12.

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## Single Technology Appraisal

### Guidance review following a period of managed access - Patient organisation submission

#### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

**PLEASE NOTE:** You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies"**. Please contact [pip@nice.org.uk](mailto:pip@nice.org.uk) if you have not received a copy with your invitation to participate.

### Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

**This form has 8 sections**

Section 1 - [About you](#)

Section 2 - [Living with the condition and current treatment in the NHS](#)

Section 3 - [Experience, advantages and disadvantages of the treatment during the Managed Access Agreement \[MAA\]](#)

Section 4 - [Patient views on assessments used during the Managed Access Agreement \(MAA\)](#)

Section 5 - [Patient population \(including experience during the Managed Access Agreement \(MAA\)\)](#)

Section 6 - [Equality](#)

Section 7 - [Other issues](#)

Section 8 - [Key messages – a brief summary of the 5 most important points from your submission](#)

## Section 1. About you

**Table 1 Name, job, organisation**

|                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <b>1. Your name</b>                                                                                                                                                                      | ██████████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>2. Name of organisation</b>                                                                                                                                                           | AMMF – The Cholangiocarcinoma Charity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>3. Job title or position</b>                                                                                                                                                          | ████████████████████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>4a. Provide a brief description of the organisation. How many members does it have?</b>                                                                                               | <p>AMMF is a charity, registered with the Charity Commission for England and Wales; Registration No. 1198095. AMMF was founded in 2002, as the world's first charity dedicated solely to cholangiocarcinoma (bile duct cancer). Today, AMMF remains the UK's only cholangiocarcinoma charity, now working nationally and across Europe, as well as actively contributing globally.</p> <p>AMMF provides information and support to those who need it, campaigns to raise awareness of this devastating disease, and encourages and supports specialised research teams in their work towards better diagnostic techniques and treatments.</p> <p>The charity is funded by donations from members of the public, and a small proportion of industry funding is received as sponsorship for specific projects, such as the annual AMMF European Cholangiocarcinoma Conference.</p> <p>AMMF is not a membership organisation.</p> |
| <b>4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the</b> | <p>AMMF has received funding from several pharmaceutical companies in the last 12 months. Each grant is outlined below:</p> <ul style="list-style-type: none"> <li>• <b>November 2024 - £5,000 – AstraZeneca</b><br/>Support for AMMF's European website.</li> <li>• <b>November 2024 - £5,000 – AstraZeneca</b><br/>Support to deliver a patient education webinar about molecular profiling.</li> <li>• <b>December 2024 - £24,993 – Taiho</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| <p><b>appraisal stakeholder list which was provided to you when the appraisal started]</b><br/><b>If so, please state the name of company, amount, and purpose of funding.</b></p> | <p>Support for AMMF's European Conference 2025.</p> <ul style="list-style-type: none"> <li>• <b>December 2024 - £15,000 – AstraZeneca</b><br/>Support to map patient pathways.</li> <li>• <b>February 2025 - £14,993 – Servier</b><br/>Support to map patient pathways.</li> <li>• <b>March 2025 - £25,000 – Jazz Pharma</b><br/>Support for AMMF's European Conference 2025.</li> <li>• <b>April 2025 - £24,993 – Servier</b><br/>Support for AMMF's European Conference 2025.</li> <li>• <b>May 2025 - £45,000 – AstraZeneca</b><br/>Support for AMMF's European Conference 2025.</li> <li>• <b>May 2025 - £10,000 – AstraZeneca</b><br/>Support for Hepatobiliary Nurse Study Day</li> <li>• <b>May 2025 - £5,000 - Boehringer Ingelheim</b><br/>Support for AMMF's European Conference 2025.</li> <li>• <b>May 2025 - £10,000 – Jazz Pharma</b><br/>Support for translating patient education materials for AMMF's European website</li> <li>• <b>July 2025 - £10,000 – Jazz Pharma</b><br/>Support for AMMF's Patient and Carers Webinars 2025</li> <li>• <b>September 2025 - £10,000 – Taiho</b><br/>Support for AMMF's Patient and Carers Webinars 2025</li> </ul> |
| <p><b>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</b></p>                                                                            | <p>No</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>5. How did you gather information about the experiences of patients and carers to include in your submission?</b></p>                                                        | <p>AMMF conducted an online survey from 27<sup>th</sup> June to 20<sup>th</sup> July 2025 to collect experiences and opinions from patients and their partners/caregivers/family. The survey received a total of 70 responses (34 patients and 36 caregivers/family). Several of the quotations within this submission are taken from responses to this survey.</p> <p>Additionally, we referenced several published papers about cholangiocarcinoma. Links have been included for these references throughout the submission.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |



## Section 2 Living with the condition and current treatment

**Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <p><b>6. What is it like to live with the condition?</b></p> <p>Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?</p> | <p><b>Symptoms</b></p> <p>Cholangiocarcinoma (CCA) causes few symptoms in its early stages. Any early symptoms that do present tend to be quite vague and non-specific. Possible symptoms include nausea, loss of appetite, abdominal discomfort, tiredness, feeling generally unwell, weight loss and high temperatures.</p> <p><i>"A lot of time was wasted in the first 2 months as my local GP just kept telling me I had pulled a muscle or got indigestion."</i> – <b>A cholangiocarcinoma patient</b></p> <p>Symptoms that are more specific, such as jaundice, typically do not present until more advanced stages when a tumour blocks the flow of bile from the liver to the intestine. Jaundice can cause yellowing of the sclera and skin (although this may be less obvious in people with darker skin tones), dark urine, pale stools and itchy skin.</p> <p>Some patients may not experience significant symptoms caused by cholangiocarcinoma, but side-effects of treatments are common, and these can severely impact quality of life.</p> <p><i>"I have just completed 8 cycles of Cis/Gem/Durva treatment, and all my symptoms were experienced during treatment (not before). The only symptom I had experienced for several years previously was bloating."</i> – <b>A cholangiocarcinoma patient</b></p> <p>A survey conducted by AMMF found that fatigue/tiredness and abdominal pain/discomfort were the most reported symptoms, experienced by almost three-in-four (72.5%) patients. Fatigue/tiredness was most reported as having the biggest impact on day-to-day life (43.5%) followed by pain/discomfort (32.3%).</p> <p>To help relieve symptoms of jaundice, many patients will have a stent inserted to hold the bile duct open and restore flow. Unfortunately, these stents can get blocked due to a build-up of thick bile or the tumour growing through it. A blocked stent may lead to a biliary tract infection (cholangitis), which can rapidly become serious and may lead to biliary sepsis. Symptoms of a blocked stent/infection include high</p> |
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|  | <p>temperature/fever, jaundice, and chills/shivering. If these symptoms develop, patients may urgently require antibiotics, and the stent may need to be replaced.</p> <p><i>“Physically the cancer itself presented me with no problems but having to have biliary stents has been painful, potentially risky and periodically this makes me very sick requiring hospital stays.” – A cholangiocarcinoma patient</i></p> <p>The lack of specific symptoms at earlier stages, together with a poor awareness at primary care level, frequently results in CCA being diagnosed late.</p> <p><b><u>Survival</u></b></p> <p>Most patients receive their diagnosis when the cancer is in advanced stages, when it is inoperable and thus a terminal diagnosis.</p> <p>Statistics provided by the National Cancer Registration and Analysis Service (NCRAS) revealed that in England between 2017 and 2019, 1-year survival was under 30%. In England between 2014 and 2016, 5-year survival was 5%.<sup>1</sup></p> <p>For many patients this diagnosis and the prognosis can be truly shocking, and they find it very difficult to assimilate the details. Patients struggle to accept that available treatment options are so limited, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left.</p> <p>For the small proportion of CCA patients who can receive potentially curative surgery, the majority will develop recurrent disease. A study by Hyder <i>et al</i> found the median recurrence-free survival of 301 patients who had resection for intrahepatic CCA was only 20 months, with 53.5% developing a recurrence during the median follow-up duration of 31 months.<sup>2</sup></p> <p><b><u>Employment</u></b></p> <p>Our survey revealed that 72.4% of patients “completely” or “somewhat” agree that their productivity at work was adversely affected by their diagnosis. More than one-in-three (35.9%) patients who responded to our survey had permanently stopped working following their diagnosis and a further 21.9% had temporarily stopped working.</p> |
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|                                                                                        | <p><i>"Before my diagnosis, I missed a lot of work and my productivity at work was affected since I was feeling ill. I had to take lots of time off for months to attend appointments to get a diagnosis. After my diagnosis I went on sick leave to focus on my health and treatment" – A cholangiocarcinoma patient</i></p> <p><sup>1</sup> Cancer Research UK - <a href="https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival">https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival</a> (accessed 18/07/25)</p> <p><sup>2</sup> Recurrence after operative management of intrahepatic cholangiocarcinoma - <a href="https://doi.org/10.1016/j.surg.2012.12.005">https://doi.org/10.1016/j.surg.2012.12.005</a></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>7. What do carers experience when caring for someone with the condition?</b></p> | <p>For loved ones and carers, understanding the diagnosis and its implications can be as difficult as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one and ask for advice on clinical trials and treatment options that are not available through the health service.</p> <p><i>"It is a terrible position to be in to watch someone you love so much face such a devastating illness as well as her facing the prospect of early death. I felt frightened and stressed every day. I felt anxious and powerless to improve her situation and watching her suffer was unbearable." – Husband of a cholangiocarcinoma patient</i></p> <p>Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms with what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'.</p> <p><i>"I had to be signed off work to care for my husband when he was discharged from hospital as I also had two young children to care for. After my husband passed, I had a further six months off work coming to terms with the shock of his diagnosis and loss within a three-week period when he'd otherwise been a relatively fit and healthy 48-year-old father of two." – Wife of a cholangiocarcinoma patient</i></p> <p>Employment and work productivity of carers is commonly affected because of responsibilities associated with caregiving. Many caregivers report having to make adjustments at their workplace, such as taking time off or reducing their contracted hours. Our online survey found that almost two-in-three (64.7%) caregivers "completely" or "somewhat" agreed that their productivity at work had been adversely affected.</p> <p><i>"For the first year of her diagnosis I was 'on-call' 24 hours a day to help with day-to-day activities when she felt unwell, to take her to her appointments when she couldn't walk, to attend ED with her. I lived 2 hours away, was working as a hospital doctor and had a 1-year-old at the time. We moved house shortly after her diagnosis so I could accommodate my mother (and my 90 y/o grandmother) for end-of-life care. I feel I have been personal doctor at</i></p> |

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|                                                                                                                                                                        | <p><i>home as well as for work – I have needed time off work as after 12 months of supporting a cholangiocarcinoma patient on chemotherapy - I was struggling with work and went down to 60% on returning.” – Daughter of a cholangiocarcinoma patient.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p><b>8. What do patients and carers think of current treatments and care available on the NHS</b></p> <p>Please state how they help and what the limitations are.</p> | <p>Currently a surgical resection or transplantation (for a small proportion of highly selected patients) are the only potentially curative treatment options for patients diagnosed with CCA. However, patients are typically diagnosed too late for surgery to be viable. An analysis of cholangiocarcinoma patient records in England from 2014-2017 found that only 12.4% received potentially curative surgery.<sup>1</sup></p> <p><i>“They told me surgery was my only chance of survival, but it might already be too late.” – A cholangiocarcinoma patient</i></p> <p>Most people diagnosed with CCA are inoperable and have no potentially curative treatment options, leaving only a very limited selection of therapies aimed at extending life. In England, between 2014-2017, over half (50.5%) of patients received no cancer-specific treatment at all.<sup>1</sup> In advanced disease, CCA patients who do not receive systemic therapy have a very short life expectancy, typically 3-4 months.<sup>2</sup></p> <p>The current standard first-line treatment for those with inoperable CCA is a combination of the chemotherapies gemcitabine and cisplatin (GemCis) with the immunotherapy, durvalumab.</p> <p><i>“[Durvalumab] has helped hold my cancer back. It gave us more birthdays, more time around the dinner table, more ordinary moments that now feel extraordinary.” – A cholangiocarcinoma patient</i></p> <p><i>“I went onto a treatment of chemotherapy combined with immunotherapy. The treatments caused side effects and made it impossible for me to function properly and certainly I couldn’t go back to work in my job as a secondary school English teacher and Head of Department. It felt like being poisoned. This treatment was effective for a fairly short time before it failed, and the immunotherapy didn’t work at all.” – A cholangiocarcinoma patient</i></p> <p>For people with whom first-line therapy is no longer controlling their disease, second-line therapy is either a targeted therapy (for those with targetable mutations) or a systemic therapy such as the combination chemotherapy FOLFOX which has a modest benefit on survival and can be poorly tolerated. Undergoing chemotherapy, which might or might not extend their life for a few months, is often at the expense of quality of life, and that of their families.</p> |

*“Starting palliative chemotherapy was difficult since you know it’s not going to be curative (although you hope this cancer might be especially sensitive) and you are told it may prolong your life only by a few months. Making this decision was particularly challenging, since my mum felt really well when she started – and you know how dreadful the side effects of chemo are. Chemotherapy was difficult for her, she had minimal quality of life due to side effects while she was taking it and although she had shrinkage of the tumour, the question was whether there was really any point since there was no-where to go after the 8 rounds, except perhaps more of the same. My mum has said repeatedly she could never go through chemotherapy again – it’s no life. She had several admissions with pain and sepsis, blood transfusions for anaemia, and finally neutropenic sepsis during cycle 7.” – Daughter of a cholangiocarcinoma patient*

There is significant regional variance in the treatment of CCA. Analysis of patient treatment data from 2014-2017 in England found that the percentage of patients who received potentially curative surgery ranged from 8.8% to 16.2% across Cancer Alliances. Similarly, the percentage of patients in receipt of systemic therapy ranged from 12.4% to 29.4%.<sup>1</sup>

*“I believe if you go to the right hospital, you will get the right treatment at the right time. Unfortunately, you go to your nearest hospital, and we found in our case they had no specialist team and the whole system takes too long from diagnosis to any treatment. My wife was made more ill in the NHS. Where she is now, her treatment has been what you would hope for.” – Husband of a cholangiocarcinoma patient*

Our survey found that more than one-in-three (36.2%) CCA patients sought a second opinion about their diagnosis and/or treatment options.

*“My care was very poor at the start, if I hadn't pushed myself for 2nd opinions, I wouldn't be here today.” – A cholangiocarcinoma patient*

<sup>1</sup> Cohort study to assess geographical variation in cholangiocarcinoma treatment in England - <http://dx.doi.org/10.4251/wjgo.v15.i12.2077>

<sup>2</sup> British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma - <https://gut.bmj.com/content/73/1/16>

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| <p><b>9. Considering all treatments available to patients are there any unmet needs for patients with this condition?</b><br/>If yes please state what these are</p> | <p>The most significant unmet need for CCA patients is earlier and faster diagnosis. Analysis of CCA patients in England from 2006-2017 found that the most common route to diagnosis was emergency presentation (49.6%)<sup>1</sup>. Only 55% of CCA patients had records with complete staging, of which 79% received a stage 3 or 4 tumour diagnosis.<sup>1</sup></p> <p>In our online survey, almost one-in-three (30%) reported that it took them over three months to receive a diagnosis of CCA from the time they first felt unwell and sought medical advice. A potential contributing factor is the rate of initial misdiagnosis. Almost one-in-three (31.4%) respondents indicated that they were initially misdiagnosed before later being diagnosed with CCA. If more CCA patients could be diagnosed at earlier stages, it could have a significant positive impact on their outcome.</p> <p><i>“Doctor thought it was gastroenteritis and sent off stool tests about one month before she went yellow” – Family member of a cholangiocarcinoma patient</i></p> <p>In addition, advancements in treatment for CCA have been very slow, with few new therapies introduced in recent decades. During this time, the improvement in survival rates for people diagnosed with CCA has fallen significantly behind improvements in survival for many other cancers.</p> <p>In the NHS there are few approved targeted therapies for CCA patients, and these are currently limited to second-line therapies for FGFR2 and IDH1 gene mutations. CCA patients who have a gene mutation without a currently approved therapy or suitable clinical trial have only one approved second-line treatment option, the combination chemotherapy FOLFOX, which has a modest benefit on survival and can be poorly tolerated. These patients need access to more effective therapies, which are better tolerated (with fewer side effects), and will improve survival. CCA patients want to be able to live longer, with a better quality of life following their diagnosis.</p> <p>Some CCA patients report difficulty in accessing molecular profiling tests to see whether they may be eligible for a targeted therapy. In our online survey, 17.6% of patients reported that molecular profiling tests had not been carried out, with a further 11.8% of respondents who were unsure whether it had been done. It is essential that all CCA patients have molecular profiling tests to identify whether they have a targetable gene fault, such as being NTRK fusion-positive. Without molecular profiling tests being carried out, some CCA patients miss out on their optimal treatment.</p> |
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|  | <p>For the small proportion of patients who have successful curative surgery, improved adjuvant therapies are needed to help reduce the significant risk of recurrence.</p> <p><sup>1</sup> Regional variation in routes to diagnosis of cholangiocarcinoma in England from 2006 to 2017 - <a href="http://dx.doi.org/10.3748/wjg.v29.i24.3825">http://dx.doi.org/10.3748/wjg.v29.i24.3825</a></p> |
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## Section 3 Experience during the managed access agreement (MAA)

**Table 3 Experience, advantages and disadvantages during the MAA**

|                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <p><b>10. What are patients' and carers' experience of accessing and having the treatment?</b></p> <ul style="list-style-type: none"> <li>Please refer to the MAA re-evaluation patient submission guide</li> </ul> | <p>AMMF is not aware of any CCA patients who have accessed larotrectinib during the MAA.</p> <p>This may be, in part, the result of some potentially eligible CCA patients not receiving molecular profiling to confirm whether they were NTRK fusion-positive. Despite larotrectinib being made available under the MAA in spring 2020, molecular profiling was not typically offered to CCA patients until after <a href="#">NICE's positive recommendation for the targeted treatment, pemigatinib (for FGFR2 gene fusions)</a>, in summer 2021.</p> <p>Whilst there has been widespread adoption of molecular profiling for CCA patients since summer 2021, it is very unlikely that any CCA patients accessed larotrectinib through the MAA due to the patient eligibility requirements being incompatible with NHS treatment pathways for CCA. Currently the NHS in England only commissions molecular profiling tests for CCA patients once their disease has progressed after systemic therapy because the targeted therapies available for CCA through the NHS (pemigatinib, futibatinib, and ivosidenib) are second- or third-line therapies. Therefore, CCA patients would not be found to have NTRK gene fusions before the first cycle of systemic anti-cancer therapy.</p> |
| <p><b>11. What do patients and carers think are the advantages of the treatment?</b></p>                                                                                                                            | <p>No comment</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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| Please refer to the MAA re-evaluation patient submission guide                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>12. What do patients or carers think are the disadvantages of the treatment?</b><br>Please refer to the MAA re-evaluation patient submission guide                                                                       | No comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>13. What place do you think this treatment has in future NHS treatment and care for the condition?</b><br>Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway. | <p>Larotrectinib should be available through the NHS for patients with NTRK fusion-positive advanced solid tumours. Currently, other targeted treatments for CCA are only available as second-line therapy when the disease has progressed on first-line treatment. However, trials of larotrectinib suggest that its use in the first-line setting could be a valuable option in a wider variety of tumours<sup>1</sup>. For CCA patients to access larotrectinib as a first-line treatment, molecular profiling for NTRK fusions should be carried out as early as possible in their pathway to ensure they are offered the most appropriate treatment for their disease, as soon as possible.</p> <p>NTRK gene fusions are rare in the CCA patient population. Studies have reported the proportion of NTRK fusion-positive CCA patients as between 0.25%<sup>2</sup> to 0.7%<sup>3</sup>. Whilst CCA represents a relatively small proportion of NTRK fusion-positive tumours enrolled in clinical trials for larotrectinib, the treatment has demonstrated rapid, potent, and durable responses regardless of tumour type<sup>4</sup>. In addition, the reported side-effect profile for larotrectinib is favourable compared with chemotherapy, which can be poorly tolerated by CCA patients.</p> <p><sup>1</sup> Efficacy and safety of larotrectinib as first-line treatment for patients with TRK fusion cancer - <a href="https://doi.org/10.1016/j.esmoop.2025.105110">https://doi.org/10.1016/j.esmoop.2025.105110</a></p> <p><sup>2</sup> NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls - <a href="https://www.modernpathology.org/article/S0893-3952(22)00943-7/fulltext">https://www.modernpathology.org/article/S0893-3952(22)00943-7/fulltext</a></p> <p><sup>3</sup> A Two-Step Diagnostic Approach for NTRK Gene Fusion Detection in Biliary Tract and Pancreatic Adenocarcinomas - <a href="https://pmc.ncbi.nlm.nih.gov/articles/PMC10322136/">https://pmc.ncbi.nlm.nih.gov/articles/PMC10322136/</a></p> <p><sup>4</sup> Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children - <a href="https://doi.org/10.1056/NEJMoa1714448">https://doi.org/10.1056/NEJMoa1714448</a></p> |

## Section 4 Patients views on assessments used during the MAA

**Table 4 Measurements, tests and assessments**

|                                                                                                                                                                                                                                                        |            |
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| <p><b>14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment.</b></p> <p><b>How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?</b></p> | No comment |
| <p><b>15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?</b></p>                                                                                                                        | No comment |
| <p><b>16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments?</b></p> <p>If not please explain what was missing.</p>                   | No comment |
| <p><b>17. What outcomes do you think have not been assessed or captured in the MAA data?</b></p> <p>Please tell us why</p>                                                                                                                             | No comment |



## Section 5 Patient population

**Table 5 Groups who may benefit and those who declined treatment**

|                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <p><b>18. Are there any groups of patients who might benefit more or less from the treatment than others?</b></p> <p>If so, please describe them and explain why.</p>                                                                   | <p>CCA patients are currently unable to access larotrectinib because the eligibility criteria for the treatment are incompatible with the NHS pathways for CCA. The NHS only commissions molecular profiling tests for CCA patients once their disease has progressed after systemic therapy. This means that CCA patients are not found to have NTRK gene fusions before the first cycle of systemic anti-cancer therapy.</p> <p>To enable patients with NTRK fusion-positive advanced cholangiocarcinoma to access larotrectinib, either:</p> <ol style="list-style-type: none"> <li>1) larotrectinib should also be made available as a second-line therapy for patients once their disease has progressed after systemic therapy.</li> <li>2) the NHS should commission molecular profiling for all CCA patients at diagnosis, enabling those with NTRK fusion-positive tumours to be stratified for treatment with larotrectinib. This would help to align practice with the British Society for Gastroenterology (BSG) guidelines for the diagnosis and management of cholangiocarcinoma, which recommends “CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise.”<sup>1</sup></li> </ol> <p><sup>1</sup> British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma - <a href="https://gut.bmj.com/content/73/1/16">https://gut.bmj.com/content/73/1/16</a></p> |
| <p><b>19. Were there people who met the MAA eligibility criteria who decided not to start treatment?</b></p> <p>Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.</p> | <p>No comment</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

## Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See [NICE's equality scheme](#) for more details.

In the UK, 47% of all cancer diagnoses and 55% of all cancer deaths are from rare and less common cancers<sup>1</sup>. This demonstrates that people diagnosed with a rare or less common cancer are more likely to die following their diagnosis than people with the four most common cancers (breast, prostate, lung, and bowel). Each person diagnosed with a rare or less common cancer is likely to face inequalities in diagnosis, treatment and outcomes throughout their care pathway.

Over the past decade, mortality rates for the four most common cancers have fallen around twice as fast as for the rare and less common cancers combined<sup>1</sup>. Whilst mortality rates for the most common cancers are falling, between 2001-2003 and 2016-2018 the age-standardised mortality for cholangiocarcinoma increased by more than 80% (from 2.6 per 100,000 person-years to 4.9 per 100,000 person-years)<sup>2</sup>.

It is important that larotrectinib, as a tumour agnostic drug, is recommended for all NTRK fusion-positive solid tumours and not just for more common cancers for which the drug's efficacy can be more reliably assessed due to their higher patient populations. People diagnosed with rarer NTRK fusion-positive tumours such as cholangiocarcinoma or sarcoma should also have access to larotrectinib to avoid increasing the disparity of outcomes when compared with the more common cancers.

To enable patients with NTRK fusion-positive advanced cholangiocarcinoma to access larotrectinib, the NHS needs to commission molecular profiling for all CCA patients at diagnosis. This would help to align practice with the British Society for Gastroenterology (BSG) guidelines for the diagnosis and management of cholangiocarcinoma, which recommends "CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise."<sup>3</sup> Without this change, if the eligibility criteria for larotrectinib are consistent with the current MAA, cholangiocarcinoma patients will be unable to access the treatment.

<sup>1</sup> Cancer52 Health Inequalities Report - <https://www.cancer52.org.uk/single-post/cancer52-health-inequalities-report>

<sup>2</sup> Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation - <https://doi.org/10.1016/j.jhepr.2023.100983>

<sup>3</sup> British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma - <https://gut.bmj.com/content/73/1/16>

## Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

CCA patients are currently unable to access larotrectinib because the eligibility criteria for the treatment are incompatible with the NHS pathways for CCA. The NHS only commissions molecular profiling tests for CCA patients once their disease has progressed after systemic therapy. This means that CCA patients are not found to have NTRK gene fusions before the first cycle of systemic anti-cancer therapy.

To enable patients with NTRK fusion-positive advanced cholangiocarcinoma to access larotrectinib:

1. Larotrectinib should also be made available as a second-line therapy for patients once their disease has progressed after systemic therapy.
2. The NHS should commission molecular profiling for all CCA patients at diagnosis, enabling those with NTRK fusion-positive tumours to be stratified for treatment with larotrectinib. This would help to align practice with the British Society for Gastroenterology (BSG) guidelines for the diagnosis and management of cholangiocarcinoma, which recommends “CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise.”<sup>1</sup>

<sup>1</sup> British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma - <https://gut.bmj.com/content/73/1/16>

## Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Cholangiocarcinoma is commonly diagnosed at late stages, when it is advanced and usually inoperable, because it typically presents with few symptoms in the early stages and those that are present tend to be vague and non-specific.
- Surgical resection or liver transplantation are currently the only potentially curative treatments for cholangiocarcinoma, but these are not viable for most patients and recurrence is common for those who have had seemingly successful surgery (R0 resection).
- For most cholangiocarcinoma patients the only treatment options include chemotherapy and immunotherapy, aimed at extending life, which is often accompanied by significant side effects negatively impacting quality of life for patients and their family.
- It is vital that all CCA patients receive molecular profiling tests at the earliest opportunity to ensure they are matched with the optimal treatment with minimal delays.
- Larotrectinib should be available for NTRK fusion-positive advanced cholangiocarcinoma patients, with eligibility criteria that are compatible with NHS pathways for this patient group.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

## Single Technology Appraisal

### Guidance review following a period of managed access - Patient organisation submission

#### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

**PLEASE NOTE:** You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies"**. Please contact [pip@nice.org.uk](mailto:pip@nice.org.uk) if you have not received a copy with your invitation to participate.

### Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

**This form has 8 sections**

Section 1 - [About you](#)

Section 2 - [Living with the condition and current treatment in the NHS](#)

Section 3 - [Experience, advantages and disadvantages of the treatment during the Managed Access Agreement \[MAA\]](#)

Section 4 - [Patient views on assessments used during the Managed Access Agreement \(MAA\)](#)

Section 5 - [Patient population \(including experience during the Managed Access Agreement \(MAA\)\)](#)

Section 6 - [Equality](#)

Section 7 - [Other issues](#)

Section 8 - [Key messages – a brief summary of the 5 most important points from your submission](#)

## Section 1. About you

**Table 1 Name, job, organisation**

|                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>1. Your name</b>                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>2. Name of organisation</b>                                                                                                                                                                                       | Sarcoma UK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>3. Job title or position</b>                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>4a. Provide a brief description of the organisation. How many members does it have?</b>                                                                                                                           | <p>Sarcoma UK is registered as a charity in England and Wales (1139869) and in Scotland (SC044260), and as a company limited by guarantee in England and Wales (7487432). We are a national charity that funds research, offers specialist support for anyone affected by sarcoma and campaigns for better treatments, and the only charity in the UK covering all types of sarcoma. All our services and priorities are developed with input from people affected by sarcoma. We communicate with people affected by sarcoma through our Involvement Network of people affected by sarcoma, comprised of patients, carers and supporters, as well as the strong relationships we have developed across the sarcoma community.</p> <p>The vast majority of our funding comes from donations and legacies. We currently employ 37 members of staff.</p> |
| <b>4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list]</b> | <p>Sarcoma UK has received no funding from Bayer, the company bringing forward Larotrectinib. We have received funding from Deciphera, who produce Ripretinib, a treatment for GIST cancer. Ripretinib is currently being assessed by NICE. It has been approved for use in Scotland by the Scottish Medicines Consortium. On 28/07/25, Deciphera awarded the value of £3000. The sum was put towards hosting our second sarcoma community day in September 2025.</p>                                                                                                                                                                                                                                                                                                                                                                                  |

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| <p>which was provided to you when the appraisal started]<br/>If so, please state the name of company, amount, and purpose of funding.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</b></p>                                   | <p>We do not have any direct or indirect links with, or funding from, the tobacco industry.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>5. How did you gather information about the experiences of patients and carers to include in your submission?</b></p>               | <p>Sarcoma UK gathered evidence from the following sources:</p> <ul style="list-style-type: none"> <li>• <b>Patients and carers:</b> evidence from patients and carers was gathered through written and verbal statements. Patients and carers were identified and contacted through our network of clinicians, who contacted patients they were presently in touch with. One carer was already within our Involvement Network.</li> <li>• <b>Healthcare professionals:</b> healthcare professionals were identified by Sarcoma UK's Healthcare Engagement Lead, who manages our networks of clinician contacts. We had informal discussions with healthcare professionals who have treated sarcoma patients using larotrectinib. These clinicians then recommended other specialists, with whom we corresponded with for further information and to put us in touch with patients.</li> <li>• <b>Sarcoma UK Support Line:</b> our specialist Support Line, run by former or practicing Clinical Nurse Specialists, is a source of primary evidence for Sarcoma UK. It has had over 30,198 calls with 6,411 individuals since 2016. It receives daily phone and email enquiries, which have included patients with NTRK fusion-positive sarcomas, some of whom have been on larotrectinib.</li> <li>• <b>Sarcoma UK's evidence:</b> we used existing evidence gathered by Sarcoma UK in our National Sarcoma Survey 2025 (responded to by over 1000 people affected by sarcoma) and Unique Among Cancers (2025), a state of the nation qualitative report of people affected by sarcoma.</li> <li>• <b>Academic literature:</b> we consulted existing clinical literature for background information on management of NTRK-fusion positive sarcomas.</li> </ul> <p>Not all sarcomas are NTRK fusion-positive, but a NTRK fusion can occur in any sarcoma, and larotrectinib can used highly effectively in a NTRK fusion-positive sarcoma of any subtype. Due to sarcoma's heterogeneity, however, it is not possible to cover each subtype within this consultation. We will therefore</p> |



|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|  | <p>focus on the experience of patients with wild-type GIST and paediatric patients with infantile fibrosarcoma. Wild-type GIST are slightly more likely than other patients to have an NTRK fusion. Infantile fibrosarcoma patients are highly likely to have an NTRK fusion, occurring in 90% of cases.</p> <p>For this consultation, we have used first-hand evidence from:</p> <ul style="list-style-type: none"> <li>• Sophie, the mother and carer of a young boy with infantile fibrosarcoma of the chest.</li> <li>• Ioana, the mother and carer of a young boy with infantile fibrosarcoma of the cheek.</li> <li>• Shounok, an adult patient with wild-type GIST.</li> <li>• Jayne, parent and carer of a young adult patient with GIST.</li> </ul> <p>Some names have been changed for patient confidentiality. Please see an appendix of full statements submitted alongside this form.</p> |
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## Section 2 Living with the condition and current treatment

**Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment**

|                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <p><b>6. What is it like to live with the condition?</b></p> <p>Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships</p> | <p>The impact of sarcoma on patients is immense physically and emotionally, often disrupting every element of a patient's life. We here use the EQ-5D criteria to demonstrate this effect.</p> <p><b>Usual activities and self-care:</b></p> <ul style="list-style-type: none"> <li>• <b>Self-care:</b> sarcoma can prevent patients partaking in their normal activities and independently caring for themselves. Carers may assist with the following activities due to a reduction in patients' independence: shopping; collecting and taking medication; attending appointments; household tasks, and personal care, including washing, dressing and using a toilet (National Sarcoma Survey, Sarcoma UK, 2025). Shounok told us how his wild-type GIST left him with limitations on 'the ability to carry out to day-to-day tasks as I used to'. Like many families living with infantile fibrosarcoma, Sophie describes living in the hospital for the first three months of her son's life, unable to partake in many formative activities and routines.</li> </ul> |
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| <p>and participate in school and social life. Is there any impact on their siblings?</p> | <ul style="list-style-type: none"> <li>• <b>Employment:</b> like many other sarcoma patients, Shounok's ability to work has been 'impacted significantly', now having to carefully manage and sometimes reduce his workload. This has created financial pressure, often experienced by patients with sarcoma due to its disruptive symptoms.</li> <li>• <b>Socialising and relationships:</b> difficulty in previously 'simple things like going out for a meal or planning a holiday' can also disrupt social life, with Shounok telling us that 'social life and relationships also feel the strain'. Children face limitations on early and formative socialisation. Like with some others, Sophie and her family were careful to avoid any public place they feared they might pick up flu, including attending 'child centres and nurseries'. She told us about the difficulty she experienced when her son could not build normal relationships with his cousins due to this isolation.</li> </ul> <p><b>Anxiety and depression:</b></p> <ul style="list-style-type: none"> <li>• Being diagnosed and living with sarcoma typically puts significant strain on a patient's mental health, with 90% saying their mental health was negatively affected. Patients have to manage many mental health stressors: their symptoms; the uncertainty surrounding disease progression and treatment; higher probability of a negative outcome than with more cancers, and more. Over 2 in 5 patients report that depression affects their daily life.</li> <li>• Babies and young children with infantile fibrosarcoma often become distressed due to their symptoms and environment, with both families we spoke to describing the emotional impact seeing their child distressed had on them.</li> <li>• Half of sarcoma patients report that anxiety affects their daily life. Shounok told us about the 'stress and anxiety' he experiences due to 'constant anxiety about the future' due to his condition.</li> </ul> <p><b>Pain and discomfort:</b> even prior to the disruptive symptoms of treatment, sarcoma patients can experience pain, nausea, swelling and other symptoms. While it is not the predominant symptom for some patients, others experience intense pain, one parent recalling their son shouting out in the night (Unique Among Cancers, Sarcoma UK, 2025). For wild-type GIST patients, this can manifest as debilitating stomach pain.</p> |
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|                                                                                        | <p><b>Mobility:</b> sarcomas can grow to a large size, typically diagnosed when the tumour is the size of a can of baked beans. This can be extremely restrictive of movement, particularly when diagnosed late, with one mother describing how her son struggled to walk before even receiving a diagnosis. For babies with infantile fibrosarcoma, a tumour can be proportionally bigger than for adults, preventing full movement in the formative early months of their life. Shounok, our patient with wild-type GIST, also told us about reduction in his energy levels, another common symptom that can change patients' mobility level.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>7. What do carers experience when caring for someone with the condition?</b></p> | <p>For NTRK fusion-positive sarcomas, as with all sarcomas, the impact on carers and their wider life can be profound.</p> <p><b>Practical support:</b> many carers for sarcoma patients take on tasks to assist the patient in tasks they previously could carry out themselves. This includes medical appointments, adjustment to diet, physical assistance, day to day care and more. 24% of carers for people with sarcoma spend 50 or more hours a week providing support or care for the patient (National Sarcoma Survey 2025).</p> <p><b>Life disruption:</b></p> <ul style="list-style-type: none"> <li>Many carers for sarcoma patients experience significant life disruption. 81% reported that their loved one's treatment had had a permanent or temporary effect on their ability to work or complete education, with 18% having to permanently stop work or education (National Sarcoma Survey, Sarcoma UK, 2025). This can have a knock-on effect to a family's financial stability.</li> <li>Evidence for this consultation showed multiple carers' ability to work had been affected, including Shounok's carer and Ioana while caring for her son. Ioana stated 'I lost my job because my child is sick', needing to watch him 24 hours a day in case of sudden deterioration.</li> </ul> <p><b>Emotional and mental health:</b></p> <ul style="list-style-type: none"> <li>Emotional strain, exhaustion and disruption lead to mental health impacts for almost all sarcoma carers. 95% of families or carers reported feeling more or constantly anxious or depressed since the diagnosis (National Sarcoma Survey 2025).</li> <li>Sarcoma carers experience immense stress in navigating developing medical needs and a complex sarcoma care system. Ioana told us that 'life was very hard', describing the fear and emotional challenges felt by the whole family in the period that her son was diagnosed and not yet on</li> </ul> |

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|                                                                                                                                                                        | <p>larotrectinib. Since English is not their first language, Ioana and her family had to navigate the system and treatment decisions through a translator.</p> <ul style="list-style-type: none"> <li>• With a five-year survival rate of just 55%, facing the possibility that their child or loved one may die can be emotionally devastating for sarcoma carers. Sophie told us how when her partner and family found out their son was sick with sarcoma, 'we were devastated'. She particularly describes her fear at the possibility that he may face a negative outcome, saying, 'the feeling of losing him when he was just born was hard and I cannot even describe it in words'. Shounok also shared how his carer's mental health struggled with the 'weight of uncertainty'.</li> <li>• Carers also struggle with exhaustion- Shounok described how 'constant vigilance and need to adapt around the patient's condition means carers rarely get true respite'.</li> </ul> <p><b>Relationships:</b> the emotional and physical demands of caring can also place strain on the relationship between the patient and their loved one, including in marriages.</p>                                                                                                                                                                                                                                           |
| <p><b>8. What do patients and carers think of current treatments and care available on the NHS</b></p> <p>Please state how they help and what the limitations are.</p> | <p>For NTRK fusion-positive tumours, conventional treatment is often not as effective as for sarcomas of the same subtype without an NTRK fusion. As there are over 100 subtypes of sarcoma, it is not possible to go through all treatment options for each within this consultation. While larotrectinib is equally as needed for every NTRK fusion-positive sarcoma, this section will therefore focus on treatment options for wild-type GIST and infantile fibrosarcoma.</p> <p><b>Wild-type GIST:</b></p> <ul style="list-style-type: none"> <li>- <b>Ineffective and limited treatment options:</b> unlike other GISTs, wild-type GIST lacks an effective treatment. The multiple existing drugs for treating GIST are rarely effective in controlling wild-type GISTs. Shounok describes how patients are left with 'very few good options'. Surgery is typically the first line of treatment. Where GIST is too big to remove via surgery, or already metastasised, targeted anti-cancer drugs are used, often as adjuvant treatment. These have low rates of effectiveness.</li> <li>- <b>Short and long term effects:</b> Shounok described the 'major life-altering consequences' of his surgery for his GIST. For many wild-type GIST patients, surgery leaves them with impaired physical function, and has a significant impact on their body image and in their ability to work full time.</li> </ul> |

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|                                                                                                                               | <p>Shounok described existing treatment options for wild-type GIST patients leading to ‘unnecessary suffering’ when larotrectinib exists as an alternative option.</p> <p><b>Infantile fibrosarcoma:</b></p> <ul style="list-style-type: none"> <li>- <b>Limited:</b> for children with infantile fibrosarcoma, treatment options include surgery, radiotherapy, chemotherapy, targeted therapies and immunotherapies. For some children, surgery is not an option due to the life-threatening damage on the rest of the body. Sophie recalled how clinicians initially refused to operate on her son’s infantile sarcoma of the chest.</li> <li>- <b>Effectiveness:</b> existing treatments have varied rates of success. Treatment is often not begun with curative intent. After Sophie’s son underwent a highly dangerous operation, his sarcoma grew back.</li> <li>- <b>Side effects:</b> the side effects of chemotherapy can be intense, which sometimes means doses must be lowered to be tolerated by the patient. Ioana described her distress at watching her son losing hair, vomiting, exhausted and with a high temperature, saying ‘it is very difficult to watch [a] young baby in pain that you cannot help’.</li> <li>- <b>Emotional impact:</b> as well as the impact on the wider family, chemotherapy can be particularly distressing for young children, who are unable to understand what they are experiencing.</li> <li>- <b>Disruptive:</b> while clinicians aim for limb sparing surgery, there are many cases in which amputation is necessary for children under two years old, creating lifelong and life altering disability. Sophie was warned that after her son’s surgery, he ‘may not be able to play football or spend time as a regular child’. Chemotherapy may also result in kidney problems, hearing problems and infertility as an adult. Ioana’s son experienced potentially long term side impacts on his liver and immunity due to chemotherapy, and was transferred to Great Ormand Street Hospital not initially for treatment of his sarcoma but for liver damage.</li> </ul> <p>Please see question 11 for explanation on why patients would like current treatments to be replaced with larotrectinib specifically.</p> |
| <p><b>9. Considering all treatments available to patients are there any unmet needs for patients with this condition?</b></p> | <p>Shounok stated that there is a ‘huge unmet need’ for ‘effective targeted therapies’ for patients with NTRK fusion-positive tumours. When an NTRK-fusion is detected, a highly effective treatment option becomes available in larotrectinib. At present, there is huge unmet need for sarcoma patients who have had a NTRK fusion identified but are not able to access larotrectinib through the NHS.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

If yes please state what these are

## Section 3 Experience during the managed access agreement (MAA)

**Table 3 Experience, advantages and disadvantages during the MAA**

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| <p><b>10. What are patients' and carers' experience of accessing and having the treatment?</b></p> <ul style="list-style-type: none"> <li>Please refer to the MAA re-evaluation patient submission guide</li> </ul> | <p>Please note, question 10 relates to one patient, Shounok, who gave sufficient detail on his experience of accessing the MMA. Shounok described the process of accessing through the MMA as adding stress to his treatment, recalling navigating approvals, the access agreement itself and waiting times. The agreement impacted his emotional and mental health, describing anxiety caused by the uncertainty of the MMA from a patient perspective. He reported concerns about 'long-term access and affordability', describing how 'being on managed access can feel precarious, with the fear of losing the treatment if funding decisions change'.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>11. What do patients and carers think are the advantages of the treatment?</b></p> <p>Please refer to the MAA re-evaluation patient submission guide</p>                                                      | <p><b>Effective:</b></p> <ul style="list-style-type: none"> <li>The top advantage was the effectiveness of the drug- for all patients, larotrectinib is the treatment that achieved significant improvements. For Shounok, larotrectinib 'provided real disease control where other options had failed'. Sophie said of the drug, 'it works, helps and it's a cure that my son can have'. Both children with infantile fibrosarcoma were described with the same phrase- getting 'better and better'. Sophie also notes the speed at which larotrectinib works as one of the 'main advantage', describing the relief of not having to 'wait a long time to find out if it works'.</li> <li>Larotrectinib does not present a high level of risk to a patient as surgery can, particularly for a paediatric patient. Sophie reports how 'we keep only getting positives from the doctors and hospitals', after previously experiencing a high risk and ineffective surgery that doctors initially said was 'too dangerous' to undertake.</li> <li>Larotrectinib also gave patients hope about their futures. Shounok told us that beginning treatment with larotrectinib 'felt like a breakthrough moment' following exhausting the limited treatment options available to them, emphasising 'his genuine relief to have a targeted option'. Ioana described how she initially only allowed herself to feel quiet hope when her son began treatment, but the treatment was so effective she was quickly 'happy to have my child back'.</li> </ul> |

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|  | <p><b>Manageable side effects:</b></p> <ul style="list-style-type: none"> <li>Side effects are far more manageable than from other treatment options, including surgeries and alternative drugs like chemotherapy (please see question 8 for further detail on side effects). Shounok told us that ‘physically, while side effects exist, they are far less debilitating than the alternatives’.</li> <li>Both families of children with infantile sarcoma described no side effects at all.</li> <li>Chemotherapy: Ioana described her son ‘not feeling as unwell’ as during chemotherapy- ‘he is not vomiting, he is not tired, he has no temperature’. Sophie also expressed the change in impact due to the targeted nature of the treatment, noting larotrectinib will not ‘cause hair loss and weakness’. There are no known long term impacts noted either, with Ioana saying she has ‘no concerns about potential side effects in the future’.</li> <li>Surgery: as described in question 8, surgery can have life-long and life-altering impacts on mobility and appearance. Larotrectinib does not have these impacts. Shounok compared side effects of the drug as manageable compared to the ‘multiple surgeries’ he would otherwise face in addition to those he had already experienced.</li> </ul> <p><b>Accessible administration:</b></p> <ul style="list-style-type: none"> <li>Due to its oral administration, larotrectinib reduces hospital stays for patients and their families. Taken twice daily in liquid or capsule form, treatment is supervised through blood tests and discussion with a nurse, doctor or specialist pharmacist. Comparatively, chemotherapy typically involves intravenous infusion through a cannula in a hospital, requiring extended stays in hospital for patients and their families.</li> <li>Ioana described how ‘everything is easier for our family’ since her son began larotrectinib, in part since ‘he does not have to have blood tests twice a week’ and they do not have to visit their local hospital or specialist care at Great Ormond Street Hospital (entailing a journey to central London) often.</li> <li>At home administration is significantly less disruptive to the lives of the patient and the family. Sophie told us how it ‘allowed me and my husband to work on normal schedules without constant visits to the hospital’. Enabling carers to continue in employment and other responsibilities can help to significantly improve their overall situation, including reducing financial instability. Sarcoma care</li> </ul> |
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|  | <p>can be more disruptive to the lives of patients and families than more common cancers, due its specialist nature. Patients must be treated by one of only sixteen centres across England and Wales, meaning many patients travel long distances for care (Unique Among Cancers, Sarcoma UK, 2025).</p> <ul style="list-style-type: none"> <li>• Taking a drug orally can also be less distressing for patients and their families, particularly for young children who do not understand what is happening to them. Sophie suggested that taking the drug through a familiar method like swallowing a pill was also a benefit, describing it as 'like a normal paracetamol dose'.</li> </ul> <p><b>Quality of life:</b></p> <ul style="list-style-type: none"> <li>• Due to the effectiveness of the treatment and the lack of side effects, all patients and carers enthusiastically describe the quality of life that it made possible.</li> <li>• As an adult patient, Shounok described how larotrectinib enabled him to 'maintain more normality in my life, continue working, and engage in family and social activities with less disruption'. The knock-on impacts here include preventing decline in emotional and mental wellbeing, relationship breakdown, independence and financial stability, all of which sarcoma patients can struggle with.</li> <li>• Socialisation and relationships also greatly improved for both young children on larotrectinib, allowing them take part in normal childhood experiences. This is in part due to increased physical wellbeing. Both children can now play again, interacting through other children through games or nursery. Ioana told us of her happiness at seeing her son 'smiling, happy going to nursery and playing with his friends'. Sophie shared how her son 'can walk, run and play with other children'.</li> <li>• Both children and their families are afforded 'a normal life' and happiness by larotrectinib. Ioana told us: 'I am happy to have my child back'.</li> </ul> <p>For all patients and carers, it is treatment that transformed their lives, not just in controlling the disease but giving them back normality.</p> |
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| <p><b>12. What do patients or carers think are the disadvantages of the treatment?</b></p> <p>Please refer to the MAA re-evaluation patient submission guide</p>                                                                       | <p><b>Side effects:</b> Shounok reported physical side effects but was willing to tolerate them for the benefits of the treatment and focused his response on side effects being ‘far less debilitating than the alternatives’.</p> <p><b>No disadvantage:</b> both families of children with infantile fibrosarcoma told us they saw <u>no</u> disadvantages of larotrectinib.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>13. What place do you think this treatment has in future NHS treatment and care for the condition?</b></p> <p>Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.</p> | <p>Larotrectinib has a place in the NHS as a highly effective drug for those who need it. For all NTRK fusion-positive tumours, not only is it effective where other drugs are not, but both as a neoadjuvant and standalone treatment, it limits the long- and short-term side effects of other treatments, including amputations. While NTRK fusions are relatively few, for those that are eligible, it is transformative, since many NTRK fusion-positive tumours lack effective targeted treatments. Larotrectinib should therefore be considered as a potential first-line of treatment for patients with NTRK fusion-positive tumours.</p> <p>For example, for the population of patients with infantile fibrosarcoma, of which over 90% have NTRK fusion-positive tumours, larotrectinib transforms standard treatment. As a first line treatment, it can immediately control disease progression and significantly reduce the need for high-risk surgeries with varied success rates and long term impacts.</p> |

## Section 4 Patients views on assessments used during the MAA

**Table 4 Measurements, tests and assessments**

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| <p><b>14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment.</b></p> <p><b>How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?</b></p> | <p>No relevant evidence given by patient. Please note, the rest of this section relates to one patient, Shounok, who gave sufficient detail on his experience of the MMA.</p> |
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| <p><b>15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?</b></p>                                                                                                   | <p>Shounok described the regular assessments as 'repetitive'. Though he understood the necessity of scans and blood tests, he reported they could be 'stressful or exhausting'.</p>                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments?</b><br/>If not please explain what was missing.</p> | <p>Shounok did not believe that the MAA tests 'fully' captured his experience of larotrectinib, stressing that he did not think quality of life and emotional benefits were adequately captured. He described the regular assessments as 'overly clinical', not taking into account that larotrectinib 'didn't just shrink tumours' but enabled him 'to keep working, to be present for family, and to live more fully'. He requested that these life changing benefits be 'recognised as part of the value of treatment'.</p> <p>Shounok shared that clinical data appeared to be 'well captured'.</p> |
| <p><b>17. What outcomes do you think have not been assessed or captured in the MAA data?</b><br/>Please tell us why</p>                                                                                                           | <p>Based on Shounok's experiences, quality of life benefits were not sufficiently recorded. This means a potential gap in data exists on the benefits of larotrectinib. Both this gap and the positive quality of life impact should be taken into consideration when reviewing data collected in the MMA tests.</p>                                                                                                                                                                                                                                                                                    |

## Section 5 Patient population

**Table 5 Groups who may benefit and those who declined treatment**

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| <p><b>18. Are there any groups of patients who might benefit more or less from the treatment than others?</b><br/>If so, please describe them and explain why.</p>                                                                   | <p>NTRK-fusions occur at different rates in different sub-types of sarcoma. Within infantile fibrosarcoma, over 90% of patients have an NTRK fusion. For this reason, a greater percentage of paediatric sarcoma patients will benefit from larotrectinib than adult patient populations. However, the efficacy of the drug remains the same. For patients with NTRK fusions at any age, it is transformative in both effectiveness and manageability of side effects. As an agnostic drug, it larotrectinib should be approved for use for all NTRK fusion-positive tumours without limitations on use by type or site of cancer.</p> |
| <p><b>19. Were there people who met the MAA eligibility criteria who decided not to start treatment?</b><br/>Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.</p> | <p>At present we have no relevant evidence on this topic.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

## Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See [NICE's equality scheme](#) for more details.

- **Rare and less common cancers:** it is important that larotrectinib, as a tumour agnostic drug, is recommended for all NTRK fusion-positive solid tumours and not just for more common cancers for which the drug's efficacy can be more reliably assessed due to their higher patient populations. Rare cancer patients already face inequalities in diagnosis, treatment and care when

compared to more common cancers, resulting in poorer outcomes. Over the past decade, mortality rates for the four most common cancers have fallen around twice as fast when compared to rare and less common cancers. Progress in improving access to treatment is significantly slower than more common cancers, in part due to a lack of investment in developing new treatments. Often, patients are treated with drugs designed for other, more common cancers. People diagnosed with rarer NTRK fusion-positive tumours such as cholangiocarcinoma or sarcoma should also have access to larotrectinib to avoid increasing the disparity of outcomes when compared with the more common cancers. (Sarcoma UK collaborated with AMMF to develop this statement as members of patient organisations within the rare cancers community).

- **Home administration:** availability of larotrectinib for all patients NTRK fusion-positive would reducing inequalities in access to specialist cancer care, due home administration. Under NHSE's Sarcoma Service Specification (2019), sarcoma patients must have their care undertaken or overseen by a sarcoma specialist centre. There are just fourteen centres across England and Wales, all located in urban areas. For many patients, this means lengthy and expensive return journeys to access care. This disproportionately effects low-income families and families in rural areas- for example, families without a car must take public transport, increasing the length and cost of the journey when compared to those who own a car (*Unique Among Cancers*, Sarcoma UK, 2025). Patients in North Wales do not have a regional specialist centre and must travel to services in Manchester or Birmingham. The routine availability of larotrectinib would reduce the inequalities lower-income and rural families face when being treated for an NTRK fusion-positive tumour, increasing their access to care and reducing the disproportionate financial impact they face.

## Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

## Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- At present, treatment options for many NTRK fusion-positive tumours are used due to a lack of targeted and more effective alternatives- larotrectinib is an effective, targeted treatment that can be used confidently as first-line with curative intent.
- Side effects of larotrectinib are significantly more manageable than alternative treatment, such as chemotherapy and surgery, thus reducing impact on physical and mental wellbeing, and enabling patients to have a better quality of life where they are more able to participate in daily activities and education or work, reducing psycho-social and financial implications.
- Larotrectinib can act as a neoadjuvant treatment for surgery, enabling surgery with curative intent for paediatric patients for whom surgery would have previously been too high risk.
- Rare cancers should not be excluded due to smaller populations, when a drug is agnostic and can be highly effective- to limit to more common cancers would be form of inequality.
- NTRK fusion-positive tumours are rare, but this should not prevent its approval- its effectiveness when used not only enacts lifesaving outcomes but can reduce likelihood of amputation and other permanent health impacts that effects the patient throughout their life, reducing medical needs throughout the lifespan of the patient.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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# LAROTRECTINIB FOR TREATING NTRK FUSION-POSITIVE ADVANCED SOLID TUMOURS- SARCOMA UK RESPONSE

## APPENDIX: PATIENT AND CARER STATEMENTS

### 1: Carer of young boy with infantile fibrosarcoma of the right cheek.

Evidence verbally given by child's mother (Ioana, name changed) through an interpreter. Child's name redacted.

#### **Living with the condition**

Living with the condition is very hard. At the diagnosis, the life was very hard, I lost my job because my child is sick. I needed to stay with him 24 hours a day. [XX] was initially on chemotherapy and I needed to be with him, to monitor him and take him to the hospital if he was unwell or spiked a fever. This was very difficult for all of the family. Chemotherapy caused problems with his liver and we were very frightened. We had to go to the hospital as an emergency and he was very unwell. We were then transferred to Great Ormond Street to treat his liver problem which was caused by chemotherapy.

#### **The life was changed since starting Larotrectinib.**

Everything is easier for our family. Our child is not feeling so unwell as he did when he had chemotherapy. He is not vomiting, he is not tired, he has no temperature, we do not need to take him to the local hospital. He does not have to have blood tests twice a week. He acts like a normal child. We are not visiting hospital (local or GOSH) very often. There are no problems with liver or immunity. Everything is getting better and better for us.

There are **no disadvantages** of this medicine. He has not had any side effects.

#### **Were you worried about side effects of Larotrectinib?**

It is human to be worried, but I take this as normal reaction. If there are some side effects I hope they will not be serious. No concerns about potential side effects in the future.

#### **Other treatment**

It is very difficult to watch young baby in pain that you cannot help. Seeing child losing hair, vomiting, not sleeping is very difficult. It was awful.

#### **Larotrectinib**

When he changed to Larotrectinib I was quietly hoping he will be better, but with time I am now happy to have my child back. He is smiling, happy going to nursery and playing with his friends. I wonder what is the price of a child's smile?

## 2. Carer of very young boy with infantile sarcoma of the chest.

Written evidence by child's mother (Sophie, name changed). Child's name redacted.

Living with the condition my son has is not easy for me as a first-time mother and also for his father and whole family. When we found out [XX] is sick we were devastated. No doctor wanted to proceed with his surgery as it was too dangerous in his state. The feeling of losing him when he was just born was hard and I cannot even describe it in words. We were told that even after the surgery, [XX] may not be able to play football or spend time as a regular child. We were living in hospital for the first 3 months of his life. This experience was very hard but also upsetting.

As for [XX]'s social life, it was never clear how his condition will develop. We were careful with public places making sure he doesn't catch any flu as it would cause us to come back to the hospital. We were avoiding Childs centres and nurseries. As a carer it was hard to watch that [XX] cannot have normal relationships with his cousins.

[XX] was diagnosed with infantile fibrosarcoma and after a very dangerous surgery the tumor had regrew. Our only option was the medicine called Larotrectinib. We were unsure about the medicine as every parent would be but it was our only option as NHS doesn't propose other medicines that would at least try to treat his condition.

The service at GOSH we had received was the best we could dream about. Doctors took care of my baby and for that I will always be grateful. They were looking for the best solution considering NHS availability.

When we decided to go with Larotrectinib we were given a written declaration to sign and we were told about possible outcomes of taking the medicine. The main advantage of the treatment is that it focuses only on the problem not like the other chemotherapy that may cause hair loss and weakness. Thanks to the medicine [XX] can have a normal life, he can walk, run and play with other children. This medicine can be dosed at home which allowed me and my husband to work on normal schedules without constant visits to the hospital. And the main advantage is that it works quick. We didn't have to wait long time to find out it works and our baby is feeling only better and better.

We don't see any disadvantages. It works, helps and it's a cure that my son can have like a normal paracetamol dose. This is the most important part, we experienced very professional and patient- focused treatment. We were supported through our journey and even now, when [XX] is much much better we keep getting only positivities from his doctors and hospitals.

## 3. Adult man with wild-type GIST

Written evidence given by Shounok.



## **What is it like to live with the condition?**

Living with NTRK fusion GIST has been life-changing on every level. Physically, the illness and surgeries (such as my proximal partial gastrectomy with Merendino jejunal interposition this January 2025) have left me with limitations around diet, energy levels, and the ability to carry out day-to-day tasks as I used to. Though I try to remain positive most of the time, emotionally, there is constant uncertainty about the future, which brings stress and anxiety not only for me but also for my loved ones.

My ability to work has been impacted significantly — while I continue to work in creative industries and some teaching, I have had to adapt schedules, reduce workload at times, and manage fatigue carefully. Financially, this adds pressure, as I cannot always sustain the same level of productivity.

Social life and relationships also feel the strain. Simple things like going out for a meal or planning a holiday can become complicated. There's also an emotional burden on family and friends, as they see me managing side effects and worry about long-term outcomes.

## **What do carers experience when caring for someone with the condition?**

Carers carry a huge emotional and practical load. They not only provide support with medical appointments, diet, and day-to-day care, but also have to hold the weight of uncertainty. It affects their own ability to work and socialise, as well as their mental wellbeing. The constant vigilance and need to adapt around the patient's condition means carers rarely get true respite.

## **What do patients and carers think of current treatments and care available on the NHS?**

Current treatments for GIST are limited and not always effective for rare subtypes like NTRK fusion. Surgery, while sometimes necessary, comes with major life-altering consequences, as I've experienced. Standard GIST medications such as imatinib are often ineffective for NTRK-driven disease. This leaves patients with very few good options.

Care in the NHS is generally excellent in terms of clinical teams and commitment, the system tries always to provide quick access to the newer targeted therapies that could make the biggest difference.

## **Considering all treatments available to patients, are there any unmet needs for patients with this condition?**

Yes — there is a huge unmet need for effective targeted therapies like larotrectinib for rare GIST patients. Current treatment pathways don't adequately address these rare genetic drivers, and without access to the right drugs, patients face poor outcomes, unnecessary suffering, and invasive surgeries.

### **What are patients' and carers' experience of accessing and having the treatment?**

Accessing larotrectinib felt like a breakthrough moment. After exhausting limited options, finally being able to try a treatment designed for my tumour type gave me hope, specially at the Paws Gist Clinic. The process wasn't always straightforward — approvals, managed access agreements, and waiting times added stress — but once on treatment, I felt genuine relief to have a targeted option.

### **What do patients and carers think are the advantages of the treatment?**

The key advantage is effectiveness. For me, larotrectinib provided real disease control where other options had failed. Side effects were generally more manageable compared to multiple surgeries. It allowed me to maintain more normality in my life, continue working, and engage in family and social activities with less disruption.

### **What do patients or carers think are the disadvantages of the treatment?**

The disadvantages are mainly around uncertainty of long-term access and affordability. Being on managed access can feel precarious, with the fear of losing the treatment if funding decisions change. Physically, while side effects exist, they are far less debilitating than the alternatives.

### **When receiving larotrectinib through the managed access agreement, were there any tests or assessments that were difficult or unhelpful?**

Some of the regular assessments felt repetitive or overly clinical, without always reflecting the day-to-day quality-of-life benefits the treatment was giving. Certain scans and blood tests, while necessary, could be stressful or exhausting.

### **Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the managed access agreement tests and assessments?**

Not fully. The clinical data is well captured, but the emotional and quality-of-life benefits often don't come through in the same way. For me, larotrectinib didn't just shrink tumours — it allowed me to keep working, to be present for family, and to live more fully. These aspects need to be recognised as part of the value of treatment.

### **4. Carer of young woman with GIST**

Written evidence given by the patient's mother, Jayne.

### **What is it like to live with the condition?**

I am responding to this question as a mother, whose daughter was diagnosed with PAWS-GIST cancer when she was just fifteen years old. It was a totally shattering experience for my daughter and our whole family and cut short a very promising future for a beautiful and talented young woman.

Some of the rare PAWS-GIST cancers have an NTRK fusion mutation. Living with one of the PAWS-GIST cancers is similar for most patients except those with an NTRK fusion have the benefit of a drug designed to treat their cancer where currently the others do not.

**Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life).**

Having digested the facts of the diagnosis, we did our best to live our lives as normally as possible. The hospital became our second home and seeking out any path that might be the answer to effective treatment became our ongoing obsession. My daughter continued with school then college and university and excelled academically despite enduring some horrific procedures to tackle the cancer. Constant transfusions, side effects of treatments that did not work and then removal of her stomach which brought a whole set of other issues impacting her ability to absorb nutrition and maintain a satisfactory weight or strong bones. Illness such as this impacts every area of life, social, financial, emotional... I became a trustee of a charity and focused on setting up infrastructure to support research which we were advised was not happening for this type of cancer. As this was a voluntary post, I became self-employed so that I could support my daughters needs and generate income for our family. When breathing became an issue we had oxygen bottles and special mattresses installed to make homelife as comfortable as possible for our daughter.

**For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?**

My daughter's school and colleges were very supportive and worked around absences with online coursework that she could complete while in hospital or recovering at home.

My daughter had a wide circle of friends and a lovely boyfriend but decided to finish the relationship as she did not feel the emotional burden her illness was placing on him was fair. Hugely courageous and the most loving person she did her best to shield all of us from the horrors she was confronted with while battling this cancer, always smiling and saying she was fine to make us feel better. We knew she wasn't fine.

We all felt helpless and absorbed the stress created in our lives by this nightmare. It has undoubtedly taken its toll on my son, my husband and me. We were all damaged by this terrible experience and continue to grieve for the loss of our beautiful girl who died aged 23 years old while in her final years at university studying for a degree in Business. Our lives will never be the same.

**What do carers experience when caring for someone with the condition?**

The initial diagnosis was earth shattering, having to break the news to my child that she had cancer was horrific. Years of standing by, feeling totally helpless and hopeless when; she had to have her stomach removed, emergency races to hospital with anaemia, the ravages of treatments, all of these traumas put enormous strain on our daughter and our loving family and friends. Our sole focus was to find an effective treatment that would allow her to survive and thrive.

Carers carry a heavy burden. One which as research advances and effective treatments are discovered will help to lighten the burden by offering hope of effective treatment and maybe even cure.

**What do patients and carers think of current treatments and care available on the NHS? Please state how they help and what the limitations are.**

Talking generally about GIST cancer. There are some types of this cancer where if surgery is not curative then for certain mutational types there are drugs that have been approved and are effective in the management of the cancer, prolonging life and in some cases, shrinking inoperable tumours so that they can be removed.

It is recommended that treatment is managed in a specialist Sarcoma/GIST hospital and where this happens the outcomes for many patients is good and they can continue to live their lives relatively normally. Problems occur for those patients whose type of GIST cancer does not have an effective treatment or in some cases an effective treatment that has been approved for use on the NHS. If a patient is fortunate to be diagnosed with GIST cancer for which there are treatments available then the outlook is favourable.

**Considering all treatments available to patients, are there any unmet needs for patients with this condition?**

The current treatments that are available for GIST on the NHS consist of Surgery, Imatinib, Sunitinib and Regorafenib (and for NTRK fusion GISTs Larotrectinib and Entrectinib under Managed access).

Everyone is very grateful that these treatments exist and are available as they enable a significant number of GIST patients to live GIST cancer free (*if the surgery is successful*) or with GIST that is manageable with drug therapy.

The guidance and centralisation of specialist care for GIST in Sarcoma and GIST centres is hugely beneficial as it means that the clinicians treating patients are very familiar with GIST and the optimum way to address them.

It is sad that there are treatments such as Avapritinib and Ripretinib which have both shown significant efficacy for GIST patients with specific types of mutations but which are not currently available on the NHS to those that would benefit and as a result their lives come to a premature end.

There are other types of GIST with unmet needs but this is because research has not yet found effective treatments.

It is recognised that NTRK fusion GISTs respond to NTRK fusion inhibitors such as Larotrectinb so this drug should be approved for use naturally on the NHS for NTRK fusion GIST patients.

## Single Technology Appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

#### Clinical expert statement

#### Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

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send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Wednesday 14 January 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

## Part 1: Treating NTRK fusion-positive advanced solid tumours and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

|                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Your name</b>                                                                                                                                                                               | Robin L Jones                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>2. Name of organisation</b>                                                                                                                                                                    | Royal Marsden                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>3. Job title or position</b>                                                                                                                                                                   | Professor                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>4. Are you (please tick all that apply)</b>                                                                                                                                                    | <input type="checkbox"/> An employee or representative of a healthcare professional organisation that represents clinicians?<br><input checked="" type="checkbox"/> A specialist in the treatment of people with NTRK fusion-positive advanced solid tumours?<br><input checked="" type="checkbox"/> A specialist in the clinical evidence base for NTRK fusion-positive advanced solid tumours or technology?<br><input type="checkbox"/> Other (please specify): |
| <b>5. Do you wish to agree with your nominating organisation's submission?</b><br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | <input checked="" type="checkbox"/> Yes, I agree with it<br><input type="checkbox"/> No, I disagree with it<br><input type="checkbox"/> I agree with some of it, but disagree with some of it<br><input type="checkbox"/> Other (they did not submit one, I do not know if they submitted one etc.)                                                                                                                                                                |
| <b>6. If you wrote the organisation submission and/or do not have anything to add, tick here.</b><br>(If you tick this box, the rest of this form will be deleted after submission)               | <input type="checkbox"/> Yes                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</b>                                                                                | None.                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Clinical expert statement



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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>8. What is the main aim of treatment for NTRK fusion-positive advanced solid tumours?</b><br/>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)</p>                                                                                                                                                                                                                                                                                                    | <p>The main aim of treatment for NTRK fusion-positive advanced solid tumours is to improve symptoms and survival for patients with metastatic disease</p> |
| <p><b>9. What do you consider a clinically significant treatment response?</b><br/>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)</p>                                                                                                                                                                                                                                                                                                                                | <p>A greater than 60% RECIST response rate.</p>                                                                                                           |
| <p><b>10. In your view, is there an unmet need for patients and healthcare professionals in NTRK fusion-positive advanced solid tumours?</b></p>                                                                                                                                                                                                                                                                                                                                                                                | <p>There is an unmet need for patients and healthcare professionals in NTRK fusion-positive advanced solid tumours.</p>                                   |
| <p><b>11. How is NTRK fusion-positive advanced solid tumours currently treated in the NHS?</b></p> <ul style="list-style-type: none"> <li>• Are any clinical guidelines used in the treatment of the condition, and if so, which?</li> <li>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)</li> <li>• What impact would the technology have on the current pathway of care?</li> </ul> | <p>NTRK fusion-positive advanced solid tumours are currently treated with conventional chemotherapy.</p>                                                  |
| <p><b>12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?</b></p> <ul style="list-style-type: none"> <li>• How does healthcare resource use differ between the technology and current care?</li> <li>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)</li> </ul>                                                                                                                             | <p>The drug will need to be funded.</p>                                                                                                                   |

Clinical expert statement

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)</li> </ul>                                                                                                                                                                                                                    |                                                                                                                   |
| <p><b>13. Do you expect the technology to provide clinically meaningful benefits compared with current care?</b></p> <ul style="list-style-type: none"> <li>Do you expect the technology to increase length of life more than current care?</li> <li>Do you expect the technology to increase health-related quality of life more than current care?</li> </ul>                   | Yes, NTRK inhibitors provide a clinically meaningful benefit in patients compared to current standard treatments. |
| <p><b>14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?</b></p>                                                                                                                                                                                                                            | The drug is effective in patients with NTRK-positive solid tumours.                                               |
| <p><b>15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?</b></p> <p>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)</p> | This agent is easier to administer than standard chemotherapy.                                                    |
| <p><b>16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?</b></p>                                                                                                                                                                                                                            | No.                                                                                                               |
| <p><b>17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?</b></p>                                                                                                                                                                    | This agent will result in substantial health-related benefits.                                                    |

Clinical expert statement

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care</li> </ul>                                                                                                                                                                                                                                |                                                                                   |
| <p><b>18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?</b></p> <ul style="list-style-type: none"> <li>Is the technology a 'step-change' in the management of the condition?</li> <li>Does the use of the technology address any particular unmet need of the patient population?</li> </ul>                                                                                                      | The technology is innovative.                                                     |
| <p><b>19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                | In general the side effects do not affect management and patient quality of life. |
| <p><b>20. Do the clinical trials on the technology reflect current UK clinical practice?</b></p> <ul style="list-style-type: none"> <li>If not, how could the results be extrapolated to the UK setting?</li> <li>What, in your view, are the most important outcomes, and were they measured in the trials?</li> <li>If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?</li> <li>Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?</li> </ul> | The clinical trials on the technology reflect current UK clinical practice.       |
| <p><b>21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                          | No.                                                                               |

Clinical expert statement

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| <p><b>22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 630 [TA630] and TA644?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                               |
| <p><b>23. How do data on real-world experience compare with the trial data?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <p>Real world data compare well with clinical trial data.</p> |
| <p><b>24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.</b></p> <p>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.</p> <p>Please state if you think this evaluation could</p> <ul style="list-style-type: none"> <li>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation</li> <li>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population</li> <li>• lead to recommendations that have an adverse impact on disabled people.</li> </ul> <p>Please consider whether these issues are different from issues with current care and why.</p> | <p>Not that I am aware of.</p>                                |

Clinical expert statement

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here](#).

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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## Single Technology Appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

#### Clinical expert statement

#### Information on completing this form

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

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## Part 1: Treating NTRK fusion-positive advanced solid tumours and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

|                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Your name</b>                                                                                                                                                                               | Dr Olga Slater                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>2. Name of organisation</b>                                                                                                                                                                    | Great Ormond Street Hospital for Children                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>3. Job title or position</b>                                                                                                                                                                   | Consultant Paediatric Oncologist, Lead for Sarcoma                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>4. Are you (please tick all that apply)</b>                                                                                                                                                    | <input type="checkbox"/> An employee or representative of a healthcare professional organisation that represents clinicians?<br><input checked="" type="checkbox"/> A specialist in the treatment of people with NTRK fusion-positive advanced solid tumours?<br><input type="checkbox"/> A specialist in the clinical evidence base for NTRK fusion-positive advanced solid tumours or technology?<br><input type="checkbox"/> Other (please specify): |
| <b>5. Do you wish to agree with your nominating organisation's submission?</b><br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | <input checked="" type="checkbox"/> Yes, I agree with it<br><input type="checkbox"/> No, I disagree with it<br><input type="checkbox"/> I agree with some of it, but disagree with some of it<br><input type="checkbox"/> Other (they did not submit one, I do not know if they submitted one etc.)                                                                                                                                                     |
| <b>6. If you wrote the organisation submission and/or do not have anything to add, tick here.</b><br>(If you tick this box, the rest of this form will be deleted after submission)               | <input type="checkbox"/> Yes                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</b>                                                                                | I have never had any links or funding from the tobacco industry                                                                                                                                                                                                                                                                                                                                                                                         |

Clinical expert statement

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>8. What is the main aim of treatment for NTRK fusion-positive advanced solid tumours?</b><br/>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)</p>                                                                                                                                                                                                                                                                                                    | <p>In paediatric population:<br/>To cure the condition either by:</p> <ol style="list-style-type: none"> <li>1. Causing complete response and eradication of the tumour</li> <li>2. Causing shrinkage of the tumour which then allows surgical resection</li> </ol>                                                                                                                                                                                                                                                                              |
| <p><b>9. What do you consider a clinically significant treatment response?</b><br/>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)</p>                                                                                                                                                                                                                                                                                                                                | <p>A reduction in the size of the tumour by either:</p> <ol style="list-style-type: none"> <li>1. Shrinkage measured in cm in comparison to previous size of the tumour on imaging – this might be complete response, partial response or stable disease</li> <li>2. Stabilisation of the size of the tumour allowing patients to live good quality of life</li> </ol>                                                                                                                                                                           |
| <p><b>10. In your view, is there an unmet need for patients and healthcare professionals in NTRK fusion-positive advanced solid tumours?</b></p>                                                                                                                                                                                                                                                                                                                                                                                | <p>Absolutely.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>11. How is NTRK fusion-positive advanced solid tumours currently treated in the NHS?</b></p> <ul style="list-style-type: none"> <li>• Are any clinical guidelines used in the treatment of the condition, and if so, which?</li> <li>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)</li> <li>• What impact would the technology have on the current pathway of care?</li> </ul> | <p>In paediatric oncology there are institutional clinical guidelines.<br/>There are also international guidelines from bodies such European Soft Tissue Sarcoma Group<br/>The pathways of care are very similar within the UK and internationally. The only difference is that access to Larotrectinib is much easier in other European countries.<br/>Allowing Larotrectinib to remain on the CDF list, especially with allowance to be used in re-treatment of progressive disease would make a huge impact on NTRK mutated malignancies.</p> |
| <p><b>12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?</b></p> <ul style="list-style-type: none"> <li>• How does healthcare resource use differ between the technology and current care?</li> </ul>                                                                                                                                                                                                                                                            | <p>Difference is astonishing.<br/>Standard, current care for children with NTRK fused malignancies is chemotherapy and surgery in children.<br/>Most common NTRK mutated cancer in children is infantile fibrosarcoma. This occurs in very young children, often in babies under 1 year of age or sometimes</p>                                                                                                                                                                                                                                  |

Clinical expert statement

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| <ul style="list-style-type: none"> <li>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)</li> <li>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)</li> </ul>                                                                                   | <p>at birth (congenital). The tumours are very often very large for the size of the child's body and surgery to resect the whole tumour can be very mutilating and can leave life long disabilities. Chemotherapy is difficult to administer in the very young children as their body systems such as kidneys and liver have not fully matured and the risk of life-threatening side effects is high.</p> <p>Larotrectinib is easy to administer, extremely effective and extremely well tolerated in this population.</p>                                                                                                                                                                                                                                                                                                                              |
| <p><b>13. Do you expect the technology to provide clinically meaningful benefits compared with current care?</b></p> <ul style="list-style-type: none"> <li>• Do you expect the technology to increase length of life more than current care?</li> <li>• Do you expect the technology to increase health-related quality of life more than current care?</li> </ul>               | <p>Larotrectinib can provide better cure than current treatment, but more importantly it provides much better health-related quality of life than current care.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?</b></p>                                                                                                                                                                                                                            | <p>All patients with NTRK mutated tumours would greatly benefit from Larotrectinib.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?</b></p> <p>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)</p> | <p>Larotrectinib is way more easier to use than current treatments – in particular chemotherapy.</p> <p>Chemotherapy requires admission to the hospital, insertion of indwelling catheters, management of serious side effects such as neutropaenic sepsis or liver failure. Patients require regular weekly blood counts and regular liver and kidney tests to ensure that chemotherapy is not overtly toxic for their very young systems.</p> <p>The monitoring and follow up while on Larotrectinib is incomparably easier and represent significantly smaller burden for the family.</p> <p>With chemotherapy, patients are limited in their daily activities, cannot attend nursery or school and their parents also have limitations of their lives as they cannot continue to work as they need to look after their sick children while they</p> |

Clinical expert statement

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | are being treated. Further to this, in the UK there are on 20 paediatric oncology centres where chemotherapy can be administered, so children and families often have to travel a long way to receive treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?</b>                                                                                                                                                                                                                                                                                                                                                                                  | The rules for stopping treatment with Larotrectinib would not differ significantly to the rules we use for stopping current standard off care therapy. They do not include any additional testing. Patients follow up during and after treatment with Larotrectinib is actually easier and less extensive than after chemotherapy.                                                                                                                                                                                                                                                                                                                 |
| <b>17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?</b> <ul style="list-style-type: none"> <li>Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care</li> </ul> | <p>Health related benefits and quality of life is incomparably better with use of Larotrectinib.</p> <p>Children can take Larotrectinib by mouth and do not require hospital admissions. Children do not have side effects associate with chemotherapy.</p> <p>Children can continue attending nursery or School, play and continue their educations without interruptions made by hospital admissions and testing before and after chemotherapy</p> <p>The quality of life of the children's carers is incomparably better. Parents/careres can continue working, looking after other children and themselves avoiding need to social support</p> |
| <b>18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?</b> <ul style="list-style-type: none"> <li>Is the technology a 'step-change' in the management of the condition?</li> <li>Does the use of the technology address any particular unmet need of the patient population?</li> </ul>                                                                                      | Larotrectinib not only addresses improved treatment of children with malignancies where current treatment comes with high cost of mutilating surgery and prolonged chemotherapies with all of its side-effects, but also addresses unmet need for the NTRK mutated cancer for which there is no recognized therapy at present.                                                                                                                                                                                                                                                                                                                     |
| <b>19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?</b>                                                                                                                                                                                                                                                                                                                                                                                | Side effects of Larotrectinib in children are minimal. Children tolerate Larotrectinib without any problems. Interruption of treatment or stopping treatment because of side effects is extremely rare and I have not had to do either of these in my practice, even in children who have been on Larotrectinib for a long time.                                                                                                                                                                                                                                                                                                                   |

Clinical expert statement

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| <p><b>20. Do the clinical trials on the technology reflect current UK clinical practice?</b></p> <ul style="list-style-type: none"> <li>• If not, how could the results be extrapolated to the UK setting?</li> <li>• What, in your view, are the most important outcomes, and were they measured in the trials?</li> <li>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?</li> <li>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?</li> </ul> | <p>Partly.</p> <p>The clinical trials in adults and children have shown that Larotrectinib is very effective in treatment of NTRK mutated malignancies.</p> <p>If the treatment with Larotrectinib is stopped and the malignancy returns, if the patient is re-treated with Larotrectinib there is high response to therapy.</p> <p>This is currently not possible as CDF does not allow re-treatment off patient who have been successfully treated with Larotrectinib but have progressed after cessation off therapy.</p> <p>It would be important that NICE changes this to allow children to be re-treated with Larotrectinib, as it is highly likely that Larotrectinib is going to be highly effective second time round, as it has been shown in clinical trials.</p> |
| <p><b>21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 630 [TA630] and TA644?</b></p>                                                                                                                                                                                                                                                                                                                                                                                          | <p>Elective Discontinuation of Larotrectinib in Pediatric Patients With TRK Fusion Sarcomas and Related Mesenchymal Tumors published in Journal of Clinical Oncology is relevant to the:</p> <ul style="list-style-type: none"> <li>a) Confirmation of excellent response in NTRK mutated malignancies to Larotrectinib</li> <li>b) Confirmation of equally good response when patient are re-treated, following progression</li> </ul>                                                                                                                                                                                                                                                                                                                                       |
| <p><b>23. How do data on real-world experience compare with the trial data?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p>Real word experience confirms the data published. I have not seen a single NTRK mutated tumour that has not responded to treatment with Larotrectinib. Side effects in real world are less common than reported in clinical trials, with the caveat that clinical trials reported on both adults and children</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of</b></p>                                                                                                                                                                                                                                                                                | <p>Young children and patients with incurable brain tumours who have NTRK mutated tumours are particularly vulnerable.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Clinical expert statement

**people with this condition are particularly disadvantaged.**

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Larotrectinib is highly effective in NTRK mutated malignancies in children
2. Larotrectinib changes lives of children and their families as it transforms their quality of life allowing children to continue with education and parents to continue to work and look after themselves and other children
3. Larotrectinib is easy to administer, has significantly lower rate of side effects and does not carry risk of any life threatening side effects such as sepsis or liver failure which are recognized side effects of chemotherapy
4. Larotrectinib should be available through CDF to patients who have stopped administration of Larotrectinib but have following this experienced relapse as there is robust evidence of Larotrectinib efficacy in these patients.
5. When compared to the cost of chemotherapy, admission for chemotherapy, follow up blood tests for chemotherapy, treatment of chemotherapy-related side effects, cost of surgery and long term surgical complications and deficits Larotrectinib is likely to make financial sense for NHS.

[Click or tap here to enter text.](#)

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

Clinical expert statement

For more information about how we process your personal data please see our [privacy notice](#).



## Single Technology Appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

#### Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

#### Information on completing this form

In [part 1](#) we are asking you about living with NTRK fusion-positive advanced solid tumours or caring for a patient with NTRK fusion-positive advanced solid tumours. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

#### Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at [pip@nice.org.uk](mailto:pip@nice.org.uk) (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Wednesday 14 January 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

## Part 1: Living with this condition or caring for a patient with NTRK fusion-positive advanced solid tumours

**Table 1 About you, NTRK fusion-positive advanced solid tumours, current treatments and equality**

|                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>1. Your name</b>                                                                                    | Shounok Ghosh                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>2. Are you (please tick all that apply)</b>                                                         | <input checked="" type="checkbox"/> A patient with NTRK fusion-positive advanced solid tumours?<br><input checked="" type="checkbox"/> A patient with experience of the treatment being evaluated?<br><input type="checkbox"/> A carer of a patient with NTRK fusion-positive advanced solid tumours?<br><input type="checkbox"/> A patient organisation employee or volunteer?<br><input type="checkbox"/> Other (please specify):                                                                                                                                                                     |
| <b>3. Name of your nominating organisation</b>                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>4. Has your nominating organisation provided a submission? (please tick all options that apply)</b> | <input type="checkbox"/> No (please review all the questions and provide answers when possible)<br><input checked="" type="checkbox"/> Yes, my nominating organisation has provided a submission<br><input type="checkbox"/> I agree with it and <b>do not wish to</b> complete a patient expert statement<br><input type="checkbox"/> Yes, I authored / was a contributor to my nominating organisations submission<br><input type="checkbox"/> I agree with it and <b>do not wish to</b> complete this statement<br><input checked="" type="checkbox"/> I agree with it and <b>will be</b> completing |
| <b>5. How did you gather the information included in your statement? (please tick all that apply)</b>  | <input checked="" type="checkbox"/> I am drawing from personal experience<br><input type="checkbox"/> I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:<br><input type="checkbox"/> I have completed part 2 of the statement <b>after attending</b> the expert                                                                                                                                                                                                                                                    |

Patient expert statement

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|                                                                                                                                                                                                                                                                         | <p>engagement teleconference</p> <p><input type="checkbox"/> I have completed part 2 of the statement <b>but was not able to attend</b> the expert engagement teleconference</p> <p><input type="checkbox"/> I have not completed part 2 of the statement</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>6. What is your experience of living with NTRK fusion-positive advanced solid tumours?</b></p> <p><b>If you are a carer (for someone with NTRK fusion-positive advanced solid tumours) please share your experience of caring for them</b></p>                    | <p>Living with an NTRK fusion-positive advanced solid tumour has been a journey marked by rarity, delayed answers, and constant uncertainty. After initial treatment failed and I underwent major gastric surgery, the cancer returned within months, leaving me with no standard treatment options and the emotional weight of facing further progression so soon after recovery. Identifying the NTRK3 fusion was a critical turning point, bringing access to targeted therapy that has shown a meaningful response, but daily life remains shaped by ongoing treatment, side effects, regular scans, and the knowledge that this is a long-term condition. The rarity of my cancer has often meant advocating for specialist testing and care, while balancing hope from effective treatment with the physical and psychological demands of living with advanced disease.</p> |
| <p><b>7a. What do you think of the current treatments and care available for NTRK fusion-positive advanced solid tumours on the NHS?</b></p> <p><b>7b. How do your views on these current treatments compare to those of other people that you may be aware of?</b></p> | <p><b>7a.</b></p> <p>The treatments and care currently available on the NHS for NTRK fusion-positive advanced solid tumours can be highly effective when accessed through specialist centres with the appropriate expertise. In my experience, identification of the NTRK fusion came later in the treatment pathway, but once it was recognised, the support, clinical guidance, and access to targeted therapy were excellent. Larotrectinib has provided meaningful disease control and improved quality of life, and the care I have received from specialist teams has been professional, responsive, and reassuring. As NTRK fusion-positive cancers are extremely rare, pathways are still evolving, and increased awareness and earlier testing could further enhance patient experience.</p>                                                                             |

Patient expert statement

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|                                                                                                                                                                                                                                                 | <p><b>7b.</b></p> <p>From speaking with and hearing about other patients with rare or NTRK fusion-positive cancers, my views broadly align with theirs. There is a shared appreciation for the effectiveness of targeted therapies and the dedication of specialist clinicians once patients reach the right services. Some patients, like myself, have experienced delays before accessing genomic testing or specialist input, but this is generally understood as a reflection of the rarity and complexity of these cancers rather than a lack of care. Overall, there is a sense that continued development of national pathways and awareness will help ensure more consistent and timely access for future patients.</p>                                                                                                                                                                                                 |
| <p><b>8. If there are disadvantages for patients of current NHS treatments for NTRK fusion-positive advanced solid tumours (for example, how they are given or taken, side effects of treatment, and any others) please describe these</b></p>  | <p>While there are some disadvantages associated with current NHS treatments for NTRK fusion-positive advanced solid tumours, many of these can be managed effectively. Targeted therapies such as larotrectinib are taken long term and can cause side effects including muscle and joint pain, numbness, dizziness, and gastrointestinal symptoms, which require ongoing monitoring and adjustment. However, with appropriate clinical support, self-awareness, and lifestyle adaptations, these side effects can be managed, allowing patients to maintain an active and meaningful daily life. Regular follow-up appointments and scans can be emotionally demanding, but they also provide reassurance and enable early intervention. Overall, despite the challenges, the benefits of effective targeted treatment and the ability to remain engaged in everyday activities significantly outweigh the disadvantages.</p> |
| <p><b>9a. If there are advantages of larotrectinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?</b></p> | <p><b>9a.</b></p> <p>Larotrectinib has clear advantages over previous treatment options available to me on the NHS, particularly in terms of effectiveness and quality of life. After my cancer recurred and there were no standard treatment options available, larotrectinib provided a targeted approach that directly addressed the genetic driver of my tumour. Since starting treatment, scans have shown an early and meaningful</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Patient expert statement

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| <p><b>9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?</b></p> <p><b>9c. Does larotrectinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these</b></p> | <p>response, which has brought significant emotional relief and restored a sense of stability. While there are side effects, they are manageable, allowing me to remain active, maintain independence, and continue engaging with work, self-care, and everyday responsibilities. Importantly, the treatment has shifted my experience from one of uncertainty and limited options to one of control and hope.</p> <p><b>9b.</b></p> <p>The most important advantage of larotrectinib is its effectiveness in controlling the disease by targeting the underlying cause of the cancer. For me, this has translated into tumour response, symptom relief, and the possibility of living with the condition rather than constantly preparing for further progression or invasive intervention. This disease control underpins all other benefits, including improved quality of life, the ability to plan ahead, and the confidence to remain physically, emotionally, and professionally engaged with life.</p> <p><b>9c.</b></p> <p>Larotrectinib helps to address several disadvantages of previous treatments, particularly the lack of effective options following disease recurrence. Unlike standard treatments that were ineffective in my case or involved major surgery, larotrectinib is a targeted, non-surgical therapy that has reduced disease activity while allowing side effects to be managed alongside an active lifestyle. This has lessened the physical and emotional burden associated with repeated interventions and uncertainty, and replaced it with ongoing disease control, regular monitoring, and a better overall balance between treatment and quality of life.</p> |
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Patient expert statement

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| <p><b>10. If there are disadvantages of larotrectinib over current treatments on the NHS please describe these.</b></p> <p>For example, are there any risks with larotrectinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why</p>                                                                               | <p>While all medications carry some potential risks, larotrectinib is generally very well tolerated compared to many conventional cancer treatments currently available on the NHS. According to clinical guidance and the SOP, most side effects reported are mild to moderate, such as fatigue, dizziness, or gastrointestinal symptoms, and are manageable with standard supportive care.</p> <p>Importantly, larotrectinib offers a targeted approach, which means it specifically inhibits TRK fusion-positive tumors, reducing the broader toxicity often associated with traditional chemotherapy. This targeted mechanism not only improves the safety profile but also supports sustained treatment, helping patients maintain quality of life.</p> <p>Overall, any potential risks are outweighed by the significant clinical benefits, particularly for patients with TRK fusion-positive cancers where alternative options may be limited. The evidence indicates that larotrectinib provides a highly effective, well-tolerated treatment option, making it a positive addition to the NHS formulary.</p> |
| <p><b>11. Are there any groups of patients who might benefit more from larotrectinib or any who may benefit less? If so, please describe them and explain why</b></p> <p>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments</p> | <p>Larotrectinib has the potential to benefit a broad range of patients with TRK fusion-positive cancers, particularly those who may have limited options with conventional treatments due to other health conditions. Its oral formulation makes it especially suitable for patients with mobility challenges, difficulties attending frequent hospital visits, or dexterity limitations that make intravenous therapies more challenging.</p> <p>Patients with comorbidities that make traditional chemotherapy or radiotherapy riskier may also benefit from larotrectinib's targeted mechanism, which generally results in fewer systemic side effects. While all patients should be assessed individually, the evidence suggests that larotrectinib offers an effective and well-</p>                                                                                                                                                                                                                                                                                                                             |

Patient expert statement

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | tolerated treatment option for patients who might otherwise struggle with standard therapies, allowing them to maintain a better quality of life during treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>12. Are there any potential equality issues that should be taken into account when considering NTRK fusion-positive advanced solid tumours and larotrectinib? Please explain if you think any groups of people with this condition are particularly disadvantaged</b></p> <p>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics</p> <p>More information on how NICE deals with equalities issues can be found in <a href="#">the NICE equality scheme</a><br/><a href="#">Find more general information about the Equality Act and equalities issues here.</a></p> | <p>As a patient representative, my view is when considering NTRK fusion-positive advanced solid tumours and larotrectinib, equality issues are relatively limited because the genetic alteration, NTRK fusion, can occur across a wide range of tumour types and patient demographics. This means larotrectinib has the potential to benefit people regardless of age, sex, race, or other protected characteristics.</p> <p>However, there could be potential inequalities in access, particularly if certain groups are less likely to be offered genomic testing to identify NTRK fusions. For example, patients in regions with limited access to molecular diagnostics, older adults, or those with less frequent interaction with specialist oncology services could face barriers. Despite this, larotrectinib's targeted mechanism and generally well-tolerated safety profile make it a treatment that can be widely beneficial and inclusive once patients are correctly identified.</p> <p>Overall, larotrectinib offers an important opportunity to deliver effective, personalised cancer care across diverse populations, supporting equity in treatment outcomes for all patients with NTRK fusion-positive tumours.</p> |
| <p><b>13. Are there any other issues that you would like the committee to consider?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>Yes. I would like the committee to consider the importance of timely access to genomic testing to identify NTRK fusion-positive tumours. Without this, patients who could benefit from larotrectinib may not be identified. I would also highlight the significant impact on quality of life: larotrectinib is generally well-tolerated and can provide meaningful symptom relief and hope for patients with advanced cancers.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Patient expert statement



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|  | Ensuring equitable access to both testing and treatment would help deliver personalised care and improve outcomes for all eligible patients. |
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## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I was diagnosed with an aggressive GIST that progressed despite standard treatment and required major surgery with a long, difficult recovery.
- When the disease recurred, I faced the prospect of further life-altering surgery until genomic testing revealed a rare NTRK3 fusion and led to treatment with larotrectinib.
- This ongoing targeted therapy rapidly is shrinking my tumour (relapse May 2025 - 35mm x 20mm and now 17mm x 09mm), avoiding additional surgery, preserved vital organs, and significantly improving my quality of life.
- Despite manageable side effects, larotrectinib is allowing me to regain physical strength, emotional stability, and continue my professional and personal life.
- As a Patient Expert, I hope to use my lived experience to support compassionate, evidence-based decisions that improve access to life-changing treatments for people with rare cancers across the NHS.

Thank you for your time.

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Patient expert statement

## **Patient Statement (Larotrectinib) – Stephen Bennett**

Following her diagnosis of renal cancer in 2017, I watched my Mother-in-law fight so hard against the disease. Bit by bit, day by day, cancer took more and more of her life away until she had nothing left to give.

In her final 12 months of her life, I watched as she tried trial drug after trial drug. One made her so sick that she barely ate for days. One made her feet blister so badly that a once very strong and proud Scottish woman had to resort to being pushed round in a wheelchair. And all for what? The hope of an extra few months or maybe just weeks or days of life? I admired her strength and determination but I often questioned whether I would personally put myself through that same torture if I were ever to find myself in that situation. She wanted more time with her family and perhaps in a small way she got that. But the hardest thing for my wife and her family was seeing their mum struggling so much and knowing there was nothing they could really do to help her.

Then came my youngest daughter's diagnosis. To say it completely shattered my world as I knew it, would be an understatement. Seeing my mother-in-law have to relentlessly fight this disease was hard but now I had to do it for my 6-year old daughter too. The chemo treatment was brutal. The endless trips to theatre were terrifying. The whole experience was harrowing and traumatic for us all. But somehow, somehow, against all the odds, she survived. If you really want to know what it is like to live through that experience, please read my book. I urge you to. In fact, I beg you to read it. In my opinion, anybody making decisions about cancer treatment in this country should try to walk in the shoes of a patient or their family for just one day and you will understand just what it takes from you and how important hope becomes.

Cancer took away 12 months of my daughter's education. It stopped her playing football. It took her hair (temporarily). It took her dignity. It took away her chance to ever have her own children. It took away some of her sparkle. But thankfully, and somewhat miraculously, it didn't take her life.

When we were told she had relapsed 12 months later, it was almost harder to take than the initial diagnosis. The sense of dread that filled me took over my life for weeks. The anticipation of trial drug after trial drug and watching my little girl suffer pain and sickness, just like her gran had. Was it fair to put her through that so that I could spend more time with her? Isn't that just selfish??

What I didn't expect was what Larotrectinib has actually given her.

Leah takes it twice a day. She still has her beautiful long teenage hair. She doesn't feel sick every day. She's now in year 9 and about to choose her options for her GCSEs. She is back to playing football. She lives about as normal as life as she can. She has regained her sparkle. We once again have hope.

I can't explain to you how important this medication is for Leah, for me, and for our wider family. It is quite simply a miracle drug and the thought of her not being able to access this medication is so unbearable that I couldn't possibly pass up the opportunity to come and talk to this group about it today.

There is a well-known saying "it's not the years in your life that matter but the life in your years"

I think that sums up perfectly why I feel Larotrectinib is so essential as an option for those who might be eligible. I have no idea how long this medication will continue to work, and I have no idea what I would do if it stopped, but I have my daughter back and have had her back for 5 years now thanks to this drug and that alone feels just miraculous.

# **EXTERNAL ASSESSMENT GROUP REPORT**

## **Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]**

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### **Produced by**

**York Technology Assessment Group**, University of York, Heslington, York, YO10 5DD

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None.

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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AL wrote the critical review of the clinical effectiveness evidence, including Section 1 (clinical issues), parts of Section 3 and contributed to the writing of Section 2.

JC performed the critical review of the economic analyses, undertook survival analysis, validated the EAG's economic model, and contributed to the writing of Section 4 and 5 of the report.

MP wrote Section 2 and parts of Section 3.

MH reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support.

KD provided methodological advice, commented on drafts of the report and reviewed the whole report, and takes responsibility for the report as a whole.

MW led the critical review of the economic analyses, conducted the EAG's additional analyses, and contributed to the writing of Sections 1, 4, and 5 of the report.

### **Note on the text**

All commercial-in-confidence (CON) data have been [REDACTED].

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## List of abbreviations

|          |                                                      |
|----------|------------------------------------------------------|
| AACR     | American Association for Cancer Research             |
| ABC      | Advanced Biliary Tract Cancer                        |
| AE       | Adverse Event                                        |
| b.d.     | Twice Daily                                          |
| BHM      | Bayesian Hierarchical Model                          |
| BMI      | Body Mass Index                                      |
| BOR      | Best Overall Response                                |
| BSA      | Body Surface Area                                    |
| BSC      | Best Supportive Care                                 |
| BTC      | Biliary Tract Cancer                                 |
| CADTH    | Canadian Agency for Drugs and Technologies in Health |
| CDF      | Cancer Drugs Fund                                    |
| CDF      | Cancer Drugs Fund                                    |
| CI       | Confidence Interval                                  |
| CMN      | Congenital Mesoblastic Nephroma                      |
| CNS      | Central Nervous System                               |
| CR       | Complete Response                                    |
| CRC      | Colorectal Cancer                                    |
| CS       | Company Submission                                   |
| CSR      | Clinical Study Report                                |
| CUP      | Cancer of Unknown Primary Origin                     |
| CQ       | Clarification Question                               |
| DCR      | Disease Control Rate                                 |
| DOT      | Duration of Therapy                                  |
| DSU      | Decision Support Unit                                |
| EAG      | External Assessment Group                            |
| ECOG     | Eastern Cooperative Oncology Group                   |
| EMA      | European Medicines Agency                            |
| ERG      | Evidence Review Group                                |
| EAR      | Evidence Assessment Report                           |
| ePAS9    | extended primary analysis set 9                      |
| EQ-5D    | EuroQoL 3-level health questionnaire                 |
| EQ-5D-5L | EuroQoL 5-level health questionnaire                 |
| ESMO     | European Society for Medical Oncology                |
| ESS      | Effective Sample Size                                |
| EU       | European Union                                       |
| FAS      | Full analysis set                                    |
| FDA      | Food and Drug Administration                         |
| FISH     | Fluorescence In Situ Hybridization                   |
| FOLFOX   | Folinic Acid, Fluorouracil and Oxaliplatin           |
| GENIE    | Genomics Evidence Neoplasia                          |
| GIST     | Gastrointestinal Stromal Tumour                      |
| GLH      | Genomic Laboratory Hub                               |
| HCRU     | Healthcare Resource Use                              |
| HMF      | Hartwig Medical Foundation                           |
| HR       | Hazard ratio                                         |
| HRG      | Healthcare Resource Group                            |
| HRQoL    | Health-related quality of life                       |
| HTA      | Health Technology Appraisal                          |
| ICER     | Incremental Cost-Effectiveness Ratio                 |
| IHC      | Immunohistochemistry                                 |

|         |                                                                                                                                   |
|---------|-----------------------------------------------------------------------------------------------------------------------------------|
| IFS     | Infantile Sarcoma                                                                                                                 |
| IPD     | Individual Patient Data                                                                                                           |
| IPTW    | Inverse Probability of Treatment Weighting                                                                                        |
| IQR     | Interquartile range                                                                                                               |
| IRC     | Independent Review Committee                                                                                                      |
| IRS     | Intergroup Rhabdomyosarcoma Study                                                                                                 |
| ITT     | Intention to Treat                                                                                                                |
| IV      | Intravenous                                                                                                                       |
| KM      | Kaplan Meier                                                                                                                      |
| LOT     | Line Of Therapy                                                                                                                   |
| LY      | Life Year                                                                                                                         |
| LYG     | Life Years Gained                                                                                                                 |
| MAIC    | Matching-Adjusted Indirect Comparison                                                                                             |
| MD      | Mean Difference                                                                                                                   |
| MHRA    | Medicines and Healthcare Products Regulatory Agency                                                                               |
| MMRM    | Mixed-Model Repeated-Measures analysis                                                                                            |
| N       | Number Of Patients                                                                                                                |
| NA      | Not Applicable                                                                                                                    |
| NC      | Not collected                                                                                                                     |
| NE      | Not estimated                                                                                                                     |
| NGS     | Next Generation Sequencing                                                                                                        |
| NHS     | National Health Service                                                                                                           |
| NHS EED | National Health Service Economic Evaluation Database                                                                              |
| NHSE    | NHS England                                                                                                                       |
| NICE    | National Institute for Health and Clinical Excellence                                                                             |
| NMA     | Network Meta-Analysis                                                                                                             |
| NR      | Not Reported                                                                                                                      |
| NSCLC   | Non-Small Cell Lung Cancer                                                                                                        |
| NTRK    | Neurotrophic Tyrosine Receptor Kinase                                                                                             |
| ON-TRK  | Prospective non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib |
| OR      | Odds Ratio                                                                                                                        |
| ORR     | Objective Response Rate                                                                                                           |
| OS      | Overall Survival                                                                                                                  |
| OWSA    | One Way Sensitivity Analysis                                                                                                      |
| PAS     | Patient Access scheme                                                                                                             |
| pCR     | Pathological Complete Response                                                                                                    |
| PD      | Progressive Disease                                                                                                               |
| PedsQL  | Paediatric Quality of Life Inventory                                                                                              |
| PfC     | Points for Clarification                                                                                                          |
| PFS     | Progression Free Survival                                                                                                         |
| PFS2    | Second progression-free survival                                                                                                  |
| PH      | Proportional Hazards                                                                                                              |
| PICOS   | Population, Intervention, Comparator, Outcomes, Study Design                                                                      |
| PR      | Partial Response                                                                                                                  |
| PRO     | Patient related outcomes                                                                                                          |
| PredI   | Prediction Interval                                                                                                               |
| PPS     | Post-progression Survival                                                                                                         |
| PS      | Performance Status                                                                                                                |
| PSA     | Probabilistic Sensitivity Analysis                                                                                                |
| PSM     | Partitioned Survival Model                                                                                                        |
| PSS     | Personal Social Services                                                                                                          |
| PSSRU   | Personal Social Services Research Unit                                                                                            |



|       |                                                  |
|-------|--------------------------------------------------|
| q.d.  | Once Daily                                       |
| QALY  | Quality-Adjusted Life Year                       |
| RNS   | Ribonucleic Acid                                 |
| RCT   | Randomised Controlled Trial                      |
| RMST  | Restricted Mean Survival Time                    |
| RR    | Response Rate                                    |
| RWE   | Real World Evidence                              |
| SACHA | SACHAxLaro study                                 |
| SACT  | Systemic Anti-Cancer Therapy data set            |
| SAEs  | Serious adverse events                           |
| SAF   | Safety Analysis Set                              |
| SAP   | Statistical Analysis Plan                        |
| SAS3  | supplementary analysis set 3                     |
| SD    | Standard Deviation                               |
| SD    | Stable Disease                                   |
| SG    | Standard gamble                                  |
| SLR   | Systematic Literature Review                     |
| SoC   | Standard of Care                                 |
| STA   | Single Technology Appraisal                      |
| STS   | Soft Tissue Sarcoma                              |
| TA    | Technology Appraisal                             |
| TEAE  | Treatment Emergent Adverse event                 |
| TP    | Transition probability                           |
| TRAE  | Treatment Related Adverse Event                  |
| TRK   | Tyrosine Receptor Kinase                         |
| TTD   | Time to Treatment Discontinuation                |
| TTNT  | Time to Next Treatment                           |
| TTO   | Time trade-off                                   |
| Tx    | stage cannot be assessed                         |
| UK    | United Kingdom                                   |
| USA   | United States of America                         |
| VIT   | Vincristine, Irinotecan and Temozolomide regimen |
| WGS   | Whole Genome Sequencing                          |

# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

## 1.1 Overview of the EAG's key issues

**Table 1 Summary of key issues**

| ID[6292] | Summary of issue                                                                                                                                                                                                                       | Impact on results | Report sections             |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------|
| 1        | The trial evidence has limited applicability to the NHS.                                                                                                                                                                               | Large/unknown     | 3.2, 3.3, 3.6, 4.2.3, 4.2.5 |
| 2        | The trial evidence does not support the assumption of a common response across tumour types.                                                                                                                                           | Large             | 3.2.2, 3.2.4, 4.2.5         |
| 3        | The magnitude of survival benefit from larotrectinib in the trial evidence is uncertain.                                                                                                                                               | Unknown           | 3.2.4.2                     |
| 4        | The impact of the limitations of the SACT evidence on cost-effectiveness estimates is uncertain                                                                                                                                        | Unknown           | 3.3.1.1, 3.3.3.1, 5.2.2     |
| 5        | The internal validity of the MAICs and applicability to the NHS are significantly limited.                                                                                                                                             | Large/unknown     | 3.4                         |
| 6        | The optimal approach to economic modelling remains uncertain. No single approach offers a robust, internally valid estimate of comparative effectiveness and cost effectiveness for larotrectinib that are applicable to NHS practice. | Large             | 1.6, 4.2.2, 4.2.5, 5.2.2    |
| 7        | Heterogeneity in cost-effectiveness estimates across key subgroups is not captured.                                                                                                                                                    | Unknown           | 4.2.2, 4.2.5,               |
| 8        | Modelled health state utilities may not reflect the quality of life of an NHS-relevant population.                                                                                                                                     | Large             | 4.2.6, 5.2.2                |
| 9        | The benefits of potentially significant subsequent therapy use (e.g. systemics/TKIs, surgery) in the larotrectinib trials has not been accounted for in the economic model, and is unlikely to reflect NHS practice.                   | Unknown           | 4.2.5, 4.2.6, 5.2.2         |
| 10       | QALY weights for severity are calculated and applied inappropriately.                                                                                                                                                                  | Large             | 4.2.2, 4.2.4, 5.3           |

MAIC: Matching Adjusted Indirect Comparison. NHS: National Health Service. ORR: Overall Response rate. OS: Overall Survival. PD: Progressive Disease. PFS: Progression Free Survival. QALY: Quality Adjusted Life Years. SACT: Systemic Anti-Cancer Data set.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The tumour site distribution and baseline characteristics should be based on the SACT dataset population.
- Larotrectinib progressed disease (PD) utility based on a weighted average of standard of care PD utilities (excluding non-reference case values).
- Health state resource use estimates for CNS/glioma are based on TA977.
- Oral treatment administration costs should be included (SB11Z).

The EAG prefers that issues relating to generalisability of the trial data and construction of an appropriate comparison with SoC be explored through the consideration of alternative modelling approaches and otherwise adopting the alternative assumptions above. The EAG produces three alternative base cases described in further detail below.

## ***1.2 Overview of key model outcomes***

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the duration of progression-free survival and overall survival
- Improving health-related quality of life in each given health state relative to the standard of care
- Reducing the burden of adverse events.

Overall, the technology is modelled to affect costs by:

- Higher treatment acquisition costs
- Longer time on treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- Modelling the costs and outcomes of the tumour sites observed in the SACT dataset rather than the larotrectinib trial under any model structure
- Constructing the efficacy of the standard of care arm using non-responders from the larotrectinib trials
- Assuming patients on larotrectinib and standard of care share a common utility in the progressed disease health state
- The method used to derive and apply severity weights to QALY gains on larotrectinib.

### 1.3 EAG's key issues

#### Issue 1 Applicability of trial evidence to the NHS

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report sections</b>                                                                  | 3.2, 3.3, 3.6, 4.2.3, 4.2.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Description of issue and why the EAG has identified it as important</b>              | <p>The patient and disease characteristics of the trial population differed substantially from the population of patients treated with larotrectinib via the Cancer Drugs Fund (CDF) presented in the Systemic Anti-Cancer Data set (SACT), including exposure to prior lines of systemic therapy (LOT) and distribution of tumour types.</p> <p>Although overall response rates (ORR) were numerically higher in SACT compared with the trial evidence, CS analyses showed evidence of substantial heterogeneity in response (see Issue 2). OS results [REDACTED] to larotrectinib in the trial evidence. Differences in reporting, study design, disease natural history, prognosis, exposure to subsequent therapies, and data maturity between the two sources significantly limit their comparability. Overall, the EAG believes that the trial evidence, which informs the company's model, has limited applicability to the NHS.</p> |
| <b>What alternative approach has the EAG suggested?</b>                                 | <p>The EAG requested from the company that they perform a matching-adjusted indirect comparison using data from the SACT to inform the efficacy of larotrectinib. Individual participant data (IPD) from SACT were requested by the company following an EAG request, but was not available due to NHSE restrictions.</p> <p>The EAG has implemented a scenario which integrates SACT pseudo-IPD directly into the model to represent the effectiveness of larotrectinib, with naïve comparisons made against literature sources.</p>                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>                 | <p>In isolation, a scenario comparing SACT against a weighted collection of tumour-specific literature sources results in a small reduction (-[REDACTED]) in the company's base-case ICER. Using evidence on NTRK fusion-positive SoC patients in the comparator arm of the VICTORIA MAIC (Brose <i>et al.</i>) results in an increase of [REDACTED] on the company's base case. The relative effectiveness and cost-effectiveness results of the proposed EAG scenario are therefore highly uncertain.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Could any additional evidence or analyses be provided to resolve this key issue?</b> | <p>A scenario that incorporates an indirect comparison between SACT and comparator evidence, using up to date methods, ideally IPD meta-regression where full IPD is available, or otherwise multilevel network meta-regression (ML-NMR), may partially resolve this issue. The EAG acknowledge that SACT data currently includes a limited number of patients, and that any unanchored indirect comparison would be limited, as it would be unlikely to account for all relevant prognostic factors and treatment effect modifiers.</p>                                                                                                                                                                                                                                                                                                                                                                                                    |

CDF: Cancer Drugs Fund. EAG: External Assessment Group. IPD: Individual Patient Data. LOT: Line of Therapy. MAIC: Matching Adjusted Indirect Comparison. NHS: National Health Service. NHSE: NHS England. NTRK: Neurotrophic Tyrosine Receptor Kinase. SACT: Systemic Anti-Cancer Data set.

## Issue 2 The trial evidence does not support the assumption of a common response across tumour types

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                                   | 3.2.2, 3.2.4, 4.2.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Description of issue and why the EAG has identified it as important</b>              | <p>The company's Bayesian hierarchical model (BHM) analysis of the trial evidence showed clear evidence of heterogeneity in ORR by tumour type, although most of the substantial heterogeneity found by the BHM was unexplained.</p> <p>An ORR that does account for this heterogeneity was estimated as █% (95% PredI: █% to █%) in the main analysis (which excluded primary CNS patients). This is numerically █ to larotrectinib █ than the unadjusted main pooled analyses (ORR 65% [95% CI 59% to 70%]). Subgroup analyses showed wide variation in response rates across tumour types and several patient characteristics.</p> <p>The EAG is concerned that pooled estimates across a wide range of patient groups (such as adults and children) and disease characteristics (including all tumour types) may not be meaningful for decision making. Given the prognostic heterogeneity across multiple tumour types, pooled PFS and OS estimates from the trial evidence are unlikely to be reliable to inform decisions across tumour types in an NHS population.</p> |
| <b>What alternative approach has the EAG suggested?</b>                                 | The EAG presents an alternative response-based model structure using tumour-specific response rates derived from the BHM. This better represents heterogeneity in site-specific outcomes, and allows tumour types to be reweighted to better represent the distribution of sites treated with larotrectinib in SACT. This approach also allows more accurate attribution of QALY weights.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>                 | The EAG's implementation of a response-based model with tumour-specific predicted response rates generates an ICER of █ with a severity modifier of 1.0, an increase of █ on the corrected company base case.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Could any additional evidence or analyses be provided to resolve this key issue?</b> | Evidence that further explains the sources of heterogeneity in NTRK fusion positive patients on larotrectinib may help to resolve this issue. Presenting and incorporating into the model disaggregated survival outcomes, at the very least by presence of primary CNS and by age group (adults, children), and BHM response rates separated for adults and children, may help to address this issue.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

BHM: Bayesian Hierarchical Model. CI: Confidence Interval. EAG: External Assessment Group. ORR: Overall Response rate. OS: Overall Survival. PFS: Progression Free Survival. QALY: Quality Adjusted Life Years. SACT: Systemic Anti-Cancer Data set.

## Issue 3 The magnitude of survival benefit from larotrectinib in the trial evidence is uncertain

|                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                      | 3.2.4.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Description of issue and why the EAG has identified it as important</b> | <p>Despite the updated data cut, OS trial data is still immature, with median OS not estimable in primary-CNS (SAS3) and non-primary CNS (ePAS9) populations. The durability of the survival benefit observed in the trial evidence is therefore uncertain. Post-progression outcomes are uncertain due to lack of maturity and there is potential confounding due to high rates of subsequent therapy use in the trial.</p> <p>The lack of control arms or comparators in the trial evidence make it difficult to determine the true magnitude of benefit of larotrectinib relative to standard of care.</p> |
| <b>What alternative approach has the EAG suggested?</b>                    | Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>What is the expected effect on the cost-effectiveness estimates?</b>                 | Sources of OS evidence adjusted for the potential confounding effect of subsequent treatment use is likely to reduce QALY gain on larotrectinib compared with the company's base case. SACT data indicate that OS may be less favourable to larotrectinib in an NHS setting. Cost-effectiveness of larotrectinib may therefore be overestimated.<br><br>Longer follow-up may reduce the influence of extreme post-progression survival predictions resulting from the immaturity of current OS data, which would reduce QALY gains and increase the ICER for larotrectinib. |
| <b>Could any additional evidence or analyses be provided to resolve this key issue?</b> | Further data cuts from studies 20289 and 20290 and robust analyses that account for the confounding impact of subsequent therapies may partly resolve this issue. However, the lack of control arm in the trial evidence will remain a limitation of the existing trial evidence.                                                                                                                                                                                                                                                                                           |

HRQoL: Health Related Quality of Life. NE: Not Estimated. OS: Overall Survival.

#### Issue 4 The impact of the limitations of the SACT evidence on cost-effectiveness estimates is uncertain

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                                   | 3.3.1.1, 3.3.3.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Description of issue and why the EAG has identified it as important</b>              | The SACT provided mature time to treatment discontinuation (TTD) and OS data in an NHS context. However, the sample size of the SACT at the latest available data cut is small, and most solid tumours are represented by few or no patients. This limited statistical power and the ability to detect differences across tumour types and other patient and disease characteristics. As with the trial evidence, ORR estimates were pooled across a wide range of tumours, and TTD and OS were pooled across a wide range of patient and disease characteristics and are likely to be affected by prognostic heterogeneity. Given the evidence of heterogeneity (see issue 2), the EAG is concerned that pooled estimates from the SACT are limited in their ability to inform decisions across all tumour types. The SACT data is not included in the company model, but is incorporated in EAG base cases. |
| <b>What alternative approach has the EAG suggested?</b>                                 | See Issue 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>                 | The effect of this issue on cost-effectiveness estimates is uncertain. The limited sample size of SACT means that decisions for the whole population based on this dataset necessarily assume a site-agnostic treatment effect in unrepresented tumour types.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Could any additional evidence or analyses be provided to resolve this key issue?</b> | See Issue 1<br><br>Although BHM analysis of the SACT data could theoretically help to quantify heterogeneity in ORR in an NHS context and provide estimates that account for heterogeneity, the EAG is concerned that the required sample size for such analyses is unlikely to be reached. Therefore, synthesis methods that integrate information from the SACT dataset into a wider evidence network could be considered.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

NHS: National Health Service. SACT: Systemic Anti-Cancer Data set.

## Issue 5 The MAICs have limited internal validity and applicability to the NHS

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                                   | 3.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Description of issue and why the EAG has identified it as important</b>              | <p>The lack of control arm in the trial evidence meant that all comparisons between larotrectinib and standard of care therapies were based on four unanchored MAICs comparing subsets of the trial evidence against observational comparator evidence. Two of these MAICs (VICTORIA for adults, and EPI-VITRAKVI for 0-21 year old patients) used full IPD and were included in the company's base case.</p> <p>The tumour types included in the MAICs represent a small subset of all solid tumour types that may harbour an NTRK fusion. VICTORIA included only five tumour types (soft tissue sarcoma, colorectal, lung [non-small cell], salivary gland and thyroid cancers), and EPI-VITRAKVI only one (infantile fibrosarcoma). Therefore, the applicability of the MAICs to most NTRK fusion positive solid tumours is unknown.</p> <p>Tumour types with more favourable ORRs with larotrectinib were over-represented, and conversely, tumour types with lower ORR (notably primary CNS, represented by 35% of the SACT) were excluded. The EAG is therefore concerned that the MAICs are at high risk of patient selection bias. The magnitude and direction of this bias are difficult to assess, notably because this will depend on the efficacy of relevant SoC therapies.</p> <p>None of MAICs were able to account for all observed and unobserved prognostic factors and treatment effect modifiers (a key assumption in unanchored MAICs), which limits their validity. All MAICs violated the proportional hazard (PH) assumption, used sub-optimal analytical methods, had imprecise results due to limited sample sizes, and potential limitations associated with comparing trial against non-trial data. Other concerns included the risk of historical bias, which may negatively impact outcomes of comparator cohorts.</p> |
| <b>What alternative approach has the EAG suggested?</b>                                 | See Issue 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>                 | See Issue 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Could any additional evidence or analyses be provided to resolve this key issue?</b> | <p>An indirect comparison between SACT and SoC evidence may partially resolve this issue, see Issue 1 for further details.</p> <p>In addition, a new, well reported indirect comparison that includes all trial evidence at the latest data cut, against standard of care evidence identified through a robust systematic review may partially resolve the issue of selection bias, using up to date methods (see Issue 1). However, this would be unlikely to account for all relevant prognostic factors and treatment effect modifiers, and would be limited by other issues affecting the trial evidence (see issues 1-3).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

EAG: External Assessment Group. IFS: Infantile Fibrosarcoma. MAIC: Matching Adjusted Indirect Comparison.

## Issue 6 The optimal approach to economic modelling remains uncertain

|                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 4.2.2, 4.2.5, 5.2.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>The MAIC-based partitioned survival model based on a pooled larotrectinib arm and assuming a site-agnostic treatment effect has several flaws. Therefore, the generalisability of cost-effectiveness estimates to the NHS is limited. The application of HRs from the MAIC, which inherently violates the PH assumption, is also inappropriate. The weighting of separately modelled adult and paediatric outcomes introduces substantial uncertainty due to the explicit modelling of clinically implausible post-progression survival in paediatric patients.</p> <p>The company's response-based model using the BHM may address some of these issues, but the company's implementation does not allow treatment response to be varied by tumour site, or the tumour type distribution of the population to be matched to that of the NHS.</p> <p>The company argue that using larotrectinib non-responder outcomes to represent SoC may overestimate its effectiveness due to the clinical benefit of achieving 'stable disease' as a best response. Whilst this argument may be valid in the context of a last-line comparison (as in TA630), the present appraisal largely compares larotrectinib to second-line systemic therapies, which are likely more efficacious than the hypothetical SoC considered in TA630. This analysis also includes cure-like post-progression survival outcomes for paediatric patients, which may overestimate the efficacy of larotrectinib as used in the NHS.</p> <p>The other modelling frameworks implemented by the company do not address issues of applicability of the trial data, immaturity of OS data for paediatric patients, heterogeneity in population makeup and treatment response, and the attribution of severity weights to QALYs generated on larotrectinib under the company's preferred approach.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | <p>No single approach offers a robust estimate of effectiveness and comparative cost-effectiveness for larotrectinib that is applicable to NHS practice. The EAG proposes three alternative structural scenarios, each of which have distinct strengths and limitations (see further discussion in Section 1.6):</p> <ul style="list-style-type: none"> <li>• A MAIC-based analysis which uses survival models based on pooled data for adults and paediatric patients, with SoC arm based on the VICTORIA MAIC.</li> <li>• Response-based model using BHM predicted response rate results by tumour site</li> <li>• A naïve comparison of SACT data with the naïve literature-based comparator or Brose <i>et al.</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | <p>The company's base-case ICER is £■■■■ using a QALY multiplier of 1.0. Using the pooled population MAIC approach increases the ICER to £■■■■. Using the tumour-specific BHM response-based model increases the ICER to £■■■■. Using the comparison of SACT with a reweighted naïve literature comparator reduces the ICER to £■■■■. The naïve comparison of SACT with Brose <i>et al.</i> increases the ICER to £■■■■.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | <p>The EAG's preference would be for a model incorporating a formal ITC with population adjustment methods including the SACT data against IPD from SoC sources (see Issue 1) to produce a more internally and externally valid comparison with SoC.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

MAIC: matching-adjusted indirect comparison. NHS: National Health Service. HR: hazard ratio. PH: proportional hazards. SoC: standard of care. BHM: Bayesian hierarchical model. TA: technology appraisal. OS: overall survival. QALY: quality-adjusted life year. ICER: incremental cost-effectiveness ratio. SACT: Systemic Anti-Cancer Therapy dataset. ITC: indirect treatment comparison. IPD: individual patient data.



## Issue 7 Heterogeneity in cost-effectiveness estimates across key subgroups is not captured

|                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 4.2.2, 4.2.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>There is a high degree of heterogeneity in disease natural history, prognosis, treatment pathways, and treatment effectiveness across the patient population. The use of a single aggregated ICER obscures potentially extreme variation in the cost-effectiveness of larotrectinib between subgroups. In particular, efficacy data on primary CNS tumours in the larotrectinib trials suggest significantly poorer treatment outcomes than for other tumour sites, particularly in adult patients. See also Key Issue 2.</p> <p>If larotrectinib is highly cost-ineffective in a prospectively identifiable subgroup, this should be presented transparently, particularly if lack of efficacy is a key driver of cost-ineffectiveness. Given the prevalence of primary CNS and brain tumours in the SACT dataset, this may be particularly relevant to NHS practice.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | Cost-effectiveness analysis in key clinical subgroups may be informative for decision making. If a single ICER is used as the basis of decision making across the population, disaggregated results demonstrating broader cost-effectiveness should still be presented. This should at a minimum explore the cost-effectiveness of larotrectinib in primary CNS tumours (adult and paediatric), non-CNS paediatric tumours, and adult non-CNS tumour sites.                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | The cost-effectiveness of larotrectinib is likely to be higher in non-CNS tumour sites in adult and paediatric patients. Larotrectinib will be less cost-effective in sites where it is less efficacious.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | <p>Subgroup analysis using subgroup-specific outcome and utility data from the larotrectinib trials for the following groups:</p> <ul style="list-style-type: none"> <li>• Adult patients with primary CNS tumours</li> <li>• Paediatric patients with primary CNS tumours</li> <li>• Adult patients excluding those with primary CNS tumours</li> <li>• Paediatric patients excluding those with primary CNS tumours</li> </ul> <p>However, these analyses are unlikely to be sufficient to address all sources of heterogeneity, as ORR heterogeneity is substantial and mostly unexplained.</p>                                                                                                                                                                                                                                                                            |

EAG: Evidence Assessment Group. ICER: incremental cost-effectiveness ratio. CNS: central nervous system. SACT: Systemic Anti-Cancer Therapy dataset. NHS: National Health Service. ORR: overall response rate.

## Issue 8 Health state utilities may not reflect the quality of life of an NHS-relevant population.

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|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 3.2.4.7, 4.2.6, 5.2.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>The company's model applies treatment-specific health state utilities. This may be appropriate for larotrectinib, reflecting a potentially lower toxicity burden and higher likelihood of complete response relative to SoC, but the magnitude and duration of treatment benefit in the PD health state is inappropriate. This assumption is a key driver of the cost-effectiveness of larotrectinib. The EAG has significant concerns about the validity of the HRQoL evidence collected in the trial.</p> <p>Larotrectinib: Utilities derived from trial HRQoL data show a very small decrement between pre- and post-progression states (■■■■), with a sustained and comparatively high PD (PD) utility. These values are higher than most published utilities for NTRK inhibitors and considerably higher than those applied to SoC. Data informing the PD health state is disproportionately informed by paediatric patients, who largely had tumour types with a typically higher HRQoL. The PD utility may be inflated by extensive use of subsequent systemic therapies and other non-palliative interventions in the larotrectinib trials, which are not representative of NHS practice. PD utilities collected in the trial may therefore be reflective of PFS2 or slowed progression on further lines of systemic therapy, and may overestimate the utility of adult patients.</p> <p>SoC: Comparator utilities are derived from a heterogeneous mixture of sources, including non-reference-case vignette-based utilities and older studies that may not reflect current NHS practice. For some tumour sites, utilities are based solely on adult populations or on proxy conditions, which may underestimate HRQoL on SoC and bias results in favour of larotrectinib.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | <p>For larotrectinib: Apply a common PD utility across treatment arms, informed by literature-based NTRK inhibitor utilities consistent with the NICE reference case, with the caveat that HRQoL immediately after progression on larotrectinib may be higher than on SoC.</p> <p>For SoC: Derive base utility from a weighted average of EQ-5D or appropriately mapped patient-reported values. Explore scenarios separating adult and paediatric utilities, particularly for primary CNS and soft-tissue sarcoma populations.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | <p>Using a shared PD utility for larotrectinib and SoC consistently increases the ICER across alternative model structures. Under the company's base-case assumptions, the deterministic ICER is increased from £■■■■ to £■■■■ using a shared PD utility (treatment effect in PFS is retained).</p> <p>Omitting non-reference case utility values from the weighted averages has a small independent impact on the ICER.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | <p>More recent utility data in the comparator population (particularly in paediatric patients) may be informative in deriving more appropriate utility values for SoC and larotrectinib, particularly in any cost-effectiveness analyses that separate adult and paediatric patients. Larotrectinib utilities separated according to adult and paediatric patients would also be informative for subgroup analysis.</p> <p>Alternative sources of SoC utilities for tumour sites currently adopting non-reference case methods may be informative, although this is unlikely to be a key driver of cost-effectiveness.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

EAG: Evidence Assessment Group. SoC: standard of care. PD: progressed disease. HRQoL: health-related quality of life. NTRK: neurotrophic tyrosine receptor kinase. NHS: National Health Service. PFS2: progression-free survival on subsequent therapy. EQ-5D: EuroQol 5-Dimension. CNS: central nervous system. ICER: incremental cost-effectiveness ratio.

## Issue 9 Subsequent therapies not costed and/or effects not accounted for

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|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 4.2.5, 4.2.6, 5.2.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>The company's model assumes that all patients receive BSC following progression. A large proportion of patients received further lines of systemic therapy (including other TRK inhibitors) after progression in the larotrectinib trials, alongside surgery and radiotherapy in a minority. Only a small proportion of patients received subsequent therapies in the SACT dataset. This may be a potential contributor to the modelled magnitude of post-progression survival benefit. The use of subsequent therapies was not accounted for through censoring or adjustment, nor were they costed. This means that the OS data in the larotrectinib trial and post-progression utility data may be inflated by patients benefiting from effective therapies not routinely used in the NHS.</p> <p>These subsequent treatments were not costed and patients were not consistently censored, meaning their survival and HRQoL effects remain embedded in the outcome data informing the model.</p> <p>The company's model is therefore likely to overestimate QALY gain on larotrectinib relative to SoC possible in NHS practice.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | <p>The EAG proposes alternative approaches, including adjustment for treatment switching/informative censoring.</p> <p>The EAG considers the OS data collected in SACT to be more representative of influence of subsequent therapies on survival outcomes in NHS practice. The EAG would prefer a formal ITC between SACT and SoC which accounts for population differences to generate a comparator arm. The subsequent therapies used in SACT should be costed in the model if these data are available.</p> <p>A state transition model (STM) may allow for the relationship between progression and mortality observed in the SACT dataset to be applied to more granular PFS data in the larotrectinib trial, whilst avoiding the use of potentially confounded OS data. This analysis should adjust the larotrectinib trial data to be more reflective of the tumour type distribution in SACT.</p>                                                                                                                                                                                                                                |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | <p>Adjustment for the use of subsequent therapies in the larotrectinib trials is likely to reduce the modelled OS benefit on larotrectinib. As the company applies HRs from a MAIC to estimate SoC outcomes, this means OS on SoC will also be reduced.</p> <p>The EAG prefers the use of SACT data to model the efficacy of larotrectinib. Total QALYs on larotrectinib are reduced from [REDACTED] in the company's base case to [REDACTED] using SACT outcomes.</p> <p>An unanchored comparison of SACT data with the naïve literature comparator sources (reweighted to match the SACT tumour distribution) results in a reduction of the company's base-case ICER from £[REDACTED] to £[REDACTED] using a QALY multiplier of 1.0. Using the VICTORIA comparator arm (Brose <i>et al.</i>) to construct the SoC arm increases the ICER to £[REDACTED].</p>                                                                                                                                                                                                                                                                            |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | <p>An adjusted ITC between SACT and an appropriate source of comparator data could provide a better comparison of NHS-relevant outcomes with SoC. Specific data on subsequent therapy use from SACT should be used to model subsequent treatment costs, if available.</p> <p>Adjustment of larotrectinib OS outcomes for use of subsequent therapies may produce more generalisable OS estimates.</p> <p>A STM approach using transition probabilities between progression and mortality from SACT may allow fuller use of the larotrectinib trial data and avoid the confounding effect of subsequent therapies, but tumour type distribution must be accounted for.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

BSC: best supportive care. TRK: tropomyosin receptor kinase. SACT: Systemic Anti-Cancer Therapy dataset. NHS: National Health Service. OS: overall survival. HRQoL: health-related quality of life. QALY: quality-adjusted life year. SoC: standard of care. ITC: indirect treatment comparison. STM: state transition model. PFS: progression-free survival. HR: hazard ratio. MAIC: matching-adjusted indirect comparison.

## Issue 10 QALY weights for severity are calculated and applied inappropriately

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|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 4.2.2, 4.2.4, 5.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>The company calculates tumour-specific severity weights and applies these to QALY gains to each tumour type, based on a site agnostic treatment effect for larotrectinib. This approach upweights QALYs according to their prevalence in the trial population, rather than where the QALYs are generated.</p> <p>The aggregation of many different severity modifiers into a single ICER for the whole population lacks transparency, resulting in an effective severity weight of 1.60 for all patients with NTRK gene fusions. This risks substantially overestimating health gains, particularly in tumour types with a high estimated QALY shortfall but poor response to larotrectinib. The selection of tumour sites contributing to this aggregated severity modifier also strongly influences its magnitude, the company prefers that shortfall be based on the composition of the larotrectinib studies.</p> <p>NICE guidance on the application of the severity modifier indicates that, within a single decision space, a single severity modifier should normally be applied at the population level, based on a weighted average QALY shortfall, even where shortfall differs across subgroups.</p> <p>In scenarios using the company's naïve literature comparison as a source of SoC QALYs, the EAG prefers that the baseline characteristics of these studies are used rather than those of the larotrectinib trial, as this approach overestimates QALY shortfall. The company also calculates QALY shortfall independently of the modelled SoC QALYs, introducing a disconnect between assumptions around the efficacy of SoC in the cost-effectiveness results, and the calculated severity modifiers. QALY weighting is also applied incorrectly to total QALYs gained on both treatment options, rather than to incremental QALYs in the ICER calculation.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | <p>The EAG's preferred approach applies a single severity modifier at the population level, derived from a tumour type-weighted QALY shortfall reflecting internally consistent assumptions about SoC efficacy, utilities, and population characteristics, in line with NICE guidance. The EAG prefers shortfall analyses to be based on the tumour type distribution of the SACT population. In almost all scenarios, a severity weighting of 1.2 is applicable. However, there remain uncertainties around QALY shortfall particularly in the paediatric primary CNS tumour population.</p> <p>Key results are presented using fixed QALY weights of 1.0, 1.2, and 1.7. The EAG applies the chosen QALY multiplier only to incremental QALYs for larotrectinib. Where analyses incorporate tumour-specific outcomes (for example, in the responder-based model with site-specific ORRs), QALY gains are weighted according to the subgroups in which they arise.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | <p>The company's probabilistic base-case ICER increases from £■■■■ using their preferred severity weighting approach, to £■■■■ using a flat QALY weight of 1.2.</p> <p>In the EAG's tumour-site specific response-based model, the effective mean QALY weight decreases to 1.39, based on the SACT tumour-site distribution and responder-model SoC QALY gain. A flat severity modifier of 1.2 is applicable in all other EAG analyses. This results in a substantial increase in the ICERs for larotrectinib.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | <p>Robust evidence on the outcomes of patients with primary CNS tumours may demonstrate whether a higher severity modifier may be applicable.</p> <p>The composition of the NHS/SACT population by tumour type <i>and</i> age may allow more accurate calculation of overall QALY shortfall.</p> <p>The EAG considers it unlikely that a QALY weight of 1.7 could be applicable in the overall eligible population (or those treated in SACT).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

QALY: quality-adjusted life year. ICER: incremental cost-effectiveness ratio. NTRK: neurotrophic tyrosine receptor kinase. SoC: standard of care. NICE: National Institute for Health and Care Excellence. SACT: Systemic Anti-Cancer Therapy dataset. CNS: central nervous system. ORR: overall response rate.

## 1.4 Secondary issues identified by the EAG

### Issue 11 Omission of disease management costs for primary CNS tumours/glioma

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|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                               | 4.2.7.4, 5.2.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>The company sourced health state resource use estimates from previous NICE appraisals. TA23 was selected for primary CNS tumours, which did not estimate resource use consistently with contemporary NICE TAs. This appraisal assumed a single MRI-based cost for patients in the PFS health state, with no ongoing disease management costs.</p> <p>This is inconsistent with other modelled tumour types, and is likely to underestimate the health state costs for patients with primary CNS tumours.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | The EAG prefer to use costs based on TA977 in BRAF V600E mutation-positive glioma in children and young people, in which PFS patients have a monthly oncologist visit, full blood count, and echocardiogram. Patients in the PD health state have a monthly multi-professional visit and a specialist cancer nurse visit. This approach more closely aligns modelled health state costs with other tumour types.                                                                                                |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | The inclusion of these health state costs increases the company's base-case ICER from £■■■■ to £■■■■.                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | The EAG considers this issue resolved.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

TA: technology appraisal. CNS: central nervous system. MRI: magnetic resonance imaging. PFS: progression-free survival. PD: progressed disease. ICER: incremental cost-effectiveness ratio. EAG: Evidence Assessment Group.

### Issue 12 Exclusion of oral administration costs

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|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Report section</b>                                                      | 4.2.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Description of issue and why the EAG has identified it as important</b> | <p>In TA630, both the EAG and the Committee concluded that oral administration costs should be included in the model. The company excluded oral administration costs in the present submission, arguing that because larotrectinib is not a traditional oral chemotherapy, the SB11Z tariff does not reflect monitoring and dispensing requirements for larotrectinib.</p> <p>Regarding the applicability of the SB11Z tariff, NHSE advised the EAG that 'the same checks and expertise are needed for dispensing of any oral systemic anti-cancer therapy so the same tariff would apply for each dispensing'. Excluding this cost results in an underestimate of the total cost to the NHS of treatment with larotrectinib treatment, and introduces bias against intravenously-administered drugs which are modelled to incur an administration cost.</p> |
| <b>What alternative approach has the EAG suggested?</b>                    | The SB11Z tariff (£247) should be applied each treatment cycle for all orally administered systemic therapies to reflect the dispensing and monitoring requirements associated with ongoing larotrectinib treatment. This does not account for administration costs of the oral solution larotrectinib formulation, as relative usage information has not been provided.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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| <b>Report section</b>                                                               | 4.2.7                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | <p>The inclusion of oral administration costs for all orally administered treatments increases the ICER from £■■■■ to £■■■■ on the company base case.</p> <p>The omission of evidence on the use of the solution formulation of larotrectinib, and resulting exclusion of the higher per day cost of the use of this option, may mean the total costs of larotrectinib are underestimated.</p> |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | Evidence on the use of the larotrectinib oral solution formulation may be informative for more complete costing of treatment acquisition and administration costs for larotrectinib.                                                                                                                                                                                                           |

TA: technology appraisal. SB11Z: NHS chemotherapy delivery tariff code. NHSE: NHS England. NHS: National Health Service. EAG: Evidence Assessment Group. ICER: incremental cost-effectiveness ratio.

### Issue 13 Out of date drug unit costs

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| <b>Report section</b>                                                               | 4.2.7                                                                                                                                                                       |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>Many of the comparator drug costs sourced from eMIT by the company were out of date.</p> <p>This resulted in a small underestimate of total costs on SoC.</p>            |
| <b>What alternative approach has the EAG suggested?</b>                             | The EAG applied the most recent average unit costs to the NHS from eMIT and MPSC in alignment with the Price Tracker provided by NICE.                                      |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | The EAG applies this change as a correction to the company model. This results in an increase of £206 to total costs for SoC compared to the uncorrected company base case. |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | The EAG considers this issue resolved.                                                                                                                                      |

SoC: standard of care. eMIT: electronic Market Information Tool. NHS: National Health Service. MPSC: minimum price for standard chemotherapy. EAG: Evidence Assessment Group. NICE: National Institute for Health and Care Excellence.

### Issue 14 Underestimation of time on treatment on larotrectinib

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| <b>Report section</b>                                                      | 4.2.5, 4.2.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Description of issue and why the EAG has identified it as important</b> | <p>The company assumes that time to treatment discontinuation (TTD) is equivalent to PFS for larotrectinib, reasoning that clinicians would stop treatment at progression and that heavy censoring and lack of TTD data for SoC mean the separate modelling of these outcomes is inappropriate.</p> <p>The EAG considers this assumption unlikely to reflect NHS practice, and notes that TTD data in the trial indicated that many patients continued treatment beyond the point of progression. There are no stopping rules for larotrectinib, and clinical expert advice indicates that, as a well-tolerated option used late in the treatment pathway, larotrectinib may be continued beyond radiological progression where patients may experience continued clinical benefit. As a result, treatment duration on larotrectinib, and therefore treatment acquisition costs, are likely to be underestimated.</p> |

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| <b>What alternative approach has the EAG suggested?</b>                             | <p>The EAG assumes that observed treatment duration in the SACT dataset is equivalent to PFS in its scenarios which base the efficacy of larotrectinib on SACT data. This approach more accurately captures treatment costs for larotrectinib, but assumes ongoing benefit equivalent to patients remaining progression-free whilst on treatment. This approach may overestimate QALY gain on larotrectinib.</p> <p>The EAG suggests that analyses basing treatment costs directly on observed time-to-discontinuation data in the larotrectinib trial would be informative, for example through separate modelling of TTD or scenario analyses applying treatment costs beyond progression for a proportion of patients.</p> |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | Treatment costs on larotrectinib are likely to be underestimated using the company's approach. It is not possible to directly quantify the impact of using treatment duration data from SACT, as PFS is not separately reported.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | The impact of the company's assumption of a proxy relationship between PFS and TTD could be assessed through analyses which directly model TTD using data from the larotrectinib trials.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

TTD: time to treatment discontinuation. PFS: progression-free survival. EAG: Evidence Assessment Group. NHS: National Health Service. SoC: standard of care. SACT: Systemic Anti-Cancer Therapy dataset. QALY: quality-adjusted life year.

#### Issue 15 Probabilistic sensitivity analysis issues

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| <b>Report section</b>                                                               | 5.2.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Description of issue and why the EAG has identified it as important</b>          | <p>During validation of the PSA, the EAG identified a critical issue with Excel's recalculation behaviour whereby, after a number of iterations, the model repeatedly returned identical results, indicating that random parameter values were no longer being resampled and propagated through the model. This results from the high degree of complexity of the executable model, which samples uncertainty across all possible model structures regardless of the assumptions selected for a given analysis. A workaround implemented by the EAG resolves this issue in part, but the model complexity leads to very long PSA run-times (in excess of 3 hours for 1,000 iterations).</p> <p>As a result, only a limited number of PSA iterations could be run for each analysis, which may be insufficient to fully characterise parameter uncertainty. In addition, the computational burden prevented the EAG from exploring all plausible scenario analyses probabilistically.</p> |
| <b>What alternative approach has the EAG suggested?</b>                             | The EAG implemented a safeguard forcing a full rebuild of all calculation dependency trees at regular intervals during the PSA. This ensured random parameter values were correctly resampled and propagated through the model. A more robust solution would be a streamlined PSA approach using separate, simplified model files for individual model structures to avoid redundant sampling.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>What is the expected effect on the cost-effectiveness estimates?</b>             | The issue does not systematically bias the ICER in a known direction but impacts the reliability of probabilistic results, including estimates of decision uncertainty and the probability that larotrectinib is cost-effective. Results incorporating the full range of parameter values are not available for all scenarios.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Could any additional evidence or analyses be provided to resolve this issue?</b> | The model requires substantive redesign with removal of redundancy to resolve this issue.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

PSA: probabilistic sensitivity analysis. EAG: Evidence Assessment Group. ICER: incremental cost-effectiveness ratio.

### ***1.5 Company's modelling errors identified by the EAG***

The EAG reviewed the company's model in detail and applied the TECHNical Verification (TECH-VER) checklist for the company's base case model structure. There was insufficient time available to separately validate the model for each of the structures included in the company's scenario analyses.

The EAG noted no substantive technical errors in the deterministic model logic with the exception of the application of the severity modifier. The company applied QALY weighting for severity to total QALYs gained in each tumour site on both interventions, rather than only to incremental QALYs gained on larotrectinib, as per the NICE reference case. The EAG also corrects a number of drug unit costs according to the Price Tracker supplied by NICE. Together these corrections result in a small reduction in the ICER relative to the company base case.

The EAG also noted issues with the probabilistic sensitivity analysis, which were addressed in part, as discussed in Issue 15.

### ***1.6 Summary of EAG's preferred assumptions and resulting ICER***

As discussed in Key Issue 6, the EAG considers there to be no single model structure able to offer a robust estimate of both generalisable effectiveness and comparative cost effectiveness for larotrectinib in NHS practice. The EAG therefore presents three alternative base case models, each addressing different limitations in the available evidence and highlighting trade-offs between internal validity, applicability to NHS practice, and clinical plausibility. No single approach resolves all uncertainties but together may offer insights into the potential cost-effectiveness of larotrectinib in the NHS. However, it should be noted that the EAG's preference is for the analyses described in Section 1.3 to be provided in order to reduce decision uncertainty on a range of Key Issues. The three base case analyses all share the following preferred assumptions:

- The tumour site distribution and baseline characteristics are based on the SACT dataset population.
- Larotrectinib progressed disease (PD) utility is based on a weighted average of standard of care PD utilities (excluding non-reference case values).
- Health state resource use estimates for primary CNS/glioma are based on TA977.
- Oral treatment administration costs should be included (SB11Z).

The EAG considers a QALY multiplier of 1.2 to be applicable in each of the EAG base case analyses. The use of a tumour-site specific QALY weighting may be an appropriate alternative in EAG base case 2.



### **EAG base case 1: Pooled trial analysis with SoC outcomes based on VICTORIA MAIC**

This approach uses survival models fitted to combined adult and paediatric data from the larotrectinib trials. Efficacy on SoC is based on the hazard ratios from the VICTORIA unanchored MAIC applied to larotrectinib OS and PFS curves. Results are summarised in Table 2.

#### ***Strengths***

- Uses the largest available body of evidence on larotrectinib and the most appropriate MAIC to generate a comparison of relative effectiveness in a more consistent population.
- Reduces the influence of clinically implausible model fits to immature (and potentially confounded) paediatric OS data by pooling adult and paediatric data.
- Removes influence of flawed EPI VITRAKVI MAIC for paediatric patients.

#### ***Limitations***

- Assumes site-agnostic treatment effect for larotrectinib, despite evidence showing significant heterogeneity across tumour sites.
- Does not address key concerns with the applicability of the larotrectinib trial to NHS practice, i.e. small, selected subset of tumour types and tumour type distribution, natural disease progression and baseline prognosis, and subsequent therapy use.
- Assumes that an assumption of proportional hazards holds where this cannot be the case, i.e. in the presence of time varying population covariate effects in a highly heterogeneous population.
- Relies on a strong unmet assumption that all prognostic and effect-modifying variables have been accounted for.

#### ***Interpretation***

This approach would provide stronger internal validity of comparison between larotrectinib and SoC (conditional on MAIC assumptions), but results have poor applicability to NHS practice. This represents a potentially improved version of the company's base case structure, but its limitations may mean it is the least informative of the three EAG base cases. The use of more robust population-adjusted ITC methods including IPD from SACT data and SoC would likely increase the value of this approach.

### **EAG base case 2: Response-based model informed by Bayesian Hierarchical Modelling**

Larotrectinib survival for each tumour type included in the model is based on a combination of survival curves fitted to data on responders to larotrectinib, and data on non-responders. The weight of the response/non-response curve is determined by the predicted response rate for each tumour site,

generated from a BHM. SoC outcomes are assumed to be equal to non-response. Whilst this analysis uses larotrectinib trial data, the distribution of tumour sites in the EAG's base case is adjusted to reflect the NHS population in the SACT dataset. Results are summarised in Table 3.

### ***Strengths***

- Explicitly represents heterogeneity in response rate between tumour types, allowing population-level outcomes to be reweighted to an NHS-relevant case mix based on SACT.
- Internally valid comparison of a single population recruited and observed under the same trial conditions.
- Avoids reliance on hazard ratios to construct a comparison with SoC.
- Enables more accurate attribution of costs and QALYs according to tumour type, supporting the calculation and application of tumour type-specific severity modifiers, if appropriate.

### ***Limitations***

- Assumes no response to SoC, despite SoC largely comprising systemic anti-cancer therapies, mostly in the 2L setting.
- SoC outcomes will include the use of subsequent systemic therapies as observed in the trial, which may not represent NHS practice, and may not be adequately costed.
- Adjustment of the tumour distribution to that observed in SACT implicitly assumes that any new tumour site treated in NHS practice that is currently unrepresented in this selection of tumour types shares the outcomes of those in SACT.
- Overall survival remains confounded by subsequent therapy use in larotrectinib trials, leading to clinically implausible post-progression survival estimates.
- Assumes absolute survival outcomes in responders are equal, regardless of the natural history of the tumour type.
- Assumes that rates of achieving stable disease on SoC are equivalent to that on larotrectinib, potentially understating benefits of larotrectinib in some tumour types.

### ***Interpretation***

Most effectively and flexibly represents heterogeneity across tumour sites on the basis of the largest body of trial data. Provides the conceptual basis for an assessment of the relative effectiveness of larotrectinib using all of the larotrectinib trial data in a comparable population. This may represent the most statistically coherent comparison of relative effectiveness in an NHS-relevant case mix, although for a number of reasons absolute outcomes may not be applicable to the NHS. Further analysis of tumour-specific response rates for adults/children (particularly in primary CNS and STS) would

improve the value of this approach. This is the only approach that allows the application of tumour-specific severity weights.

### **EAG base case 3: Naïve comparison using data collected in SACT with a literature-based SoC**

The effectiveness of larotrectinib is modelled directly using survival models fitted by the EAG to SACT pseudo-IPD on OS, and assuming a proxy relationship between treatment duration and PFS. SoC outcomes are represented by tumour-specific published literature sources, weighted for tumour prevalence in SACT. An alternative scenario in Section 5.2.4 provides a naïve comparison with the SoC population in Brose *et al.* (used in the VICTORIA MAIC). Results are summarised in Table 4.

#### ***Strengths***

- Larotrectinib population and outcomes most applicable to NHS practice in terms of tumour type distribution and patient characteristics.
- SACT data represent most mature survival data for larotrectinib, outcomes can be estimated with a higher degree of certainty than using the trial data.
- SoC arm only includes data on a comparable selection of tumour types.
- Removes influence of unrepresentative subsequent therapy use observed in the trials on overall survival.
- Continued use of larotrectinib post-progression is better reflected in treatment costs.

#### ***Limitations***

- SACT provides only a relatively small sample size, with a limited spread of tumour types. This analysis assumes that unrepresented tumour types will exhibit the outcomes of the small sample included.
- Relies on naïve, unadjusted comparison with literature SoC sources, representing an incomplete depiction of the population (e.g. no paediatric primary CNS tumours, not an NTRK-fusion positive population), and subject to a high degree of uncertainty.
- Assumes ongoing benefit for patients remaining on larotrectinib beyond progression.

#### ***Interpretation***

This analysis presents the strongest external validity for NHS-relevant costs and outcomes on larotrectinib but cannot provide a robust comparison of comparative effectiveness. This analysis also implies that outcomes of any patient diagnosed with an NTRK gene fusion in the NHS will be equivalent to the population included in SACT. That is, a site-agnostic treatment effect is assumed. This may be reasonable given the composition of the sample already treated in the NHS.

**Table 2 Summary of EAG's preferred assumptions: EAG base case 1 (MAIC)**

| Scenario                                                 | Incremental cost | Incremental QALYs | ICER (QALYs x1.0)<br>(change vs corrected company base case) | ICER (QALYs x1.2) |
|----------------------------------------------------------|------------------|-------------------|--------------------------------------------------------------|-------------------|
| Company's base case                                      | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| EAG-corrected company base case                          | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| SACT tumour site distribution [Multiple issues]          | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| Structure: Pooled population MAIC [Issue 6]              | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| SoC utility excludes non-reference case values [Issue 8] | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| Laro PD utility shared with SoC [Issue 8]                | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| CNS/glioma health state costs included [Issue 11]        | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| Include oral administration cost SB11Z [Issue 12]        | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| <b>EAG base case 1 (deterministic)</b>                   | ■■■              | ■■■               | ■■■                                                          | ■■■               |
| <b>EAG base case 1 (probabilistic)</b>                   | ■■■              | ■■■               | ■■■                                                          | ■■■               |

CNS: Central Nervous System. EAG: External Assessment Group. ICER: Incremental Cost Effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. QALY: Quality-adjusted life years. SoC: Standard of Care

**Table 3 Summary of EAG's preferred assumptions: EAG base case 2 (BHM)**

| Scenario                                                                 | Incremental cost | Incremental QALYs | ICER (QALYs x1.0)<br>(change vs company's base case) | ICER (QALYs x1.2) |
|--------------------------------------------------------------------------|------------------|-------------------|------------------------------------------------------|-------------------|
| Company's base case                                                      | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| EAG-corrected company base case                                          | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| SACT tumour site distribution [Multiple issues]                          | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Structure: BHM/response-based model [Issue 6]                            | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| SoC utility excludes non-reference case values [Issue 8]                 | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Laro PD utility shared with SoC [Issue 8]                                | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| CNS/glioma health state costs included [Issue 11]                        | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Include oral administration cost SB11Z [Issue 12]                        | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| <b>EAG base case 2 (deterministic)</b>                                   | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| <b>EAG base case using site-specific QALY weightings (deterministic)</b> | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| <b>EAG base case 2 (probabilistic)</b>                                   | ■■■              | ■■■               | ■■■                                                  | ■■■               |

CNS: Central Nervous System. EAG: External Assessment Group. ICER: Incremental Cost Effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. QALY: Quality-adjusted life years. SoC: Standard of Care

**Table 4 Summary of EAG's preferred assumptions: EAG base case 3 (SACT)**

| Scenario                                                 | Incremental cost | Incremental QALYs | ICER (QALYs x1.0)<br>(change vs company's base case) | ICER (QALYs x1.2) |
|----------------------------------------------------------|------------------|-------------------|------------------------------------------------------|-------------------|
| Company's base case                                      | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| EAG-corrected company base case                          | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| SACT tumour site distribution [Multiple issues]          | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Structure: SACT naïve comparison [Issue 6]               | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| SoC utility excludes non-reference case values [Issue 8] | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Laro PD utility shared with SoC [Issue 8]                | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| CNS/glioma health state costs included [Issue 11]        | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| Include oral administration cost SB11Z [Issue 12]        | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| <b>EAG base case 3 (deterministic)</b>                   | ■■■              | ■■■               | ■■■                                                  | ■■■               |
| <b>EAG base case 3 (probabilistic)</b>                   | ■■■              | ■■■               | ■■■                                                  | ■■■               |

CNS: Central Nervous System. EAG: External Assessment Group. ICER: Incremental Cost Effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. QALY: Quality-adjusted life years. SoC: Standard of Care

### ***1.7 Outline of confidential comparator or subsequent treatment prices***

The confidential appendix to the EAR includes analyses using confidential pricing arrangements for lenvatinib, lomustine, nintedanib, pembrolizumab, regorafenib, trabectedin, and trifluridine and tipiracil hydrochloride. This includes the results of the company base-case analysis, sensitivity and scenario analyses and the results of exploratory analyses conducted by the EAG, with results reflecting the application of confidential pricing arrangements.

## 2 BACKGROUND

This report critiques the company submission for larotrectinib for treating NTRK fusion-positive advanced solid tumours.

### ***2.1 Critique of the company's description of underlying health problem***

The company provides a comprehensive description of the aetiology, epidemiology, prognosis and diagnosis of Neurotrophic Tyrosine Kinase (NTRK) fusion-positive solid tumours, which is described in brief below.

#### **2.1.1 Aetiology**

The NTRK genes (NTRK1, NTRK2 and NTRK3) encode the tropomyosin receptor kinase (TRK) receptors (TRKA, TRKB, and TRKC respectively). These TRK receptors normally bind with neurotrophins, such as Nerve Growth Factor (NGF), which triggers neuronal growth and repair processes through the TRK signalling pathway. However, fusion of a section of the NTRK genes with a separate gene leads to the expression of an aberrant TRK fusion positive protein. This TRK fusion positive protein may then promote tumour development and growth via the same TRK signalling pathway.

#### **2.1.2 Epidemiology**

The company states that NTRK fusion-positive cancer affects 1.34% of paediatric and 0.28% of adult cancers. This is based on evidence from the global FoundationCORE database which comprises 290,431 adult cancer patients and 4,388 paediatric cancer patients.<sup>1</sup> Forty-five cancer types were covered in this database,<sup>1</sup> with the most prevalent being salivary gland, soft-tissue sarcoma, thyroid, uterus sarcoma and bone sarcoma. However, the EAG has found evidence in a recent systematic review<sup>2</sup> suggesting that NTRK fusion-positive cancers may have a prevalence between 0.44% to 3.33% in children with cancer, and between 0.03% and 0.7% of in adults with cancer. These covered 429 specific cancer types, making it a more comprehensive source of information. The heterogeneous range of prevalences from different studies may, according to the authors, be driven by different testing methods.<sup>2</sup> Therefore, the EAG considers that the prevalence of NTRK-fusion positive cancer may be less certain than that suggested by the company.

NTRK tumours tend to be of low prevalence (<0.1 to 3%) in the more common histologies, such as small cell lung cancer or colorectal cancer, but highly prevalent (>90%) in rarer histologies, such as secretory breast carcinoma or infantile fibrosarcoma.

Data from the Systemic Anti-Cancer Therapy (SACT) database shows that between 31 July 2018 and 31 December 2024, 40,472 unique patients had a record in the NDRS molecular dataset; 39,363

(97%) had a cancer registered in the cancer registration dataset when the SACT report was produced. Of those, 404 (0.11%) patients had a positive or borderline NTRK fusion positive result; 251 (62%) had a gene fusion that was captured in the NDRS molecular dataset. For over 60% in this cohort testing was performed using immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR), and confirmed by NGS in genomic laboratory hubs (GLHs).<sup>3</sup>

### 2.1.3 Prognosis

The company stated that the prognosis of NTRK tumours is worse than that of non-NTRK tumours, based on evidence from the VOYAGER1<sup>4</sup> and VOYAGER2<sup>5</sup> studies. For example, in VOYAGER2, a retrospective study that included patients enrolled in the Genomics England 100,000 Genomes Project (which had linked clinical data from UK databases), the HR for mortality for NTRK fusion *positive* patients (untreated with an NTRK inhibitor) versus those with NTRK fusion *negative* cancers (also untreated with an NTRK inhibitor) was 1.47 (95% CI 0.39 to 5.57). This was consistent with findings from VOYAGER 1, a previous US study (HR 1.44 [95% CI 0.61 to 3.37]). The difference was not statistically significant in both studies (as acknowledged by the company). This was echoed by the VOYAGER study authors. Bridgewater (2022)<sup>5</sup> suggested that “NTRK gene fusion is not a prognostic indicator itself”. Furthermore, Bahzenova (2021)<sup>4</sup> concluded that “patients with NTRK gene fusions do not have a statistically worse or better prognosis than patients with NTRK wild-type”. The EAG asked the company for further clarification [Clarification Question (CQ) A21], and the company responded by referring to a meta-analysis by Lassen (2023),<sup>6</sup> which pooled three studies (including VOYAGER studies 1 and 2); the pooled hazard ratio suggested that NTRK positive status is associated with an estimated 51% increased risk of mortality (HR 1.51 [95% Credible Interval, 1.01 to 2.29, tau=0.10]). The EAG accepts that this suggests that NTRK positive fusions may be a negative prognostic factor compared with NTRK fusion negative patients, although the magnitude of the association is uncertain given the wide credible interval.

### 2.1.4 Diagnosis

Diagnosis of NTRK fusion positive cancers is through genomic testing, particularly Next Generation Sequencing (NGS). The company states that although genomic testing is open to anyone in the UK with a solid tumour (via the National Genomic Test Directory), in practice it is prioritised to those with cancers where fusions are more prevalent, such as lung, primary CNS and thyroid tumours. Provision also varies by geography, clinician awareness and urgency. The EAG clinical advisers agree with this and added that although NGS is accessible through genomic laboratory hubs, Whole Genome Sequencing (WGS) is still not readily accessible or in general use. NGS testing typically has excellent sensitivity and specificity. In addition, expression-based assays are far less accurate, though fortunately not in standard use.

## ***2.2 Critique of the company's overview of current service provision***

Current service provision for NTRK fusion-positive cancers that are locally advanced or metastatic, where surgery would significantly increase morbidity and where there are “no satisfactory treatment options” is monotherapy with larotrectinib which is currently on managed access agreement through the Cancer Drugs Fund (CDF). Entrectinib, an alternative ‘histology-independent’ TRK inhibitors, was available through the CDF until it was terminated in January 2026.<sup>7</sup> Where these conditions are not met, then Standard of Care (SoC) treatment (established clinical management) directed at the histology is used, through more traditional chemotherapy, radiotherapy, immunotherapy and surgical options. The exact nature of SoC varies by tumour type, tumour size or whether the tumour is locally advanced or metastatic.

Because of the ambiguous definition of eligibility for TRK inhibitors (exemplified by the inclusion criterion of “no satisfactory treatment options”), some variability in treatment line may exist. In the SACT database,<sup>3</sup> only 2% of fusion positive patients were treated with larotrectinib first-line. The EAG’s clinical advisers noted some patients may be started on first-line standard of care treatment before NTRK fusion-positive status is confirmed.

## ***2.3 Critique of company's definition of decision problem***

The population, intervention, comparator and outcomes are all fully in line with the NICE final scope, but the EAG considers that further clarity is required for the population and comparator definitions. The company only partially addressed the subgroups in the NICE scope. These issues are discussed below and summarised in Table 5.

### **2.3.1 Population**

The population addressed in the CS is adult and paediatric patients with solid tumours who have a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and no satisfactory treatment options. This is in line with the anticipated marketing authorisation. As in TA630, the EAG is concerned that the wording of the eligible population, for whom “there is no satisfactory option” is subjective. The company encourages a nuanced approach, stating in the CS (p89) that “the decision to initiate larotrectinib should remain at the discretion of the treating clinician, guided by the clinical context and aligned with the principles of precision oncology and individualised patient care.” The EAG is concerned that the relative lack of clarity and subjective wording of the indication “no satisfactory treatment options”, may lead to variations in interpretation and prescribing practices, which the company acknowledge. The EAG agrees with the company that the implications for this lack of clarity are a potential equity issue: “the subjective interpretation of the phrase “no



satisfactory treatment options” within the indication can lead to inconsistent application across treatment centres, potentially resulting in inequities in access” (CS p200).

### **2.3.2 Comparator**

A fuller description of the SoC that would be used for each histological type is required. At present, because the selection of comparators was not based on a systematic review, it is unclear if the comparators used in the MAICs were representative of those used in this population. The company were asked to clarify the SoC for each tumour type included in the CS (CQ A1, Table 1) and responded with the SoC treatments for 12 tumour types. These were all second line therapies recommended by ESMO guidelines<sup>9-20</sup> for the tumour type, and the specific drugs were selected by UK clinical experts. Although the list of comparators excludes most tumour types that may harbour an NTRK fusion, it includes the most prevalent tumour types in the trial evidence and in SACT and was informed by the company clinical advisers. A clinical adviser to the EAG noted that, as larotrectinib may sometimes be used as first-line treatment (where it is considered that no other satisfactory treatment options are available), the exclusion of first-line comparators for some tumour types from the decision problem may not be appropriate. One EAG clinical adviser disagreed with the company that cisplatin and vinorelbine were standard of care for salivary cancer.

#### *Sub-grouping*

The company did not consider presenting subgroup results by specific tumour types in the cost-effectiveness analysis.

**Table 5 Summary of decision problem**

|                          | <b>Final scope issued by NICE</b>                                                                                                                                                                                                                                                                                                      | <b>Decision problem addressed in the company submission</b>                                                                                                                                                                                                                                                                            | <b>Rationale if different from the final NICE scope</b>                        | <b>EAG comment</b>                                                                                                                                                 |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population</b>        | For the treatment of adult and paediatric patients with solid tumours who have:<br>- a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and<br>- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and<br>- no satisfactory treatment options | For the treatment of adult and paediatric patients with solid tumours who have:<br>- a tumour with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, and<br>- a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and<br>- no satisfactory treatment options | NA                                                                             | Aligned with the NICE scope. However, “No satisfactory treatment options” is subjective and may lead to differences in interpretation and inequities in provision. |
| <b>Intervention</b>      | Larotrectinib                                                                                                                                                                                                                                                                                                                          | Larotrectinib                                                                                                                                                                                                                                                                                                                          | NA                                                                             | Aligned with the NICE scope.                                                                                                                                       |
| <b>Comparator(s)</b>     | Established clinical management without larotrectinib                                                                                                                                                                                                                                                                                  | The comparator selected is in line with the final scope issued by NICE                                                                                                                                                                                                                                                                 | NA                                                                             | In response to a clarification request (CQ A1) from the EAG, the company specified the SoC comparators for only 12 tumour types.                                   |
| <b>Outcomes</b>          | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rate<br>• duration of response<br>• adverse effects of treatment<br>health-related quality of life.                                                                                                                  | The outcome measures considered include:<br>• overall survival<br>• progression-free survival<br>• response rate<br>• duration of response<br>• adverse effects of treatment<br>health-related quality of life.                                                                                                                        | NA                                                                             | None                                                                                                                                                               |
| <b>Economic analysis</b> | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of                                                                                                                                                                                                                                | Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year. The                                                                                                                                                                                                                                       | NTRK fusion testing is funded within the NHS through the National Genomic Test | Following consultation with NHSE, the EAG agrees with the company’s position that                                                                                  |

|  | Final scope issued by NICE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                                                                                                                                                   | Rationale if different from the final NICE scope                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | EAG comment                                                                    |
|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|  | <p>incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p> <p>The availability and cost of biosimilar and generic products should be taken into account.</p> <p>The use of larotrectinib is conditional on the presence of NTRK fusion. The economic modelling should include the costs associated with diagnostic testing for NTRK fusion in people with advanced solid tumours who would not otherwise have been tested. A sensitivity analysis should</p> | <p>company's submission adopts a cost-utility approach using partitioned survival analysis and adheres closely to the reference case and previously accepted submission approaches.</p> <p>The time horizon for estimating clinical and cost-effectiveness is set to a lifetime.</p> <p>Costs are considered from an NHS and Personal Social Services (PSS) perspective.</p> <p>Testing costs are not included in the base case analysis but are explored in sensitivity analyses.</p> | <p>Directory and delivered via the Genomic Laboratory Hub network, meaning the cost of testing is already incorporated within the healthcare system. While the infrastructure is in place and testing is performed, in practice, it is often prioritised for rare and paediatric cancers where NTRK fusions are more common. In prevalent tumour types, detection typically occurs incidentally through broader next-generation sequencing (NGS) panels conducted for other molecular drivers.</p> <p>NTRK fusions are not the only biomarkers included in the testing panel, and as such, the cost of the test should not be borne by the company. Furthermore, NTRK fusions are typically rare, meaning that any diagnostic testing conducted will not be exclusively to support the use of larotrectinib.</p> <p>In addition, the expansion of genomic testing is a strategic priority for the NHS in England and ensuring that such testing is publicly funded aligns with national healthcare objectives.</p> | <p>genomic testing costs should not be included in the base case analysis.</p> |

|                                                                       | Final scope issued by NICE                                                                                                                             | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Rationale if different from the final NICE scope                                                                                                                                                                                                                                                                                                      | EAG comment                                                                |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
|                                                                       | be provided without the cost of the diagnostic test.                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                       |                                                                            |
| Subgroups                                                             | If evidence allows, subgroup analyses by: <ul style="list-style-type: none"><li>• tumour site</li><li>• previous therapy will be considered.</li></ul> | No subgroups are considered in the cost-effectiveness analysis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Larotrectinib acts as a histology-independent precision medicine. As such, there are no subgroups considered in the cost-effectiveness analysis. While supportive analyses were conducted to assess consistency across selected subgroups, the study designs and patient numbers do not allow for robust conclusions to be drawn from these analyses. | Subgroup analyses by tumour type and prior lines of therapy were provided. |
| Special considerations including issues related to equity or equality |                                                                                                                                                        | <p>Larotrectinib is an innovative therapy and a ‘step change’ in the management of NTRK fusion-positive cancers. It is a precision medicine, designed to selectively target NTRK fusion cancer, providing a specific treatment for NTRK fusion-positive solid tumours where previously no treatment was available. Larotrectinib is a histology-independent therapy, offering treatment for both adults and children under a single indication. It is approved by EMA as the first histology-independent drug in the EU.</p> <p>As a rare disease, the data supporting its use come from single-arm basket studies, which are considered best suited to assess the efficacy of targeting genomic alterations that occur at low frequencies across a wide variety of tumour types <sup>21</sup>. Indeed, the MHRA agreed that a single-arm study was an appropriate design to support a Marketing Authorisation Application, given the extreme rarity of NTRK fusion cancers.</p> <p>While in the Cancer Drugs Fund (CDF), larotrectinib continued to demonstrate efficacy and safety, mitigating the uncertainty inherent in the clinical trial design and modelling choices from the first submission.</p> | Variation in access to WGS and subjective interpretation of population eligibility criteria may lead to variations in access to treatment                                                                                                                                                                                                             |                                                                            |

|  | Final scope issued by NICE | Decision problem addressed in the company submission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Rationale if different from the final NICE scope | EAG comment |
|--|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------|
|  |                            | <p>The company submission aligns closely to NICE reference case. However, ongoing workstreams aimed at evaluating the suitability of health technology assessments methods for precision medicines indicate that deviations from the reference case are likely to occur. The trial design and the high number of comparators are reflective of the rarity of the gene fusion and the innovative nature of this product. It is crucial to consider these factors to ensure that patients with rare gene fusions are not disproportionately disadvantaged.</p> <p>Furthermore, it is essential that eligible patients are not denied access to this treatment while HTA methods continue to evolve.</p> |                                                  |             |

Sources: based on CS Table 1, Clarification Document, A1, Table 1

CDF: Cancer Drugs Fund. CS: Company Submission. EAG: External Assessment Group. EMA: European Medicines Agency. EU: European Union. HTA: Health Technology Appraisal. MHRA: Medicines and Healthcare Products Regulatory Agency. NA: Not Applicable. NGS: Next Generation Sequencing. NHS: National Health Service. NICE: National Institute for Clinical and Health Excellence. NTRK: Neurotrophic Tyrosine Receptor Kinase. ORR: Objective Response Rate. PSS: Personal Social Services. SoC: Standard of Care.

### 3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the methods of the company's review of clinical efficacy and safety evidence. Section 3.2 provides a critique of the trial evidence, and Section 3.3 discusses observational evidence. Section 3.4 critiques the indirect comparisons presented by the company. Conclusions on the clinical effectiveness are provided in Section 3.6.

#### ***3.1 Summary and critique of the methods of the company's systematic review***

The original systematic literature review (SLR), conducted for the first submission in 2019, aimed to identify and synthesise the evidence around the efficacy and safety of larotrectinib (compared to standard of care treatment), as per the NICE scope. This led to the inclusion of 9 publications. An update to the SLR was conducted in May 2025 (CS, Appendix B). This focused on any evidence involving patients with NTRK fusion-positive tumours. An additional 16 publications were included in the update, supplemented by a further 4 from a hand search, making a total of 29 publications resulting from both the 2019 and 2025 SRs. These 29 publications covered 5 larotrectinib trials.

##### **3.1.1 Critique of the searches**

The company searches to identify studies of treatments for NTRK fusion-positive solid tumours were included in Appendix B of the submission. The searches were designed to update the original company searches carried out for their previous submission in 2019.

Several mistakes within the search syntax of the search strategies were identified by the EAG which may have affected optimal retrieval of all relevant studies. The company corrected and tested some of these mistakes in their response to CQ C3 and confirmed that these did not affect retrieval. However not all mistakes were corrected and tested.

The EAG had concerns that the searches for non-randomised studies were not comprehensive. In the company response to CQ C1 several more search terms for non-randomised studies were tested. After screening the new search results retrieved by the extra search terms the company found that no further studies were identified. However, the testing was only carried out in Embase and the new terms selected for testing were not comprehensive, for example terms for cohort studies were missing. Concerns over comprehensive retrieval of non-randomised studies have been raised in the literature.<sup>22</sup> A study design search filter for comprehensive retrieval of controlled non-randomised studies in MEDLINE has been developed however this was not used in the company searches.<sup>23</sup>

The search for systematic reviews, meta-analysis and pooled analyses was fairly limited. Databases of systematic reviews such as Epistemonikos, KSR Evidence, PROSPERO, and the INAHTA database,

were not searched. In addition, the searches of MEDLINE and Embase did not contain terms for systematic reviews, meta-analyses or pooled analyses. Therefore the EAG cannot be certain that these study types would have been identified by the searches presented in Appendix B.

### 3.1.2 Critique of the inclusion criteria

The company's inclusion and exclusion criteria are given in Table 6.

**Table 6 Eligibility criteria used in the company SLR**

|                                  | <b>Inclusion criteria</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Exclusion criteria</b>                                                                                                                           |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population</b>                | <ul style="list-style-type: none"> <li>Patients with NTRK fusion-positive solid tumours</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Tumours not classed as solid e.g. leukaemia</li> <li>Non-human</li> </ul>                                    |
| <b>Intervention / Comparator</b> | <ul style="list-style-type: none"> <li>Larotrectinib</li> <li>Any treatment or treatment combination specifically targeting NTRK fusion-positive solid tumours</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>Studies not assessing the intervention or relevant comparator</li> <li>Surgical procedures only</li> </ul>   |
| <b>Outcomes of interest</b>      | <ul style="list-style-type: none"> <li>Overall survival</li> <li>Progression-free survival</li> <li>Response rate / criteria e.g. ORR, CR</li> <li>Adverse effects of treatment</li> <li>Health-related quality of life</li> </ul>                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Outcomes other than those specified in the inclusion columns</li> </ul>                                      |
| <b>Study design</b>              | <ul style="list-style-type: none"> <li>RCTs</li> <li>Non-randomised studies</li> <li>Pooled analyses</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>Reviews</li> <li>Opinion, editorial, letters</li> <li>Case reports</li> <li>Retrospective studies</li> </ul> |
| <b>Time limit</b>                | <ul style="list-style-type: none"> <li>Original SLR: <ul style="list-style-type: none"> <li>Full text published articles: inception to 11<sup>th</sup> March 2019</li> <li>Conference abstracts – 2016, 2017 and 2018 (search conducted between 9<sup>th</sup> and 13<sup>th</sup> April 2019)</li> </ul> </li> <li>Updated SLR: <ul style="list-style-type: none"> <li>Full text published articles: 2019 to 6<sup>th</sup> May 2025</li> <li>Conference abstracts 2023 to June 2025 (search conducted between 5<sup>th</sup> and 13<sup>th</sup> June 2025)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Studies published outside of the time limit specified in the inclusion column</li> </ul>                     |

Sources: Appendix B Table 6

CR: Complete Response. NTRK: Neurotrophic Tyrosine Receptor Kinase. ORR: Overall Response Rate. RCT: Randomised Clinical Trial. SLR: Systematic Literature Review

The inclusion and exclusion criteria are appropriate in terms of the population, outcomes, study design and time limits. However, the definition of comparators does not fit with the final NICE scope. The NICE scope permits comparators to be standard of care for the cancer histology, and, in contrast to the SLR criteria, does not specify that the comparator has to target NTRK fusion-positive solid tumours. The NICE scope definition of the comparator is more relevant for the purposes of this submission, as it follows the current treatment pathway, where histology-specific standard of care treatments would be the alternative to NTRK-targeted treatments.

The EAG thinks it is unlikely that any relevant trials of larotrectinib were missed by these approaches, but as the eligibility criteria did not include established clinical management without an NTRK fusion inhibitor, the systematic review was not suited to identify all relevant comparator evidence.

### **3.1.3 Critique of data collection**

Methods used for the screening of papers followed all the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,<sup>24</sup> with duplicated title/abstract and full text screens performed according to prespecified inclusion/exclusion criteria, along with hand-searching. Data extraction was also appropriately conducted, using standard methodology.

### **3.1.4 Critique of quality**

Quality assessment of each included trial used the Downs and Black checklist. This is a comprehensive checklist comprising 27 items that cover all relevant criteria. The score-based approach is not appropriate for quality assessment. Amongst other reasons, this approach gives the same weight to all items, and therefore may not adequately account for methodological areas (such as lack of randomisation).<sup>24</sup>

### **3.1.5 Summary of evidence synthesis**

The 5 studies included in the SLR (in 29 separate publications) are described below.

Three single-arm interventional clinical studies (Study 20288 [LOXO-TRK-14001],<sup>25</sup> Study 20289 [NAVIGATE],<sup>26</sup> and Study 20290 [SCOUT])<sup>27</sup> were included. These studies had underpinned the previous SR, but in this updated SR a more recent data cut-off (20<sup>th</sup> July 2024) was used for each. These three updated studies were pooled, by simple addition of the complete patient data. A summary and critique of the pooled analysis is presented in Section 3.2.

Two other trials were also included in the systematic review, but excluded from the pooled analyses. Laetsch et al. (2025)<sup>28</sup> was a single arm trial evaluating efficacy and safety of first line larotrectinib in 18 children (median age 2 months) with NTRK fusion-positive infantile fibrosarcoma, and 15 children (median age 9 years) with other NTRK fusion-positive soft tumours. Thavaneswaran et al. (2024)<sup>29</sup> was a single arm trial comprising one adult with NTRK fusion-positive glioblastoma and one adult with an NTRK fusion-positive peripheral nerve sheath tumour. Fifteen other adults had NTRK overexpression rather than fusions. The results of these two studies are included in Appendix B. The EAG considers their exclusion from the pooled analyses to be generally appropriate. Although the reasons for their absence from the main evidence are unclear, they are likely to be due to the populations being very different to that of NHS clinical practice, which would be a reasonable rationale. For example, Laetsch (2025)<sup>28</sup> used a wholly first line sample, and only 11% in the Thavaneswaran (2024)<sup>29</sup> sample had NTRK fusion positive cancers.



This SLR does not include the “real-world studies” described in section 2.7 of the CS (ON-TRK,<sup>30</sup> SACT,<sup>3</sup> LAROTRACKING<sup>31</sup> and SACHA<sup>32</sup>), and which were utilised by the company as supportive evidence. Reasons for the lack of these relevant studies in the SR are not explained in the CS, but may relate to the fact that they were retrospective studies and therefore met the exclusion criteria for the review.

### ***3.2 Critique of the trials and pooled analyses of the technology of interest***

#### **3.2.1 Critique of the trial evidence**

The submission included three single-arm, open-label trials:

- Study 20288 (n=13): a phase 1 dose escalating clinical trial in adult patients with advanced solid tumours (named as LOXO-TRK-14001 in TA630, NCT02122913).
- Study 20289 (n=215): a phase 2 basket trial of patients over the age of 12, with recurrent, advanced solid tumours with a documented NTRK fusion (LOXO-TRK-15002, NAVIGATE, NCT02576431).
- Study 20290 (n=146): a phase 1/2 study in children with advanced solid or primary CNS tumours (LOXO-TRK-15003, SCOUT, NCT02637687).

The study designs are summarised in Table 7, with further details in CS Sections 2.2 and 2.3, and CS Appendix N.

All three trials are multi-site studies that recruited patients with locally advanced or metastatic solid tumours, or primary central nervous system (CNS) tumours who were previously treated with standard therapy where available and possible. Study 20288 was completed in April 2021. Study 20289 was completed in September 2025, and the latest data cut (July 2025) which will include final results, is still under analysis (CQ A4). Study 20290 is still ongoing. The CS presented results for studies 20289 and 20290 at the 20<sup>th</sup> July 2024 data cut.

All three studies were pooled by simple addition of the individual trial results for patients with confirmed NTRK fusion. The methods for determination of NTRK fusion status were not clearly reported in the CS or CSRs. One study confirmed that NTRK fusion status for the NAVIGATE data were determined solely by Next-Generation Sampling (NGS),<sup>26</sup> but methods used for the other studies (SCOUT and LOXO-TRK-14001) were mixed, comprising NGS, reverse transcriptase polymerase chain reaction, polymerase chain reaction, or fluorescence in situ hybridization (FISH).<sup>33, 34</sup> Studies 20288, 20289 and 20290 contributed 13, 210 and 141 patients to the pooled analyses respectively. The CS did not specify why 2.7% of the total NTRK population across all three studies (five from each of studies 20289 and 20290) did not contribute to the pooled analyses. Studies 20288 and 20290 had dose-finding phases, so some patients included in the pooled analysis did not receive the MHRA

licensed dose of 100mg twice daily (for adults) or 100mg/m<sup>2</sup> twice daily (for children). In the pooled analyses, the starting dose was as per the licence in nearly all adults (>99%); in the paediatric population, 90% received 100mg/m<sup>2</sup> twice daily in the ePAS9, and 100% in the SAS3. Subgroup analyses by starting dose did not show evidence of a difference in response rates for patients who started larotrectinib at a dose below or above the licence (CS Appendix C).

The pooled analysis of efficacy is presented as two datasets – ePAS9 and SAS3 at the 20<sup>th</sup> July 2024 data cut. ePAS9 or ‘Extended Primary Analysis set 9’, reflects an updated version of ePAS2 in the original TA630 CS, and includes paediatric and adult patients with locally advanced or metastatic non-CNS primary solid tumours with an NTRK fusion who received at least one dose of larotrectinib. SAS3 or ‘Supplementary analysis set 3’, includes paediatric and adult patients with primary CNS tumours who otherwise met the ePAS9 eligibility criteria. Definitions of ePAS9 and SAS3 and safety analysis sets are presented in CS Table 7. ePAS9 included 304 patients (≥1 dose larotrectinib) with NTRK fusion cancer using RECIST, version 1.1 at baseline (excluding primary CNS tumours and patients without measurable disease) (as of 20<sup>th</sup> July 2024). SAS3 included 60 patients (≥1 dose larotrectinib) with primary CNS tumours assessable according to RECIST v.1.1 or RANO criteria.

Following a clarification request from the EAG (CQ A2), the company stated that 20<sup>th</sup> July 2024 was the most recent available data cut, as the July 2025 for ePAS9 and SAS3 is still under analysis and expected to be submitted to the EMA in March 2026.

**Table 7 Clinical effectiveness studies of technology of interest**

|                                                        | Study 20288                                                                                                                                    | Study 20289                                                                                                                      | Study 20290                                                                                                                                 | Pooled analyses of studies 20288, 20289, 20290 (ePAS9 and SAS3)                                                                                                            |
|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Role in this evaluation                                | Pooled analyses of 20288, 20289 and 20290 are the main source of clinical effectiveness evidence and inform the company's base case.           |                                                                                                                                  |                                                                                                                                             |                                                                                                                                                                            |
| Study name in original TA630                           | LOXO-TRK-14001                                                                                                                                 | LOXO-TRK-15002 (NAVIGATE)                                                                                                        | LOXO-TRK-15003 (SCOUT)                                                                                                                      | ePAS2 dataset<br>SAS3 dataset                                                                                                                                              |
| Study type                                             | Phase 1, open-label, US multicentre, dose escalation and dose expansion study                                                                  | Phase 2, open-label, international multicentre, basket study <sup>f</sup>                                                        | Phase 1/2, open-label, international multicentre <sup>g</sup>                                                                               | Pooled analysis of patients with prospectively identified NTRK fusion cancers enrolled and treated in 20288, 20289 or 20290 (ePAS9 and SAS3 datasets)                      |
| Population                                             | Adults ( $\geq 18$ yrs) patients with locally advanced or metastatic, solid tumours refractory to standard therapies.<br><br>n=13 <sup>+</sup> | Adults and adolescents ( $\geq 12$ yrs) with advanced or metastatic NTRK fusion-positive solid tumour.<br><br>n=215 <sup>^</sup> | Paediatric patients ( $\leq 21$ yrs) with locally advanced or metastatic solid tumour or primary CNS tumours.<br><br>n=146 <sup>&amp;</sup> | Adults and children with locally advanced or metastatic NTRK fusion positive solid tumour.<br><br>ePAS9 (n=304): non-CNS primary tumour<br>SAS3 (n=60): primary CNS tumour |
| Participant numbers contributing to pooled analyses    | n=13<br>ePAS9: n=13<br>SAS3: n=0                                                                                                               | n=210<br>ePAS9: n=191<br>SAS3: n=19                                                                                              | n=141<br>ePAS9: n=100<br>SAS3: n=41                                                                                                         | n=364<br>ePAS9: n=304<br>SAS3: n=60                                                                                                                                        |
| Original TA630 numbers contributing to pooled analyses | n=8                                                                                                                                            | n=62                                                                                                                             | n=32                                                                                                                                        | n=102<br>ePAS2: n=93<br>SAS3: n=9                                                                                                                                          |

|              | Study 20288                                                                                                                                                                                                                                                                                                                                              | Study 20289                                                           | Study 20290                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Pooled analyses of studies 20288, 20289, 20290 (ePAS9 and SAS3)                                                                                                                                                                                                                                                                                                                               |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Subgroups    | No pre-specified subgroup analyses                                                                                                                                                                                                                                                                                                                       |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ORR investigated by sex, age group, race, tumour type, baseline disease characteristics, and NTRK gene fusion type, ECOG status, number of metastasis sites, primary cancer diagnosis, prior therapies, BOR, starting dose and administration frequency of larotrectinib.                                                                                                                     |
| Intervention | <b>Dose escalation:</b><br>Oral larotrectinib, once- or twice-daily, on a continuous 28-day schedule, in increasing dose levels according to a standard 3+3 dose escalation scheme.<br><br>Dose levels: 50 mg q.d. / 100 mg q.d. / 200 mg q.d. / 100 mg b.d. / 150 mg b.d. / 200 mg b.d.<br><br><b>Expansion Phase</b><br>Oral larotrectinib 100 mg b.d. | Oral larotrectinib 100 mg b.d. in 28-day cycles (capsules or liquid). | <b>Dose escalation:</b><br>Oral larotrectinib (capsule or liquid)<br>Cohort 1: Doses ranging from 17%–96% of the BSA-adjusted recommended adult phase 2 dose of 100 mg b.d.<br>Cohort 2: Doses ranging from 30%–208% of the BSA-adjusted adult dose of 150 mg b.d.<br>Cohort 3: 100 mg/m <sup>2</sup> b.d.<br>Dosing was continuous for 28-day cycles.<br><br><b>Phase II:</b> Oral (capsule or liquid). 100 mg/m <sup>2</sup> b.d., not to exceed 100 mg b.d. | According to the dose expansion or phase II portion of the study protocol the patient was treated under.<br><br>Starting dose (adults):<br>100mg b.d. (ePAS9: >99%; SAS3: 100%)<br>150mg b.d. (ePAS9:<1%)<br><br>Starting dose (paediatrics):<br>100mg/m <sup>2</sup> b.d. (ePAS9: 90%; SAS3: 100%)<br>9.6-55mg/m <sup>2</sup> b.d. (ePAS9: 3%)<br>17.3-120mg/m <sup>2</sup> b.d. (ePAS9: 7%) |
|              | Larotrectinib was administered until disease progression, the occurrence of unacceptable toxicity, or the withdrawal of patient consent.                                                                                                                                                                                                                 |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                               |
| Comparator   | Not applicable (single-arm)                                                                                                                                                                                                                                                                                                                              |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                               |

|          | Study 20288                                                                                                          | Study 20289                                                                                                                                                                                                                                                                                                  | Study 20290                                                                                                                                                                                                               | Pooled analyses of studies 20288, 20289, 20290 (ePAS9 and SAS3)                                                                                                                                                                                                                                                           |
|----------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outcomes | <ul style="list-style-type: none"> <li>• Primary: safety</li> <li>• Secondary endpoints: ORR (CR+PR), DoR</li> </ul> | <ul style="list-style-type: none"> <li>• Primary: ORRc (CR+PR)</li> <li>• Secondary: BOR, DoR, PFS, OS, DCR, TRR, safety</li> <li>• Exploratory: HRQoL</li> </ul>                                                                                                                                            | <ul style="list-style-type: none"> <li>• Primary: Phase 1: safety<br/>Phase 2: ORR</li> <li>• Secondary: Phase 1*: ORR, DoR, BOR, DCR, HRQoL, safety<br/>Phase 2: DoR, BOR, DCR, OS, PFS, TRR, safety</li> </ul>          | <p>Primary: ORR by IRC assessment.</p> <p>Secondary: ORR (investigator assessment), DoR, PFS, OS, DCR, safety.</p> <p>Others/exploratory: time to response / best response, time on treatment, HRQoL</p>                                                                                                                  |
| Duration | May 2014 – September 2021                                                                                            | October 2015 – September 2025                                                                                                                                                                                                                                                                                | December 2015 – ongoing                                                                                                                                                                                                   | March 2015 –July 20 <sup>th</sup> 2024 (latest analysis data cut)                                                                                                                                                                                                                                                         |
| Location | USA<br><br>8 sites                                                                                                   | Australia, North America (Canada, USA), South America (Argentina, Brazil, Colombia), Europe (Belgium, Czechia, Denmark, France, Germany, Italy, Ireland, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden), Asia (China, India, Japan, South Korea, Singapore, Taiwan, Turkey)<br><br>98 sites | Australia, North America (Canada, USA), Europe (Czechia, Denmark, France, Germany, Italy, Ireland, Netherlands, Poland, Spain, Sweden, Switzerland, UK), Asia (China, Israel, Japan, South Korea, Turkey)<br><br>45 sites | Patients included in the analysis to date are from: Asia (China, India, Japan, Singapore, South Korea, Taiwan, Turkey), Europe (Denmark, France, Germany, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, UK), North America (Canada, USA), South America (Argentina, Brazil)<br><br>121 sites |

Sources: CS Table 4, CS Appendix N Table 2, CS pages 44–45, Bayer\_Larotrectinib\_Summary of Clinical Efficacy\_2024\_Data on file Table 3-7,<sup>35</sup> TA630 EAG report (2019) Table 6.

b.d.: twice daily. BOR: best overall response. BSA: body surface area. CNS: central nervous system. CR: complete response. DCR: disease control rate. DoR: Duration of Response. ECOG: Eastern Cooperative Oncology Group. ePAS9: extended primary analysis set. HRQoL: health-related quality of life. IRC: independent review committee. N:number of patients. NTRK: Neurotrophic Tyrosine Receptor Kinase. ORR: overall response rate. OS: overall survival. PFS: progression-free survival. PR: partial response. q.d.: daily. SAS3: supplementary analysis set 3.

<sup>‡</sup> From protocol version 9.0 (08 OCT 2019), onwards the recruitment of the basket study stopped, and a new prospective cohort was introduced, to increase the number of patients across more common tumour types where NTRK gene fusions are rare.

<sup>§</sup> Phase 1: Open-label study with a dose escalation and a dose expansion portion. Phase 2: Single-arm, open-label study in IFS, other extracranial solid tumours, and primary CNS tumours

<sup>+</sup> n=13 with documented NTRK fusion. No documented NTRK fusion: n=62.

<sup>^</sup> A local amendment in South Korea allowed patients over 5 years of age to be enrolled from protocol version 6.4. From protocol version 9.0 onwards, patients were at least 18 yrs.

<sup>&</sup> Phase 1 portion (dose expansion: n=17; dose escalation: n=24), included patients with or without NTRK gene fusions whereas the Phase 2 portion (n=113), was restricted to patients with NTRK gene fusions.

\* Although not specified in the phase 1 protocol, all patients across phases 1 & 2 were included in the OS analysis (CQ response A7).

Table 8 compares the volume and maturity of evidence submitted in the original TA630 submission and the current CS. Compared with the original TA630 CS, the trial evidence includes a significantly larger sample size (■■■■ vs. 102), and a larger number of tumour types (28 vs. ■■■). The current evidence includes ■■■ patients with primary CNS tumours, compared with ■ in the original submission. Median follow-up for OS is significantly longer (■■■■ months, vs. ■■■ months) and OS maturity is improved, although median OS is still not estimable.

**Table 8 Pooled analyses of larotrectinib trial evidence: summary of characteristics**

|                           | Original TA630 submission (2019)                 | TA630 review submission (2025)                                          |
|---------------------------|--------------------------------------------------|-------------------------------------------------------------------------|
| Sample size               | 102                                              | 364                                                                     |
| Patients with CNS tumours | 9                                                | 60                                                                      |
| Number of tumour types    | ■■■                                              | 28                                                                      |
| Data cut                  | 30 <sup>th</sup> July 2018                       | 20 <sup>th</sup> July 2024                                              |
| Median follow-up          | ■■■■ months                                      | ■■■■ months                                                             |
| OS data maturity          | Median OS not reached.<br>12-month OS rate: ■■■* | Median OS not estimable<br>72-month OS rate: ■■■ (ePAS9),<br>■■■ (SAS3) |

Sources: CS Table 6, TA630 submission<sup>36</sup>

CNS: Central Nervous System. ePAS9: extended primary analysis set 9. SAS3: supplementary analysis set 3. TA: technology appraisal. OS: overall survival. \*Full cohort, N=137

### 3.2.2 Critique of the design of trials and pooled analyses

The increased sample size, longer follow-up duration and increased maturity of the trial evidence are positive improvements from the original TA630 CS. However, the EAG still has significant concerns about the appropriateness of the design of the trials and pooled analyses, given the potential for heterogeneity across tumour types and other participant characteristics.

Study 20289 has a basket trial design, in which patients are recruited to gain knowledge of a drug's efficacy in distinct cancer types - or baskets - to evaluate therapies which have a mechanism of action based on targeting a specific genomic alteration, irrespective of tumour histology. In a basket trial, the response rate results from pooling outcomes observed for all tumour types, representing the overall average among all indications. Although this approach increases statistical power, it assumes that the treatment generates agnostic (or global) effects across different tumour types. By doing so, it ignores the potential for heterogeneity in efficacy across tumour types. Where heterogeneity is present, and in case of imbalanced enrolment (which is common among basket trials), this approach risks erroneous conclusions as outcomes from over-represented tumour types may be extrapolated to less or under-represented histologies.<sup>37</sup>

Despite being 'tumour agnostic' in *target*, basket trial therapies might show heterogeneity of effectiveness across different tumour types in terms of treatment response and in the development of resistance or loss of response and its subsequent impact on PFS and OS. A systematic review of

basket and umbrella trials in oncology concluded that response rates varied not only by drug target, but also by tumour type within the same molecular target.<sup>38</sup>

Although studies 20288 and 20290 are not formally described as basket trials (notably due to the initial inclusion of patients with and without an NTRK fusion), they partially function as basket trials as they evaluate a treatment across a range of tumour types with a shared molecular target (NTRK fusion). Only patients with laboratory confirmed NTRK fusion solid tumours were included in the pooled analyses.

Given the targeted mode of action of larotrectinib, and the similarity of trial designs (single-arms with similar eligibility criteria) this approach to data pooling is understandable. However, as with the original TA630, the EAG is concerned by the appropriateness of pooling all the trial results data together, given the heterogeneous populations included in these trials (e.g. tumour types, age groups). The ERG's clinical advisers thought that tumour types are likely to influence PFS and OS following treatment with larotrectinib due to differences in prognosis. It may also be inappropriate to pool data from adults and children together since there may be considerable variation in time to progression and in subsequent overall survival.

As the included trials were not designed to test the assumption of heterogeneity of response across subgroups, the EAG considered it inappropriate to assume a common response rate independent of tumour histology. In absence of subgroup data at the time, an analysis of heterogeneity was performed by the company using a Bayesian Hierarchical Modelling (BHM) framework, to estimate the overall response rate that accounts for and explores the potential heterogeneity in effects across tumour types. This analysis found evidence of substantial heterogeneity, and is discussed in Section 3.2.4.1.

### 3.2.3 Critique of baseline characteristics

Table 9 presents baseline characteristics in the ePAS9 and SAS3 datasets, alongside the SACT dataset of patients who have received larotrectinib via the CDF, to assess the applicability of the trial evidence to NHS practice.

Across ePAS9 and SAS3, a total of 28 different tumour types were represented with the most common being soft tissue sarcoma (STS) (19.8%), [REDACTED], infantile fibrosarcoma (13.4%), lung cancer (8.8%), thyroid cancer (8.5%), [REDACTED] and [REDACTED].

The median age of patients was 44.5 years (range 0.0 to 90.0) for non-CNS solid tumours and [REDACTED] for primary CNS tumours. The proportion of females was [REDACTED] in both cohorts. Most patients had an ECOG performance status 0 or 1 ([REDACTED] of non-primary CNS and [REDACTED] of primary CNS patients). In ePAS9, [REDACTED] of patients had metastatic disease; [REDACTED] were naïve to prior systemic

therapy, compared with █████ in the SAS3 cohort. Most patients in ePAS9 had either NTRK1 or NTRK3 gene (█████ and █████ respectively), whereas most SAS3 patients had NTRK2 (█████). The rate of stable brain metastases at baseline was unknown (patients with symptomatic or unstable brain metastases were excluded from the pooled analyses).

The characteristics of the trial population differed from the population of patients treated with larotrectinib via the CDF in several ways. The distribution of prior lines of systemic therapy varied significantly between the trial and SACT evidence: █████ were treatment naïve across ePAS9 and SAS3, compared with only 2% in the SACT; █████ and █████ of the trial evidence had one and two prior LOT, respectively and █████ had three or more prior LOT. In contrast, the large majority of SACT patients had one prior LOT (80%), 8% had two prior LOT and 10% had three. A █████ proportion of patients in ePAS9 had metastatic disease (█████) compared with the SACT database (40%). The proportion of females was █████ higher in the trial evidence compared with SACT.

**Table 9 Baseline characteristics of trial evidence and SACT population**

| Characteristic                  | Categories                                                      | ePAS9<br>(n=304) | SAS3<br>(n=60) | SACT<br>(n=60) |
|---------------------------------|-----------------------------------------------------------------|------------------|----------------|----------------|
| Age (yrs)                       | Median age                                                      | 44.5 (0.0-90.0)  | █████          | -              |
|                                 | 0 to <20 for SACT [0 to <18 for trials]                         | █████            | █████          | 22 (37%)       |
|                                 | 20 to <50 for SACT [18 to 45 for trials]                        | █████            | █████          | 17 (28%)       |
|                                 | >50 for SACT [>45 for trials]                                   | █████            | █████          | 21 (35%)       |
| Sex                             | Female                                                          | █████            | █████          | 26 (43%)       |
| Performance status              | 0                                                               | █████            | █████          | 11 (18%)       |
|                                 | 1                                                               | █████            | █████          | 14 (23%)       |
|                                 | 2                                                               | █████            | █████          | 3 (5%)         |
|                                 | 3                                                               | █████            | █████          | 0              |
|                                 | NR                                                              | █████            | █████          | 32 (53%)       |
| Type of disease                 | Metastatic disease                                              | █████            | █████          | 24 (40%)       |
|                                 | Locally advanced with systemic therapy                          | █████            | █████          | 18 (30%)       |
|                                 | Locally advanced with surgical resection resulting in morbidity |                  | █████          | 17 (28%)       |
|                                 | Not captured                                                    | █████            | █████          | 1 (2%)         |
| Prior lines of systemic therapy | 0 (larotrectinib 1 <sup>st</sup> line)                          | █████            | █████          | 1 (2%)         |
|                                 | 1                                                               | █████            | █████          | 47 (78%)       |
|                                 | 2                                                               | █████            | █████          | 5 (8%)         |
|                                 | ≥3                                                              | █████            | █████          | 6 (10%)        |
| NTRK gene                       | NTRK1                                                           | █████            | █████          | 22 (37%)       |
|                                 | NTRK2                                                           | █████            | █████          | 18 (30%)       |
|                                 | NTRK3                                                           | █████            | █████          | 19 (32%)       |
| Brain metastases                | None                                                            | -                | █████          | 51 (85%)       |
|                                 | Brain metastases                                                | █████            | █████          | 8 (3%)         |
|                                 | Not captured                                                    | -                | █████          | 1 (2%)         |
| Race                            | White                                                           | █████            | █████          | -              |
|                                 | Asian                                                           | █████            | █████          | -              |



| Characteristic              | Categories                          | ePAS9<br>(n=304) | SAS3<br>(n=60) | SACT<br>(n=60) |
|-----------------------------|-------------------------------------|------------------|----------------|----------------|
|                             | Black or African American           | ■                | ■              | -              |
|                             | American Indian or Alaska Native    | ■                | ■              | -              |
|                             | Native Hawaiian or Pacific Islander | ■                | ■              | -              |
|                             | Multiple                            | ■                | ■              | -              |
|                             | Other                               | ■                | ■              | -              |
|                             | Not reported                        | ■                | ■              | -              |
| Time from diagnosis (years) | median (range)                      | ■                | ■              | -              |
| Tumour stage at diagnosis   | 0                                   | ■                | ■              | -              |
|                             | I                                   | ■                | ■              | -              |
|                             | II                                  | ■                | ■              | -              |
|                             | III                                 | ■                | ■              | -              |
|                             | IV                                  | ■                | ■              | -              |
|                             | Not reported, unknown               | ■                | ■              |                |

Sources: CS Tables 6 and 28.

ePAS9: extended primary analysis set 9. NR: Not Reported. NTRK: Neurotrophic Tyrosine Receptor Kinase. SACT: Systemic Anti-Cancer Therapy. SAS3: supplementary analysis set 3.

Table 10 presents the tumour types in the trial evidence and SACT population. The proportion of patients with primary CNS was significantly lower in the trial evidence (■) compared with the SACT (35%). Other differences included IFS (13% in trial evidence vs. 7% in SACT), lung (9% vs. 17%), and gastrointestinal tumours (■ vs. 5%) although comparisons are limited by small numbers of patients. Nearly half of the tumour types (13 of 28) in the trial evidence were not included in the SACT database (breast cancer, melanoma, pancreatic cancer, GIST, cholangiocarcinoma, gastric cancer, cervical cancer, CMN, prostate cancer, appendix cancer, duodenal cancer, external auditory canal and hepatic cancers) although these represented typically rarer types, and ■ of the trial evidence population. Two tumour types were only included in the SACT (forearm spindle cell sarcoma and head adenocarcinoma). The NTRK2 gene was more frequently expressed in the SACT (30% vs. ■), whereas NTRK3 was more common in the trial evidence (■ vs. 32%). NTRK1 expression was comparable between the trial evidence (■) and the SACT (37%). The proportion of patients with a record of brain metastases at baseline was higher in the SACT than in ePAS9 (13% vs. ■%)

Differences and limitations in reporting of age characteristics and other variables (including ECOG status, race, tumour stage and time from diagnosis) make further comparisons across trial evidence and the SACT difficult.

**Table 10 Primary tumour type in the trial evidence and SACT population**

|  | ePAS9 and SAS3 (n=364) | SACT (n=60) |
|--|------------------------|-------------|
|--|------------------------|-------------|

|                               |          |          |
|-------------------------------|----------|----------|
| Primary CNS                   | ■        | 21 (35%) |
| Soft tissue sarcoma           | 72 (24%) | 12 (20%) |
| Infantile fibrosarcoma        | 49 (16%) | 4 (7%)   |
| Lung adenocarcinoma           | 32 (11%) | 4 (7%)   |
| Non-squamous NSCLC            |          | 4 (7%)   |
| Lung (other)                  |          | 2 (3%)   |
| Thyroid                       | 31 (10%) | 3 (5%)   |
| Papillary thyroid carcinoma   |          | 2 (3%)   |
| Colorectal                    | ■        | 2 (3%)   |
| Forearm spindle cell sarcoma  | ■        | 1 (2%)   |
| Head adenocarcinoma           | ■        | 1 (2%)   |
| Oesophagus                    | ■        | 1 (2%)   |
| Salivary gland carcinoma      | ■        | 1 (2%)   |
| Salivary gland adenocarcinoma |          | 1 (2%)   |
| Breast                        | ■        | 0        |
| Melanoma                      | ■        | 0        |
| Pancreas                      | ■        | 0        |
| GIST                          | ■        | 0        |
| Cholangiocarcinoma            | ■        | 0        |
| Gastric                       | ■        | 0        |
| Cervix                        | ■        | 0        |
| CMN                           | ■        | 0        |
| Prostate                      | ■        | 0        |
| Appendix                      | ■        | 0        |
| Duodenal                      | ■        | 0        |
| External auditory canal       | ■        | 0        |
| Hepatic                       | ■        | 0        |
| Lipofibromatosis              | ■        | 0        |
| Testes                        | ■        | 0        |
| Thymus                        | ■        | 0        |
| Urothelial                    | ■        | 0        |
| Uterus                        | ■        | 0        |

Sources: CS Tables 6 and 28.

CNS: Central Nervous System. CMN: Congenital Mesoblastic Nephroma. ePAS9: extended primary analysis set 9. GIST: Gastrointestinal Stromal Tumour. NSCLC: Non-Small Cell Cancer. SACT: Systemic Anti-Cancer Therapy. SAS3: supplementary analysis set 3.

Overall, the EAG is concerned that the trial evidence may not be reflective of patients who are eligible for larotrectinib in the NHS. Differences in patient and disease characteristics, including the distribution of tumour types and prior lines of therapy, may affect response and survival outcomes and mean that the results of the trial evidence have limited applicability to the NHS. Clinical effectiveness results for the trial evidence are discussed in Section 2.3.2, and the SACT population outcomes are discussed in Section 3.3.3.

### 3.2.4 Critique of the results of the trials of the technology of interest

#### 3.2.4.1 Overall response rate

The primary outcome was ORR (i.e. CR or PR) as determined by Independent Review Committee (IRC) assessments, based on RECIST (Response Evaluation Criteria in Solid Tumours) v1.1 for non-CNS solid tumours, and RANO (Response Assessment in Neuro-Oncology) criteria for primary CNS tumours. The EAG agrees with the company that RANO is an appropriate choice for assessing responses in primary CNS patients as it is more suitable than RECIST.<sup>39</sup>

Table 11 shows that in the ePAS9 analysis set the ORR was 65% (95% CI 59 to 70), with confirmed response in 198 out of 304. This included 66 (22%) complete responses, 20 (7%) with CR by surgery/pathology (pCR), and 112 (37%) partial responses. In addition, ■ (■%) had stable disease lasting 16 weeks or more. In the SAS3 population, ORR was ■ (95% CI ■ to ■). This included ■ (■%) complete responses, and ■ (■%) partial responses. In addition, ■ (■%) had stable disease.

The CS did not discuss differences in response rates between primary CNS and other primary tumours. In response to a request for clarification from the EAG (CQ A14), the company noted that response was assessed with RANO, which has more stringent criteria than RECIST v1.1. The EAG accepts that this likely limits the comparability of responses between ePAS9 and SAS3. Although some research indicates that larotrectinib may have more limited brain penetration than other targeted therapies, to the EAG's knowledge, there is no conclusive evidence to explain the lower ORR and CR observed in primary CNS patients.<sup>40</sup>

**Table 11 Overall response in ePAS9 and SAS3 analysis sets**

|                                                         | <b>ePAS9<br/>(n=304)</b> | <b>SAS3<br/>(n=60)</b> |
|---------------------------------------------------------|--------------------------|------------------------|
| Number (%) of patients with OR<br>(confirmed CR/pCR/PR) | 198 (65)                 | ■                      |
| ORR, % [95% CI]                                         | 65 [59, 70]              | ■                      |
| <b>BOR*, n (%)</b>                                      |                          |                        |
| Any CR                                                  | 86 (28)                  | ■                      |
| CR                                                      | 66 (22)                  | ■                      |
| pCR                                                     | 20 (7)                   | ■                      |
| PR                                                      | 112 (37)                 | ■                      |
| SD ≥16 weeks                                            | ■                        | ■                      |

Source: CS Table 9

CR: complete response. ePAS9: extended primary analysis set 9. OR: Objective Response. ORR: Overall response Rate. pCR: pathological complete response. PR: partial response. SAS3: Supplementary Analysis Set 3. SD: Stable Disease

\* Response classification based on independent radiologist and independent clinical assessments for patients assessed by RECIST v1.1 (non-CNS patients) and based on independent radiologist assessments, clinical status, and corticosteroid use for patients assessed by RANO (CNS patients).

### ***Heterogeneity and subgroups***

As discussed in Section 3.2, the pooled analysis does not account for sources of heterogeneity other than the presence of primary CNS tumours. The company conducted additional analyses of ORR using the ePAS9 analysis set with three objectives: 1) To assess heterogeneity in response rates across tumour types, 2) generate an adjusted estimates of ORR that accounts for this heterogeneity, 3) predict the expected distribution of response rates in new, to be observed tumour types.

Two statistical approaches were used: a BHM, and a logistic regression model incorporating a random effect for tumour type.

### ***Bayesian Hierarchical Model***

The methods of the BHM are described in CS Appendix Q, Section Q1, with further details in an unpublished report.<sup>41</sup> The company carried out an analysis on overall response data across the different histology types with a Bayesian Hierarchical Model (BHM), using the ePAS9 data (July 2024 data cut). The aims of the analysis were to:

1. evaluate the heterogeneity in overall response rates (ORRs) across different histology types
2. to determine a heterogeneity-adjusted ORR, and
3. to predict the distribution of ORR in a new sample with undefined histology type.

The methods applied reflect those used by the EAG in TA630 EAG report section 4.6,<sup>42</sup> which follow Thall (2003)<sup>43</sup> and use a modified prior specification of the variance parameter according to Cunanan (2019).<sup>44</sup> The BHM estimates posterior probabilities of response for each tumour type, a pooled posterior probability of response across all tumour types, accounting for the potential heterogeneity of effect across tumours, and a predictive distribution that models the possible response in new and as yet untested tumour types using a Monte Carlo simulation.

The model uses the response rates per tumor type from the ePAS9 data and considers the data to follow a binomial distribution, with response rate varying per tumor type. The BHM assumes that for each of the tumour types, the log-odds of response are exchangeable and follow a normal distribution. Prior distributions are set-up for the pooled mean response and between-tumour heterogeneity and are likely to have some influence on the posterior estimates, particularly where a small number of tumour types are included.<sup>43, 44</sup> Primary CNS tumours (from SAS3) were excluded from the main BHM analysis but were included in a sensitivity analysis. Two other sensitivity analyses excluded tumour types with less than two and less than five patients studied respectively.

Results of the BHM are presented in CS Appendix Q, Section Q2. An ORR that does account for this heterogeneity was estimated as █████% (95% Prediction interval [PredI]: █████% to █████%) in the

main analysis, which is less favourable to larotrectinib than the unadjusted, main pooled analyses of ePAS9 (ORR 65% [95% CI 59% to 70%]).

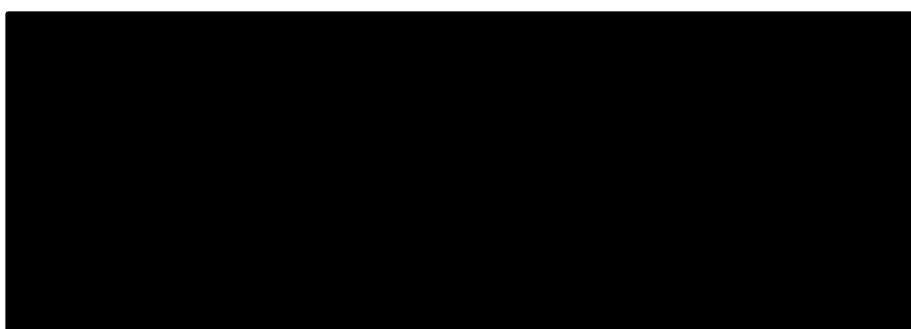
An estimate for the distribution of the predicted response rate of an as-yet unevaluated tumor type is presented in Figure 1 and shows a very wide spread across tumour types; this predicts that [REDACTED]% of all as-yet unevaluated tumor types with an NTRK gene fusion would show response rates of 50% or higher. Heterogeneity-corrected response rate per tumor type are presented in Figure 2 and illustrate the wide spread of response across tumour types, as well as uncertainty within tumour type.

Response rate for primary CNS (SAS3) was predicted as [REDACTED]% (95% PredI: [REDACTED]% to [REDACTED]%). Sensitivity analyses including the primary CNS cohort into the model (CS Appendix Q 1.3) yielded an ORR of [REDACTED]% (95% PredI: [REDACTED]% to [REDACTED]%) and residual variance was 30.29.

The main BHM analysis showed clear evidence of heterogeneity in ORR by tumour type  $\tau^2$ = [REDACTED] (95% PredI: [REDACTED] to [REDACTED]). A standard deviation of [REDACTED] on the logit scale indicates [REDACTED] of response rates on the original scale, regardless of the average response rate. The residual deviance (average variance of the observed estimates around their tumour-specific true effects) was 28.68. This is significantly larger than  $\tau^2$ , indicating that most (roughly 95%) of the total variance may be attributed to within-tumour variability (such as sampling error, sparse data in several tumour types and other unexplained within-group variability) rather than from between-tumour differences.

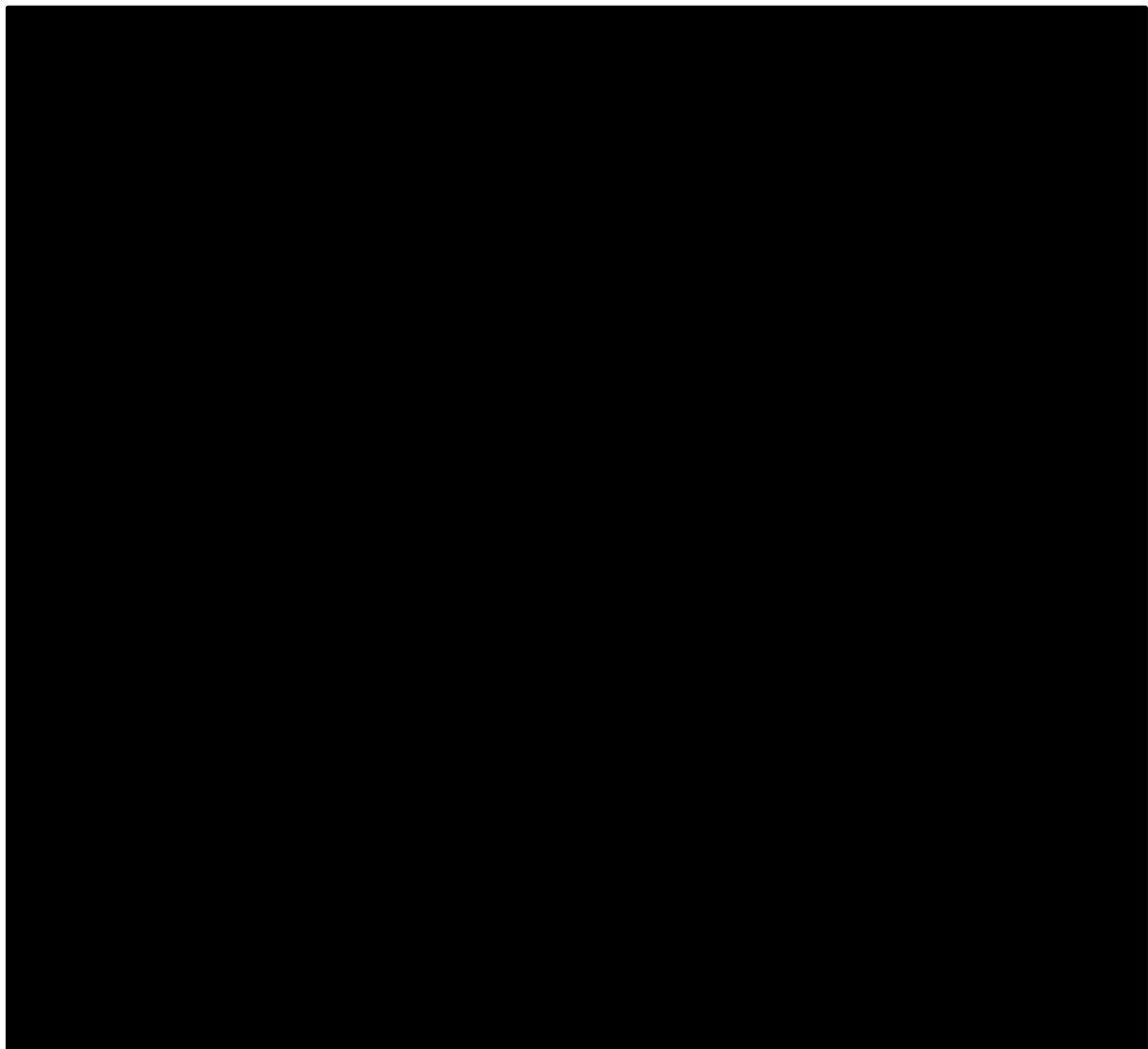
The main analysis of the BHM is based on the ePAS9 database which contains both adults (n=[REDACTED]) and children (n=[REDACTED]). Given subgroup differences observed between these subgroups (CS Appendix C), the EAG requested that the company re-run the base-case BHM analysis for adults and children separately (including overall and tumour-specific responses), and to provide a separate BHM analysis for the SAS3 database (CQ A13). The company declined to perform such analyses, because the resulting subgroups “would become extremely small” and lead to “unstable and highly uncertain estimates.” Although the EAG agrees that subgrouping would reduce power and precision, these subpopulations would be of the same size as those presented by the company in CS Appendix C (subgroup analyses), and these additional BHM analyses could provide a more robust approach to quantify the extent to which age differences may contribute to heterogeneity.

**Figure 1 Predicted density for response rate in a newly studied tumour type (ePAS9 BHM)**



Source: Figure 1; Bayer. Data on file. Larotrectinib BHM report. July 2024  
ORR:overall response rate.

**Figure 2 Forest plot of predicted response rates (with 95% PredI), by tumor type**



Source: Figure 2; Bayer (2025)<sup>41</sup>

CMN: Congenital Mesoblastic Nephroma. CUP: Cancer of unknown primary origin. GIST: Gastrointestinal Stromal Tumour. IFS: Infantile Sarcoma. ORR= overall response rate.

To assess the impact of tumor types that could not yet be studied in larger numbers, sensitivity analyses with fewer than two patients per tumour type were conducted (CS Appendix Q 1.4). These showed somewhat more favourable results to the main analyses, albeit with a similar spread of responses (pooled mean response ████% (95% PredI: ████% to ████%,  $\tau^2=1.49$ ). Sensitivity analyses excluding tumour types with fewer than five patients (CS Appendix Q 1.5) showed a higher weight towards higher ORR values compared to the main analyses (pooled mean response ████% (95% PredI: ████ to ████,  $\tau^2=NR$ ). It is unclear whether these sensitivity analyses were prespecified, and the choice of threshold (e.g. fewer than five patients) appears somewhat arbitrary. The exclusion of less represented tumour types may lead to selection bias, as these tumour types tended to show lower response rates; the risk that these tumour types were less represented in the trial evidence in part due

to their lower response to therapy cannot be excluded. Overall, the EAG considers that these sensitivity analyses fail to explain most of the heterogeneity observed in the main BHM analyses and may be biased in favour of larotrectinib.

The BHM is the EAG's preferred approach to explore heterogeneity by tumour type. It provides a probabilistic posterior distribution of between-tumour heterogeneity, an adjusted overall ORR estimate that integrates uncertainty and is able to yield predictive distributions for new tumour types that propagate between-group variance uncertainty. A frequentist approach that uses a random-effect logistic regression (conducted by the company as requested by the EMA but not reported)<sup>41</sup> is cruder as it does not characterise or integrate uncertainty as effectively and does not yield true posterior predictive distributions. Although we acknowledge that results can be sensitive to prior assumptions, the larger number of tumour types and greater sample size of the 20<sup>th</sup> July 2024 data cut mean that the results of the BHM are likely to be more robust than the original TA630 BHM analyses. Despite the large residual variance, the ORR estimate appropriately reflects heterogeneity and uncertainty, unlike the ePAS9 pooled analyses. However, it indicates significant unexplained heterogeneity, therefore ORR estimates across the ePAS9 dataset may not be informative.

### *Subgroup analyses*

Subgroup analyses were reported for ORR (IRC) in CS Appendix C, according to the following subpopulations: age at enrolment, paediatrics vs. adults, sex, race, ECOG status, NTRK gene, NTRK gene fusion, primary cancer diagnosis, cancers considered pathognomonic for NTRK gene fusions, disease status, number of prior systemic therapies, number of prior systemic regimens in the metastatic/unresectable setting and excluding radioactive iodine, best overall response (BOR) to most recent prior systemic regimen or treatment course, and starting dose of larotrectinib and frequency of administration. Although these subgroups were described as pre-planned by the company, no subgroup analyses were conducted for the pooled analyses of the same trials at the earlier data cut submitted in the original TA630.

Table 12 summarises subgroup results by patient characteristics at baseline, with further details in CS Appendix C1. A [REDACTED] ORR was seen in the paediatric population compared to adults, and males compared to females in both ePAS9 and SAS3. In ePAS9, patients with locally advanced disease had a [REDACTED] ORR ([REDACTED]% [95% CI [REDACTED] to [REDACTED]]) than those with metastatic disease ([REDACTED]% [95% CI [REDACTED] to [REDACTED]]). Although no tests for subgroup differences were reported, 95% confidence intervals between these subgroups did not overlap, indicating that these differences were statistically significant. In ePAS9, treatment naïve patients had a higher ORR ([REDACTED]%) than patients with one or more prior line of systemic therapy (ORR [REDACTED]% to [REDACTED]%), whereas there was no notable trend in SAS3. Fitter patients (ECOG 0) tended to have [REDACTED] response rates, and IRC-assessed ORRs ranged from [REDACTED] across NTRK



genes, although confidence intervals were wide especially (and unsurprisingly) in the smaller subgroups.

**Table 12 ORR by baseline characteristics (ePAS9 and SAS3, data cut 20th July 2024)**

|                                          | ePAS9          |                         |                | SAS3           |                         |                |
|------------------------------------------|----------------|-------------------------|----------------|----------------|-------------------------|----------------|
|                                          | Total patients | Patients with CR/pCR/PR | ORR % [95% CI] | Total patients | Patients with CR/pCR/PR | ORR % [95% CI] |
| <b>Overall</b>                           | 304            | 198                     | 65 [59, 70]    | 60             | ■                       | ■              |
| <b>Age</b>                               |                |                         |                |                |                         |                |
| Adults (≥18 years)                       | ■              | ■                       | ■              | ■              | ■                       | ■              |
| Paediatrics (<18 years)                  | ■              | ■                       | ■              | ■              | ■                       | ■              |
| <b>Sex</b>                               |                |                         |                |                |                         |                |
| Male                                     | ■              | ■                       | ■              | ■              | ■                       | ■              |
| Female                                   | ■              | ■                       | ■              | ■              | ■                       | ■              |
| <b>Baseline ECOG performance status</b>  |                |                         |                |                |                         |                |
| 0                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| 1                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| 2                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| 3                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| <b>Baseline disease status</b>           |                |                         |                |                |                         |                |
| Metastatic                               | ■              | ■                       | ■              | ■              | ■                       | ■              |
| Locally advanced                         | ■              | ■                       | ■              | ■              | ■                       | ■              |
| <b>NTRK gene</b>                         |                |                         |                |                |                         |                |
| NTRK3                                    | ■              | ■                       | ■              | ■              | ■                       | ■              |
| NTRK1                                    | ■              | ■                       | ■              | ■              | ■                       | ■              |
| NTRK2                                    | ■              | ■                       | ■              | ■              | ■                       | ■              |
| <b>Number of prior systemic regimens</b> |                |                         |                |                |                         |                |
| 0                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| 1                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| 2                                        | ■              | ■                       | ■              | ■              | ■                       | ■              |
| ≥3                                       | ■              | ■                       | ■              | ■              | ■                       | ■              |

Source: Adapted from CS appendix C, Tables 1, 3 and 4.

CI: confidence interval. CR: complete response. ECOG: Eastern Cooperative Oncology Group. ePAS9: Extended Primary Analysis Set 9. IRC: Independent Review Committee. ORR: overall response rate. pCR: pathological CR. PR: partial response. SAS3: Supplemental Analysis Set 3

Response rates varied widely by tumour types (CS Appendix C2). In tumour types with five or more patients, response rates ranged from ■% (95% CI ■ to ■) in pancreatic cancer, to ■ (95% CI ■% to ■%) in IFS. ■ response was observed in ■ of the ■ tumour types with only one or two cases.

In response to an EAG request for clarification (CQ A12), the company stated that the variation in ORR is primarily explained by prognostic factors rather than differential drug activity. Whilst the EAG agrees that the company's analyses indicate wide variation in ORR according to prognostic factors, they are exploratory and do not provide sufficient evidence to rule out the modifying effect of other variables. For instance, EAG clinical advisers considered that the limited brain penetration of larotrectinib (relative to entrectinib) was a plausible hypothesis that might have contributed to the limited observed response in patients with primary CNS in the trial evidence and in observational studies,<sup>45</sup> although further evidence is required.<sup>40</sup>

Overall, the subgroup analyses show wide variation in response rates across tumour types and several patient characteristics. The large number of subgroups and limited sample size of the pooled datasets mean that many of these analyses lack power and may lead to chance findings (no tests for between-subgroup differences were reported). However, along with the results of the BHM analyses, these findings support the EAG's conclusion that the pooled estimates of ORR from ePAS9 and SAS3, which do not account for heterogeneity across widely different populations, are likely to be misleading.

#### 3.2.4.2 Overall survival

In the ePAS9 dataset, median follow-up period was [REDACTED] months. The median OS was not estimable at the data cut-off on 20<sup>th</sup> July 2024, with [REDACTED] ([REDACTED]%) death events recorded. The probability of being alive at 72 months was [REDACTED]% (95% CI: [REDACTED] to [REDACTED]).

In the SAS3 dataset, median follow-up period was [REDACTED] months. The median OS was not estimable, and [REDACTED] ([REDACTED]%) death events were recorded. The probability of being alive at 72 months was [REDACTED]% (95% CI: [REDACTED] to [REDACTED]).

Although OS follow-up duration and the sample size of the cohorts with and without primary CNS are substantially greater than in the original TA630 CS, OS is still immature, with median OS not reached in ePAS9 and SAS3.

Sources of heterogeneity were not explored in the CS (other than presence of primary CNS), although following a CQ from the EAG, post-hoc subgroup analyses were presented for OS and PFS by age group (adults and paediatrics), separately for ePAS9 and SAS3. Median OS and PFS estimates are presented in Table 13, with Kaplan Meier data presented in the company response to CQ A15 and reproduced below (Figure 3). This data shows [REDACTED] in median OS estimates according to age group and the presence of primary CNS. In ePAS9, [REDACTED]% of paediatric patients were still alive at 72 months, compared with [REDACTED]% of paediatric patients in SAS3; median OS was [REDACTED] in children included in ePAS9 and SAS3, indicating that the paediatric data for OS is still immature. In ePAS9 adults, median OS was [REDACTED] months (95% CI [REDACTED] to [REDACTED]), compared to [REDACTED] months in SAS3 (95% CI [REDACTED] to [REDACTED]).

Although in theory, the BHM can be applied to OS, assuming exchangeability of effects of treatment on survival outcomes across histologies is harder to justify than the equivalent assumption made for response outcomes and is likely to be confounded by prognostic heterogeneity across different tumour types. Therefore, the EAG considers that the lack of BHM analysis for OS (and other time to event outcomes) across all tumour types and age groups in ePAS9 is appropriate.<sup>46</sup> Given the results of the subgroup analyses, prognostic heterogeneity across several patient characteristics and 28 tumour

types, and the evidence of heterogeneity for ORR, the EAG considers that unadjusted pooled OS estimates from the ePAS9 and SAS3 are unlikely to be reliable to inform decisions across tumour types.

Given the differences in distribution of tumour types and patient characteristics between the clinical trial evidence and the SACT (see Section 3.2.3), the EAG is concerned these pooled OS estimates may not be applicable to NHS practice.

**Table 13 Summary of PFS and OS for adults and paediatric populations in ePAS9 and SAS3 (data cut 20th July 2024)**

|                             | No primary CNS tumour (ePAS9) |                   | Primary CNS tumour (SAS3) |                   |
|-----------------------------|-------------------------------|-------------------|---------------------------|-------------------|
|                             | Adults (n=██)                 | Paediatrics (n=█) | Adults (n=██)             | Paediatrics (n=█) |
| Median PFS, months (95% CI) | ██                            | ██                | ██                        | ██                |
| Median OS, months (95% CI)  | ██                            | ██                | ██                        | ██**              |

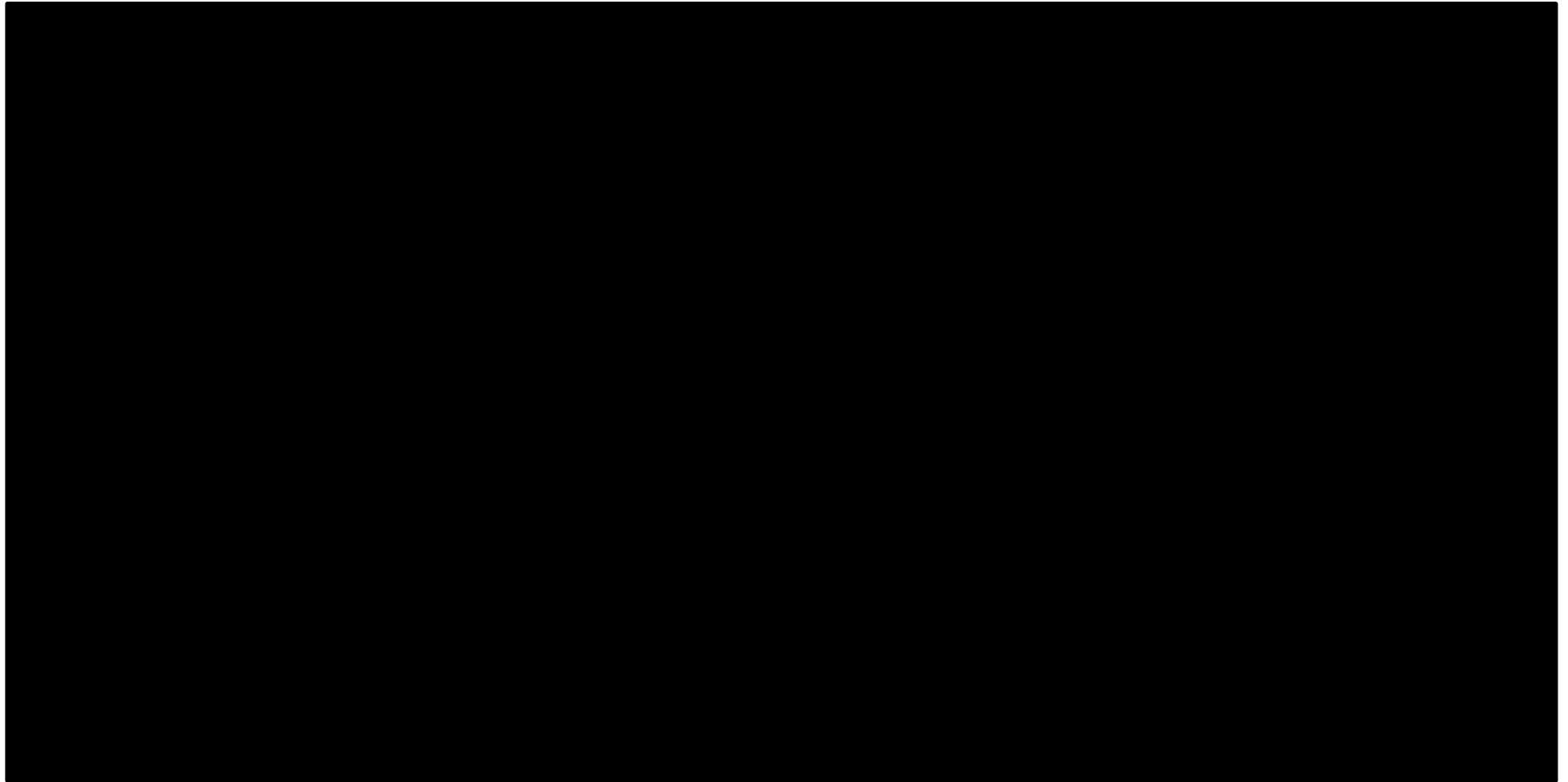
Source: Company response to point for clarification A15, Tables 6-13.

CI: Confidence Interval. CNS: central nervous system. ePAS9 = Extended Primary Analysis Set 9. NE: not estimable. PFS: progression-free survival. ORR: Overall response Rate. OS: overall survival. SAS3 = Supplemental Analysis Set 3.

██% still alive at 72 months.

\*\*██% still alive at 72 months

**Figure 3 Kaplan-Meier curves of overall survival for adults and children, in ePAS9 and in SAS3**



Source: Company response to point for clarification A15, Figures 9-12

### *Subsequent therapies*

CS Section 2.7 states that only █ of patients received subsequent therapies after treatment with larotrectinib, however, this figure is misleading as it appears to only include a subset of patients (i.e. only those who received another subsequent NTRK inhibitor and were censored in ePAS9 (CS Table 18). In response to CQs from the EAG, the company provided a breakdown of subsequent therapies for paediatric and adult patients in ePAS9 and SAS3. These are reproduced below (Table 14 and Table 15). In ePAS9, across all ages, █ (█%) received a subsequent NTRK inhibitors, and █ (█%) had another systemic therapy. In SAS3, █ (█%) received other systemic therapies and █ (█%) had radiotherapy.

This raises two potential concerns. Firstly, the relatively high rates of subsequent therapies further support the EAG's view that the ePAS9 and SAS3 populations have limited applicability to NHS practice, where patients receive larotrectinib where no other satisfactory treatment option is available, and would not be eligible for subsequent NTRK inhibitor treatment.

Secondly, the EAG is concerned that OS outcomes are at risk of confounding bias due to the use of subsequent systemic therapies following progression on larotrectinib. Post-hoc analyses of ePAS9 that censored data for █ (█%) patients who received subsequent therapies after treatment with larotrectinib are reported in CS Section 2.7. Median follow-up period was █ months, and median duration of OS was █ months (95% CI █ to █). The probability of being alive at 72 months was █% (compared with █% in the pooled analyses). The median OS █ though this excludes most subsequent anticancer therapies (systemic and non-systemic) received by patients, and is therefore likely to underestimate the potential impact of subsequent treatments. Post-hoc analyses of SAS3 that censored █ patients (█%) because they started a subsequent treatment showed that median OS was █ (█ months [95% CI █ to █]), and the percentage of patients alive at 72 months was unclear. PFS2 analyses could not be provided, as all progression assessments were relative to the original trial baseline, and not be reevaluated against baseline assessments following progression on larotrectinib (see company response to CQ A11). Overall, the magnitude of confounding bias due to subsequent anticancer therapies in ePAS9 and SAS3 is uncertain.

**Table 14 Summary of subsequent therapies (ePAS9)**

| Subsequent Therapy         | Paediatrics (Age < 18 years)<br>N=99 (100%) | Adults (Age ≥18 years)<br>N=205 (100%) | Total<br>N=304 (100%) |
|----------------------------|---------------------------------------------|----------------------------------------|-----------------------|
| NTRK inhibitor therapies   | ■                                           | ■                                      | ■                     |
| Other systemic therapies   | ■                                           | ■                                      | ■                     |
| Radiotherapy               | ■                                           | ■                                      | ■                     |
| Surgery                    | ■                                           | ■                                      | ■                     |
| Cryoablation of tumor      | ■                                           | ■                                      | ■                     |
| Radioactive iodine therapy | ■                                           | ■                                      | ■                     |

Source: Company response to clarification questions B9, Table 21

ePAS9: Extended Primary Analysis Set 9. SAS3: NTRK: Neurotrophic Tyrosine Receptor Kinase

Note: Patients may be counted in more than one row

**Table 15. Summary of subsequent therapies (SAS3)**

| Subsequent Therapy         | Paediatrics (Age < 18 years)<br>N=■ (100%) | Adults (Age ≥ 18 years)<br>N=■ (100%) | Total<br>N=■ (100%) |
|----------------------------|--------------------------------------------|---------------------------------------|---------------------|
| Other systemic therapies   | ■                                          | ■                                     | ■                   |
| Radiotherapy               | ■                                          | ■                                     | ■                   |
| Radioactive iodine therapy | ■                                          | ■                                     | ■                   |
| Surgery                    | ■                                          | ■                                     | ■                   |
| Systemic and radiotherapy  | ■                                          | ■                                     | ■                   |

Source: Company response to clarification questions A10, Table 3

SAS3: Supplemental Analysis Set 3

Note: Patients may be counted in more than one row

### 3.2.4.3 Progression-free survival

In ePAS9, the median PFS (IRC) was 28.0 months (95% CI 22.0 to 38.2), with a median follow-up of ■ months. In SAS3, median PFS was ■ months (95% CI: ■ to ■), and the median follow-up duration was ■ months.

PFS data is more mature than in the original TA630 (July 2018 data cut) and is based on IRC assessments therefore these PFS analyses address some of the uncertainty highlighted in the original EAG report.<sup>42</sup> Subgroup analyses by age group showed wide variation in PFS outcomes between adults and children in both ePAS9 and SAS3 (see Table 7, and CQ response A15). Similarly to OS, the EAG is concerned by the prognostic heterogeneity across patient characteristics and 28 tumour types, and the evidence of heterogeneity in ORR. Therefore, the EAG considers that unadjusted pooled PFS estimates from the ePAS9 and SAS3 are unlikely to be informative.

The differences between the clinical trial and the SACT populations mean that, similarly to OS, the EAG is concerned that these pooled PFS estimates may not be applicable to NHS practice.

3.2.4.4 Time to response

Time to response (TTR) outcomes are presented in CS Section 2.6.1.2.4. Median TTR in responders was similar between ePAS9 (■ months) and SAS3 (■ months). Whilst most responders had their first response within two months of initiating treatment in ePAS9 (■%) and SAS3 (■%), the range of time to first responses was wide in ePAS9 (■ to ■) and SAS3 (■ to ■), and a ■ of patients had their first response after 9 months of therapy (■% in ePAS9 and ■% in SAS3), raising questions about the appropriate duration of treatment with larotrectinib when a response is not observed (i.e. a stopping rule).

3.2.4.5 Duration of response

In ePAS9, 198 patients (65%) in ePAS9 had achieved a response (IRC). The median follow-up was 45.1 months and the median duration of response (DoR) was 43.3 months. The probability of retaining a response was ■% (95% CI: ■) at 6 months, and ■% (95% CI: ■) at 60 months.

In SAS3, ■ patients (■%) achieved a response (IRC), with median follow-up of ■ months and median DoR of ■ months<sup>47</sup>. The probability of retaining a response at six months was ■% (95% CI: ■) and ■% (95% CI: ■) at 60 months.

Observed duration of response was ■ in patients with primary CNS than patients without primary CNS. However, these results do not account for tumour-specific prognosis in ePAS9, which is likely to vary across the wide range of tumour types included in ePAS9, nor the wide range of patient characteristics in the trial evidence, therefore these pooled estimates may not be informative.

3.2.4.6 Adverse effects

Data on adverse events were derived from the safety analysis cohort of ■ patients who had received at least one dose of larotrectinib and a documented NTRK fusion cancer at the 20<sup>th</sup> July 2024 data cut (NTRK Gene Fusion Cancers Safety Analysis Set, NFCSAS). Results were reported in CS Section 2.11, and a summary is presented in Table 16. The median time on treatment was ■ months (range ■ to ■); mean time on treatment was ■ months (SD ■).

Grade 3 or 4 treatment-emergent adverse events (TEAEs) occurred in ■% of patients; ■ patients (■%) had a grade 3 or 4 TEAE considered to be related to larotrectinib. A total of ■ (■%) fatal TEAE occurred, although none were considered related to larotrectinib.

Table 16 Overall summary of adverse events (data cut-off 20<sup>th</sup> July 2024)

|          | Incidence, n (%)<br>NTRK Gene Fusion Analysis Set<br>(N=■) |
|----------|------------------------------------------------------------|
| Any TEAE |                                                            |

|                                                      | Incidence, n (%)<br><i>NTRK</i> Gene Fusion Analysis Set<br>(N=■) |
|------------------------------------------------------|-------------------------------------------------------------------|
| All                                                  | ■                                                                 |
| Related to larotrectinib                             | ■                                                                 |
| <b>Grade 3 or 4 TEAE</b>                             |                                                                   |
| All                                                  | ■                                                                 |
| Related to larotrectinib                             | ■                                                                 |
| <b>TEAE leading to larotrectinib discontinuation</b> |                                                                   |
| All                                                  | ■                                                                 |
| Related to larotrectinib                             | ■                                                                 |
| <b>Serious TEAE</b>                                  |                                                                   |
| All                                                  | ■                                                                 |
| Related to larotrectinib                             | ■                                                                 |
| <b>Fatal TEAE</b>                                    |                                                                   |
| All <sup>a</sup>                                     | ■                                                                 |
| Related to larotrectinib                             | ■                                                                 |

Source: CS Table 24

TEAE: treatment emergent adverse events. *NTRK*: Neurotrophic Tyrosine Receptor Kinase

The most frequent TEAEs of any cause were gastrointestinal disorders (n=■), general disorders and administration site conditions (n=■), infections and infestations (n=■), investigations (n=■), nervous system disorders (n=■), respiratory, thoracic and mediastinal disorders (n=■), and metabolism and nutrition disorders (n=■). The most common TEAE that were related to larotrectinib included increased ■ (■%), increased ■ (■%), ■ (■%), ■ (■%), ■ (■%) and decreased ■ (■%), ■ (■%), ■ (■%), increased ■ (■%), ■ (■%), and decreased ■ (■%).

Half of the NFCSAS patients (■ [■]%) had a TEAE leading to either larotrectinib dose modification (dose reduction or different frequency) or interruption. Among ■ patients (■%) who experienced TEAEs leading to permanent treatment discontinuation, ■ (■%) were directly related to larotrectinib.

Considering the stage of disease at which patients receive larotrectinib, and their limited treatment alternatives, the ERG considers the safety profile of larotrectinib to appear acceptable.

#### 3.2.4.7 Health-related quality of life

Health-related quality of life (HRQoL) was an exploratory endpoint measured in studies in 20289 and 20290 up to the data cut of 20<sup>th</sup> July 2021 (ePAS6). The EAG requested from the company that they clarify why HRQoL data was not available for ePAS9 (CQ A8). The company replied that although HRQoL data were collected for ePAS9, a formal analysis has not yet been conducted, due to the extensive nature of this analysis and the need to prioritise the completion of the EQ-5D analysis for the economic model. However, utilities that informed the company base case analysis are based on the July 2024 data cut.



Of the [REDACTED] patients under treatment at baseline in studies 20289 and 20290, [REDACTED] ([REDACTED]%) patients ([REDACTED] adults, [REDACTED] infants, and [REDACTED] children) had at least one assessment during the study and were included in the HRQoL analyses; [REDACTED] ([REDACTED]%) had HRQoL measured at baseline and at least once after baseline.<sup>48</sup>

Results were presented for the following outcome measures: EORTC QLQ-C30 and EQ-5D-5L for adults, and PedsQL and FACES for children, expressed as number of patients with median and best post-baseline scores at or above their baseline score, and as number of patients with sustained improvement. A summary is presented in CS Table 15, with further details in CS Appendix N.

The EAG considers that the HRQoL results have several important limitations. These data are based on subjective, self-assessed outcomes in an open-label, single arm study. This means it is not possible to distinguish the treatment effect from any patient expectation of effects of a targeted therapy. Bias will also have been introduced by reporting results for the ‘best change’ from baseline, rather than changes from baseline at specific time points. HRQoL results are only presented for a data cut from July 2021, even though data were collected for the July 2024 data cut for ePAS9, raising the risk of selective reporting bias. The data cut presented only includes a subset of the ePAS9 population and therefore exclude primary CNS patients; population characteristics were not presented in the CS and it is unclear to what extent this population represents NHS patients without primary CNS. These analyses are exploratory and post-hoc, as the original protocol and SAP for the combined analysis of 20289 and 20290 did not pre-specify HRQoL. Only [REDACTED] of patients included in the HRQoL assessments had a follow-up assessment. Although missing follow-up HRQoL data is not unusual in cancer trials, and the missing assessment reasons were reported as due to administrative reasons or to error ‘for many patients’, there are missing assessments without a reason (numbers not reported).<sup>48</sup> Data was assumed to be missing at random in mixed models for repeated measurements, and no alternative analyses were presented to explore the potential impact of missing data. Assuming that HRQoL data is missing at random is a strong assumption that may not hold in trials of cancer patients with advanced and metastatic disease. For instance, patients who are sicker or have lower HRQoL may be less likely to fill in HRQoL questionnaires. Therefore, the EAG is concerned that further bias may have been introduced by missing data. Although the magnitude and direction of overall bias are difficult to predict, the EAG expects that the addition of these potential biases may favour larotrectinib.

### 3.3 Critique of observational studies

#### 3.3.1 Critique of design of observational studies

Four additional single-arm studies containing observational data about the efficacy and safety of larotrectinib have been cited by the company as ‘supportive evidence’. These are a) SACT,<sup>3</sup> b) the prospective non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib (ON-TRK),<sup>30</sup> c) Larotracking<sup>31</sup> and d) French National Prospective Observational Cohort Aiming to be Comprehensive of Paediatric Patients Treated with Larotrectinib for Locally Advanced or Metastatic Tumours with NTRK Gene Fusion (SACHA).<sup>32</sup> No sources of RWE were used to directly inform the company’s economic modelling.

##### 3.3.1.1 SACT

SACT<sup>3</sup> is based on CDF (Blueteq) applications made for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours between 20<sup>th</sup> April 2020 and 31<sup>st</sup> December 2024. Of 62 unique patients, the SACT analysis included 60 patients with locally advanced or metastatic tumours with NTRK gene fusion for whom CDF funding was requested and granted (1/62 died before treatment and the data of 1/62 were missing). NTRK-fusion status was determined by a nucleic-acid based assay organised and validated by regional genomic labs hub. Larotrectinib was given for a median 818 days. The EAG considers this database to be highly relevant to the target population because patients were treated in the NHS following NICE TA630 guidance.

The sample size of the SACT was small, and there was no stratification for potential outcome modifiers such as CNS/non-CNS site, or age-group. The EAG requested stratified data in CQ A17 and A18, but the company reported that the SACT team were unable to provide such information, as “these were not outlined in the Data Collection Arrangement”. Time to treatment discontinuation (TTD) was reported, but PFS and safety were not measured. Although response outcomes were made with a RECIST radiological assessment, this was only performed on 43 participants at 10 weeks.

##### 3.3.1.2 ON-TRK

ON-TRK<sup>30</sup> is an ongoing, prospective, open-label, multicentre, non-interventional global study including children and adult patients with locally advanced or metastatic tumours with NTRK gene fusion (NCT04142437). The method used to determine NTRK-fusion status was not reported. This study includes patients from Asia Pacific, Europe and US. The primary objective of this study was to describe the incidence of TEAEs, and secondary outcomes included describing the effectiveness of larotrectinib by local investigator assessment. The results included 120 patients in the safety analysis set, and 111 in the full analysis (efficacy) set at the 19<sup>th</sup> December 2024 data cut. No information was provided on outcomes monitoring and evaluations. The study is funded by Bayer.<sup>35</sup>

### 3.3.1.3 *Larotracking*

The Larotracking<sup>31</sup> is a French national, open-label, retrospective and prospective, observational study funded by Bayer comprising 26 adult patients derived from clinical centres in France, who were given larotrectinib (starting dose of 100mg twice daily for 25 patients) for a median 549 days. NTRK-fusion status was determined by RNA-based sequencing (n=20) and ‘various technologies’ (n=6).<sup>31</sup> The primary objective was to measure efficacy, though safety data were also collected. Patients were adults (>25 years old) with locally advanced or metastatic tumours with NTRK gene fusion. ORR data were collected according to RECIST. Results were presented in a report from the final analysis (December 2024 data cut).

### 3.3.1.4 *SACHA*

The SACHA (or SACHAxLaro) study is a prospective, multicentre, national observational registry (NCT04477681)<sup>32</sup> that includes children and adults ≤25 years old with NTRK fusion-positive locally advanced or metastatic solid tumours, who were given a median starting dose of larotrectinib of 100mg twice daily for a median 249 days. NTRK-fusion status was determined by FISH for one participant,<sup>32</sup> but the method for others was not reported. Interim results from this ongoing study were presented for 23 patients in a report that included data from May 2021 until December 2024. The study protocol indicates that larotrectinib treatment was to be provided through the French early access authorization and compassionate use programs or as an off-label treatment.<sup>49</sup>

No information was provided on outcomes monitoring and evaluations, such as those for ORR. SACHA is a collaboration between Bayer France and the Gustave Roussy Institute.<sup>32</sup>

### 3.3.1.5 *Overall limitations of the studies*

In addition to the specific limitations that have been outlined for each study, none of the studies were published, and information from the unpublished reports were very limited. In addition, all studies were single arm, with small numbers. Finally, the EAG has concerns about how these observational trials were selected for consideration, as they were not derived from the SLR, and no explanation for their selection was provided. This is a concern for the EAG, as in the absence of systematic inclusion criteria, it is possible that these studies were hand-picked.

## 3.3.2 **Critique of baseline characteristics**

The baseline characteristics of these four databases are shown in Appendix Table 48. Differences with the SACT data in sex, performance status, tumour types, disease characteristics and prior LOT limit the applicability of the non-UK observational studies to NHS practice.

### 3.3.3 Critique of the results of observational studies

Efficacy results from the SACT,<sup>3</sup> ON-TRK,<sup>30</sup> Larotracking<sup>31</sup> and SACHA<sup>32</sup> observational studies (alongside the trials, for comparison) are shown in Table 18.

The internal validity of the efficacy data is limited, as the lack of any comparator makes it impossible to distinguish treatment effects from intervening effects. Alongside the other limitations outlined in section 3.2.2, means that any interpretations of efficacy should be made with caution.

#### 3.3.3.1 SACT

Median follow-up was 19.4 months. Median OS was 45.2 months and 22/60 (36.7%) had died by the end of follow up. Confidence intervals could not be produced due to insufficient number of events. Complete response was achieved by 3/43 (7%) of participants, 28/43 (65%) achieved partial response, 12/43 (28%) had stable disease and none had progressive disease. At data cut-off, 32/60 (53%) were identified as being no longer on treatment; nearly half of those (47%, 15/32) stopped treatment due to disease progression. Time to treatment discontinuation (TTD) was a median of 26.9 months. The EAG requested a Kaplan Meier graph for TTD (CQ A19), but the company replied that the data to create the KM plot were not available from the SACT team.

Table 17 presents OS rates at time intervals in the SACT, alongside ePAS9 and SAS3. Any naïve comparisons between data sources are limited and should be made with caution, due to immature data, censoring, small patient numbers, study designs and differences in populations.

**Table 17 OS rates at time intervals in SACT, ePAS9 and SAS3**

|            | <b>SACT [% (95% CI)]<br/>(N=60)</b> | <b>ePAS9 [% (95% CI)]<br/>(N=304)</b> | <b>SAS3 [% (95% CI)]<br/>(N=60)</b> |
|------------|-------------------------------------|---------------------------------------|-------------------------------------|
| ≥6 months  | 93 [87, 100]                        | ■                                     | ■                                   |
| ≥12 months | 86 [77, 95]                         | ■                                     | ■                                   |
| ≥18 months | 69 [57, 83]                         | ■                                     | ■                                   |
| ≥24 months | 69 [57, 83]                         | ■                                     | ■                                   |
| ≥36 months | 60 [47, 77]                         | ■                                     | ■                                   |
| ≥48 months | 49 [34, 69]                         | ■                                     | ■                                   |
| ≥60 months | NE                                  | ■                                     | ■                                   |
| ≥72 months | NE                                  | ■                                     | ■                                   |
| ≥84 months | NE                                  | ■                                     | ■                                   |

Source: CS Table 14 and 32

SACT: Systemic Anti-Cancer Therapy database. NE: Not estimable

#### 3.3.3.2 ON-TRK

Outcomes from the ON-TRK study were stratified into non-CNS (n=66) and CNS (n=30) tumour types.

For the non-CNS subgroup, the median OS and median duration of response were not reached, at a mean follow up of 12.45 months. Median PFS was 20.21 months. A complete response was observed in 22.7% of participants, partial response in 37.9%, stable disease in 21.2% and progressive disease in 18.2%. The disease control rate at 24 weeks was 77.3%.

For the CNS population, the median OS was 12.3 months, at a mean follow up of 7.2 months. Median PFS was 4.12 months. A complete response was observed in 6.7% of participants, partial response in 16.7%, stable disease in 46.7% and progressive disease in 30.00%. The disease control rate at 24 weeks was 55.3%, and the disease control rate at 24 weeks was 53.3%.

Adverse events were pooled across both strata; 88.3% of participants experienced treatment emergent adverse events, 59.2% had treatment related adverse events. 9.17% of adverse events were fatal. More details are provided in Table 19.

#### *3.3.3.3 Larotracking*

Median OS was 38 months, at a mean follow up of 53.9 months, and overall mortality was 57.7%. Median PFS was 16.3 months. Complete response was seen in 15.4%, partial response in 53.8%, stable disease in 11.5% and progressive disease in 19.2%. The median duration of response was 18.75 months. Treatment cessation due to disease progression was 57.7%, and treatment cessation due to disease progression or death was 69.2%; 23.1% had targeted post-larotrectinib treatment. Safety data showed 34.6% had an adverse event grade 2 or higher. More details are provided in Table 19.

#### *3.3.3.4 SACHA*

Overall mortality was 26.1%, but no data were available for OS or PFS. Complete response was seen in 9%, partial response in 59%, stable disease in 13.5% and progressive disease in 18.5%. Treatment cessation due to disease progression occurred in 58%, and 21.7% had post larotrectinib treatment with targeted therapy. Only 13% of participants were reported to experience adverse events (see Table 19).

**Table 18 Effectiveness results from the observational evidence**

| Outcomes                                                                       | SACT 2025<br>(n=60)          | ON-TRK [FAS,<br>non-CNS, n=■] | ON-TRK<br>[FAS, CNS,<br>n=■] | LAROTRACKING<br>[N=26]           | SACHA [n=■]   |
|--------------------------------------------------------------------------------|------------------------------|-------------------------------|------------------------------|----------------------------------|---------------|
| Median duration of follow up for OS (95% CI) months                            | 19.4 [min: 3.7, max: 59.5]   | ■                             | ■                            | 53.9 (45.1, 61.1)                | -             |
| Median OS (95% CI) months                                                      | 45.2                         | ■                             | ■                            | 38.3(12.3, NE)                   | -             |
| Overall mortality (%)                                                          | 22/60 at end of FU (36.7)    | -                             | -                            | 15/26 (57.7)                     | 6/23 (26.1)   |
| Median PFS (95% CI) months                                                     | -                            | ■                             | ■                            | 16.3(4, 34.8)                    | -             |
| Time to treatment discontinuation (95% CI) months                              | 26.9 (14.4, 45.4)            |                               |                              |                                  |               |
| ORR                                                                            | 31/43 (72%)                  | ■                             | ■                            | 18/26 (69.2%)                    | 15/22 (68%)   |
| Complete Response (CR)                                                         | 3/43 (7%)                    | ■                             | ■                            | 4/26 (15.4%)                     | 2/22 (9%)     |
| Partial Response (PR)                                                          | 28/43 (65%)                  | ■                             | ■                            | 14/26 (53.8%)                    | 13/22 (59%)   |
| Stable Disease (SD)                                                            | 12/43 (28%)                  | ■                             | ■                            | 3/26 (11.5%)                     | 3/22 (13.5%)  |
| Progressive Disease (PD)                                                       | 0                            | ■                             | ■                            | 5/26 (19.2%)                     | 4/22 (18.5%)  |
| Median duration of Response (95% CI) months                                    | -                            | ■                             | ■                            | 18.7(5.7,42.3)                   | -             |
| Treatment cessation due to disease progression [disease progression and death] | 10/60 (17%)<br>[32/60 (53%)] | -                             | -                            | 15/26 (57.7%)<br>[18/26 (69.2%)] | 11/19 (58%)   |
| Post-larotrectinib targeted drug therapy                                       | 4/60 (6.7%)**                | -                             | -                            | 6/26 (23.1%)*                    | 5/23 (21.7%)* |

Sources: Based on CS Tables 9,12,13,14 and 26, and the SACT,<sup>30</sup> ON-TRK, Larotracking<sup>31</sup> and SACHA<sup>32</sup>) observational studies.

CI: Confidence Interval. CNS: Central Nervous System. ePAS9: extended primary analysis set 9. FAS: Full analysis set. NE: Not estimable. NR: not reported. ON-TRK: Prospective non-interventional study in patients with locally advanced or metastatic. ORR: objective response rate. PFS: progression free survival. SACHA: SACHAxLaro study. SACT: Systemic Anti-Cancer Therapy. SAF: Safety Analysis Set. SAS3: supplementary analysis set 3.

\*Post treatment was an NTRK inhibitor (selitrectinib, repotrectinib, entrectinib, other)

\*\*These 4 participants had the targeted drugs carbozantinib, entrectinib, lenvatinib and repotrectinib. An additional 2 participants had chemotherapy, and a further 2 were reported to have gone on to an undefined trial.

\*\*\*Some of these 6 participants may also have had another drug therapy, but it is unclear how many. An additional 5 participants had one or more of the following drugs: antiangioma, chemotherapy and immunotherapy.

\*\*\*\*Of the 5 with targeted therapy, 3 had selitrectinib and 2 had repotrectinib. An additional 8 participants had surgery, local RT or VP16.

**Table 19 Safety results from the observational evidence**

| Outcomes                                  | ON-TRK [SAF, non-CNS and CNS combined, n=■] | LAROTRACKING [N=■]       | SACHA [n=■] |
|-------------------------------------------|---------------------------------------------|--------------------------|-------------|
| AEs - overall                             | -                                           | ■ [grade 2 or more only] | ■           |
| Treatment Emergent Adverse Events (TEAE)  | ■                                           |                          |             |
| Treatment Related Adverse Events (TRAE)   | ■                                           |                          |             |
| TEAE leading to permanent discontinuation | ■                                           | -                        | -           |
| TRAE leading to permanent discontinuation | ■                                           | -                        | -           |
| Fatal TEAE                                | ■                                           | -                        | -           |
| Fatal TRAE                                | ■                                           | -                        | -           |
| AEs – weight gain                         | ■                                           | ■                        | ■           |
| AEs - neutropenia                         | -                                           | ■                        | ■           |
| AEs - psychiatric                         | -                                           | ■                        | -           |
| AEs – vascular                            | -                                           | ■                        | -           |
| AEs - neurological                        | -                                           | ■                        | -           |
| AEs - hepatobiliary                       | -                                           | ■                        | -           |
| AEs- fatigue                              | ■                                           | ■                        | -           |
| AEs- ear + labyrinth                      | -                                           | ■                        | -           |

| Outcomes                                   | ON-TRK [SAF, non-CNS and CNS combined, n=■] | LAROTRACKING [N=■] | SACHA [n=■] |
|--------------------------------------------|---------------------------------------------|--------------------|-------------|
| AEs - eye                                  | -                                           | ■                  | -           |
| AEs – alanine aminotransferase increased   | ≥grade 3: ■                                 | ■                  | -           |
| AEs – aspartate aminotransferase increased | ≥grade 3: ■                                 | ■                  | -           |
| AEs - nausea                               | ≥grade 3: ■                                 | -                  | -           |

Sources: Based on CS Tables 24 and 27, Appendix N Tables 10 and 11,<sup>3</sup> ON-TRK,<sup>30</sup> Larotracking<sup>31</sup> and SACHA<sup>32</sup> observational studies.

AE: adverse event. CNS: central nervous system. NTRK: Neurotrophic Tyrosine Receptor Kinase. ON-TRK: Prospective non-interventional study in patients with locally advanced or metastatic. SACHA: SACHAxLaro study. SAF: Safety Analysis Set. TEAE: Treatment Emergent Adverse event. TRAE: Treatment Related Adverse Event



### **3.4 Critique of the indirect treatment comparisons**

Given the absence of a comparator arm in the larotrectinib trials, indirect treatment comparisons were conducted, aiming to evaluate the relative effectiveness of larotrectinib against standard of care (SOC). Individual patient data (IPD) from subsets of the larotrectinib trial evidence were matched and compared against data from observational cohorts of patients with NTRK fusion positive locally advanced or metastatic solid tumours who received systemic therapy without an NTRK inhibitor, in four unanchored matching-adjusted indirect comparisons (MAICs). Three MAICs were reported in adults (VICTORIA, FLATIRON, HMF)<sup>50-53</sup> and one included children and adults  $\leq 21$  years old with IFS (EPI-VITRAKVI).<sup>54</sup>

VICTORIA and EPI VITRAKVI informed the company's base-case, and FLATIRON and HMF were included as alternatives to VICTORIA in scenario analyses for the adult population. All MAICs were funded by Bayer.

Details of the design and results of MAICs presented in the CS (CS Section 2.10) were limited. In response to a request for clarification from the EAG, the company provided further details, although no information that was not already contained in these publications (CQ response A23).

This section provides a summary and critique of the MAICs methods and results. Sections 3.4.1 to 3.4.6 discuss the methods and population of the ITC, Section 3.4.7 discusses the results, and 3.4.8 provides a summary of key ITC issues.

#### **3.4.1 Design**

A summary of the design of the MAICs is reported in Table 20.

##### **3.4.1.1 VICTORIA**

In the comparator cohort, individual patient data were extracted retrospectively from five historical data sources covering a period between January 2013 and June 2023: the American Association of Cancer Research [AACR] GENIE database, Cardinal Health Study, Flatiron Health-Foundation Medicine clinico-genomic database [FH-FMI CGDB], ORIEN, and a global chart review. AACR GENIE database is an international cancer registry between 19 leading cancer centres worldwide, which links NGS data with clinical outcomes from routine medical practice. The Cardinal Health study is a Bayer-sponsored retrospective cohort study of US patients with TRK fusions. The US-based Flatiron Health-Foundation Medicine clinico-genomic database (FH-FMI CGDB) includes retrospective longitudinal clinical data originating from approximately 280 US cancer clinics. The ORIEN data sources include electronic medical records, pharmacy records, and cancer registries from eight academic centres led by the University of Utah. The global chart review included 6 sites across

six countries. Out of a total of 512 patients across these data sources, 144 patients had one of the five predefined cancer types and were identified for 1: 1 matching. From the larotrectinib trial evidence, 272 patients were assessed for eligibility and of those, 126 met the eligibility criteria for the MAIC. Reasons for exclusion are reported in Brose.<sup>50</sup> Across the trial and ‘real-world (‘RW’) evidence, most patients were excluded because they did not have one of the five eligible primary tumour types.<sup>50</sup> In total, 164 patients were matched 1:1 (82 in each cohort) by tumour type and line of therapy (LOT), and for thyroid cancer, by histology. It is unclear why VICTORIA restricted its inclusion to only five tumour types, given availability of data for other tumour types, and the tumour agnostic nature of larotrectinib.

Matching was done without replacement, so that once a patient was matched, that patient was not eligible for further matching. Matching was conducted in descending order of LOT to ensure that patients at later LOT had a chance to be matched, and patients were randomly selected for a specific LOT. Propensity scores were generated after identifying matched ‘RW’ patients to patients from larotrectinib clinical trials. Weighting of the trial IPD against the comparator cohort was performed using inverse probability of treatment weighting (IPTW). Following propensity score weighting, patient-level data were aggregated across the comparator data sources to inform the efficacy analyses. This approach is critiqued in Section 3.4.8.

Treatments received in the comparator group were mostly chemotherapy (49%), followed by small molecule-targeted therapy (27%), chemotherapy+targeted therapy (11%), or an immune checkpoint inhibitor (10%); no further details were provided.

**Table 20 Design of matching-adjusted indirect comparisons and comparator sources (VICTORIA, FLATIRON, HMF, EPI VITRAKVI)**

|                               | VICTORIA                                                           | FLATIRON                                                                                                       | HMF                                                                                                | EPI VITRAKVI                                                   |
|-------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| <b>Numbers of patients</b>    | Laro: 82<br>Comparator: 82                                         | Laro: 85<br>Comparator: 28                                                                                     | Laro: 120<br>Comparator: 24                                                                        | Laro: 51<br>Comparator: 42                                     |
| <b>Population</b>             | Adults with locally advanced/metastatic TRK fusion-positive cancer |                                                                                                                |                                                                                                    | ≤21 years with locally advanced or metastatic IFS              |
| <b>Number of tumour types</b> | 5                                                                  | 10                                                                                                             | 9                                                                                                  | 1                                                              |
| <b>Tumour types/location</b>  | NSCLC, CRC, thyroid cancer, sarcomas, and salivary gland carcinoma | Uterine, biliary, stomach, endometrial, cancer of unknown primary, breast, salivary gland, NSCLC, STS, and CRC | Bone/soft tissue, breast, colon/rectum, head & neck, lung, pancreas, prostate, skin, urinary tract | IFS                                                            |
| <b>Selection criteria</b>     | Confirmed NTRK fusion (NGS, PCR, reverse PCR, or FISH)             | NGS confirmed NTRK fusion                                                                                      | WGS confirmed NTRK fusion                                                                          | IFS (including advanced or metastatic congenital hypercellular |

|                                        |                                                                                                                            |                                                                                                                                        |                                                                       |                                                                                                                                                                  |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        | No 2 <sup>nd</sup> primary cancer <sup>#</sup>                                                                             | No prior or current TRK inhibitor<br><br>No visit gap >90 days after diagnosis<br><br>No prior unlabelled study drug in clinical trial |                                                                       | mesoblastic nephroma)<br><br>patients with an unknown NTRK gene fusion status<br><br>No prior or current TRK inhibitor<br><br>≥0 prior non-TRKi regimens         |
| <b>Larotrectinib trial source</b>      | Subset of pooled analysis of 20288, 20289, 20290                                                                           |                                                                                                                                        |                                                                       | Subset of 20290                                                                                                                                                  |
| <b>Trial evidence data cut</b>         | July 2022 (ePAS7)                                                                                                          | July 2020 (ePAS5)                                                                                                                      | July 2023 (dataset NR)                                                | July 2021 (ePAS6)                                                                                                                                                |
| <b>Comparator source</b>               | Aggregated IPD from AACR, GENIE, Cardinal, Flatiron <sup>^</sup>                                                           | Published aggregated data from Flatiron/Foundation Medicine database <sup>45, 55</sup>                                                 | Published aggregated data from Hartwig Medical Foundation             | IPD from Institut Curie, Cooperative Weichteilsarkom Studiengruppe                                                                                               |
| <b>Countries</b>                       | International <sup>-</sup>                                                                                                 | USA                                                                                                                                    | Netherlands                                                           | Germany, France                                                                                                                                                  |
| <b>Year</b>                            | Jan 2013-June 2023 <sup>+</sup>                                                                                            | Jan 2011-Dec 2019                                                                                                                      | 2012-2020                                                             | 2000-2022                                                                                                                                                        |
| <b>Treatments included</b>             | Chemotherapy (49%), small molecule-targeted therapy (27%), chemo+targeted therapy (11%), immune checkpoint inhibitor (10%) | Chemotherapy (48%), chemo+targeted therapy (23%), chemo+hormone (5%), others/NR (24%)                                                  | NR                                                                    | Chemotherapy (100%)                                                                                                                                              |
| <b>Effective sample size</b>           | NR                                                                                                                         | 13.1                                                                                                                                   | 36*                                                                   | NR                                                                                                                                                               |
| <b>Covariates matched</b>              | See Table 21                                                                                                               |                                                                                                                                        |                                                                       |                                                                                                                                                                  |
| <b>Matching method</b>                 | IPTW                                                                                                                       | NR                                                                                                                                     | IPTW                                                                  | IPTW                                                                                                                                                             |
| <b>Main analysis methods</b>           | Cox PHM, RMST.                                                                                                             | Cox PHM                                                                                                                                | Cox PHM                                                               | Cox PHM, RMST.                                                                                                                                                   |
| <b>Sensitivity/additional analyses</b> | Left truncation, 5% PS trimming                                                                                            | RMST, alternative matching, left truncation, PS trimming.                                                                              | RMST, addition of patient sex and tumour location as matching factors | PS trimming, exact matching, subgroup analyses by LOT                                                                                                            |
| <b>Outcomes</b>                        | OS, DOT, TTNT, PFS, RR                                                                                                     | OS                                                                                                                                     | OS                                                                    | Treatment failure <sup>‡</sup> , OS<br>Subsequent systemic treatment, radiation therapy, time to complete surgical resection, TEAE discontinuation, PFS ORR, DCR |
|                                        |                                                                                                                            |                                                                                                                                        |                                                                       |                                                                                                                                                                  |

Sources: CS, pages 75-82, Brose (2025),<sup>50</sup> Bokemeyer (2023),<sup>51</sup> Orbach, (2024)<sup>54</sup>

AACR: American Association for Cancer Research. CRC: Colorectal Cancer. ePAS: Extended Primary Analysis Set. DCR: Disease Control Rate. DOT: Duration of Therapy. ECOG: Eastern Cooperative Oncology Group. FISH: Fluorescence In Situ Hybridization. GENIE: Genomics Evidence Neoplasia. HMF: Hartwig Medical Foundation. IFS: Infantile Sarcoma. IRS: Intergroup Rhabdomyosarcoma Study. IPD: Individual Patient Data. IPTW: Inverse Probability Of Treatment Weighting. HR: Hazard Ratio. LOT: Line of Therapy. MAIC:

Matching-Adjusted Indirect Comparison. NGS: Next Generation Sequencing. NR: Not Reported. NSCLC: Non-Small Cell Lung Cancer. NTRK: Neurotrophic Tyrosine Receptor Kinase. ORR: Objective Response Rate. OS: Overall Survival. PCR: Pathological Complete Response. PFS: Progression-Free Survival. PS: Performance Status, or Propensity Score. PHM: Proportional Hazards Model. RMST: Restricted Mean Survival Time. RR: Response Rate. STS: Soft Tissue Sarcoma. TEAE: Treatment Emergent Adverse Event. TRK: Tyrosine Receptor Kinase. TTNT: Time To Next Treatment. WGS: Whole Genome Sampling.

~ US, Canada, France and the Netherlands, Australia, China, Japan, and global retrospective chart review data

<sup>†</sup> up to January 2022 for the Cardinal Health Study, December 2022 for FH-FMI CGDB and AACR GENIE, February 2023 for ORIEN, and June 2023 for the global chart review

\*decreased to 12 with addition of tumour location as matching factor; # patients enrolled might have received prior or current TRK inhibitors, in which case only the line(s) of therapy before this TRKi were considered.

<sup>‡</sup> Subsequent systemic therapy, radiotherapy, mutilating surgery, or death due to any cause, whichever came first.

### 3.4.1.2 FLATIRON

FLATIRON MAIC matched 85 patients from the pooled analyses (July 2020, ePAS5) against published, aggregate data from 28 patients included in the US Flatiron database (Jan 2011-Dec 2019) across 10 tumour types.<sup>55</sup> Most patients (71%) included in FLATIRON had a primary diagnosis of either CRC (32%), STS (21%) or NSCLC (18%). It is unclear whether any of the comparator cohort patients were also included in the VICTORIA MAIC. The most common therapies in the comparator cohort were chemotherapy (48%), followed by chemotherapy+targeted therapy (23%). No details of actual treatments and regimens were reported, making the assessment of applicability to NHS practice difficult.

### 3.4.1.3 HMF

HMF MAIC compared 120 patients from the pooled analyses (July 2023 data cut) against aggregate data from 24 NTRK fusion positive patients treated without an NTRK inhibitor from the Dutch HMF database. Further details are reported in Table 20.

### 3.4.1.4 EPI-VITRAKVI

EPI VITRAKVI is a retrospective, observational, externally controlled study (NCT05236257). Data of patients aged  $\leq 21$  years with locally advanced or metastatic IFS treated with larotrectinib study 20290 were compared with data from a retrospective historical cohorts pooled from French and German clinical practice treated with a chemotherapy-based regimen between 2000 and 2022. Data sources were identified via a systematic review. IPTW was used to balance between-group differences.

## 3.4.2 Population

Selection criteria are reported in Table 20.

### 3.4.2.1 Applicability and selection bias (all MAICs)

The EAG is concerned by the exclusion of most solid tumour types from the MAICs. VICTORIA, HMF and FLATIRON restricted their inclusions to five, nine and ten tumour types/locations respectively, and EPI-VITRAKVI was restricted to a single tumour type (IFS). Therefore, the applicability of the MAICs to most solid tumour types is uncertain.

VICTORIA and FLATIRON over-represented certain tumour types, particularly STS, CRC, salivary gland and NSCLC. The BHM and subgroup analyses from the pooled analyses found ORRs tended to be higher for these tumour types. Conversely, all MAICs excluded primary CNS patients, and the majority of other solid tumours in the trial evidence, which tended to show lower response rates in the pooled analyses. Therefore, the EAG is concerned that the exclusion of most tumour types (including primary CNS) from the MAICs may have introduced selection bias favouring larotrectinib. It is not possible to predict the magnitude of this bias on survival outcomes, as it will partly dependent on the effectiveness of SoC options and tumour-specific prognosis.

#### *3.4.2.2 Restriction of comparator population to NTRK fusion positive patients (all MAICs)*

In response to a request for clarification from the EAG (CQ A21), the company provided justification for restricting the MAIC comparator populations to NTRK fusion positive patients. A meta-analysis of studies comparing survival outcomes between untreated NTRK fusion positive and NTRK fusion negative patients found that, in patients not treated with TRK inhibitor therapies, those with NTRK positive solid tumours have an estimated 51% increased risk of mortality within 10 years from diagnosis or the start of standard therapy compared with those with NTRK negative status (HR 1.51; 95% CI, 1.01 to 2.29). Evidence was consistent across the four studies included in the meta-analysis. Based on this evidence, the EAG considers that the restriction of NTRK fusion positive patients to the MAICs is likely to be appropriate.

### **3.4.3 Outcomes**

Outcomes evaluated in the MAICs are summarised in Table 20. VICTORIA and EPI-VITRAKVI reported ORR, OS and PFS, as well as other time-to-event outcomes. FLATIRON and HMF only reported OS.

As all MAICs comparator evidence is from historical, retrospectively collected data from multiple ‘RW’ sources outside of a trial context, there is a risk that the quality of comparator data may be more variable in quality. Standardized clinical trial criteria, such as RECIST 1.1, are not typically captured in medical chart reviews and differences in the frequency of tumour assessments in practice may introduce bias.<sup>50</sup> There were differences in outcome definitions between trial and comparator sources in VICTORIA, as PFS and response rates were by imaging or oncologist assessment without RECIST in the comparator arm. Results comparing RR between clinical trials and ‘RW’ studies should also be interpreted with caution as the two different approaches may produce different results.<sup>56</sup>

All time-to-event outcomes were expressed as HR. Cox proportional hazards rely on the assumption that hazards are constant across the larotrectinib and comparator groups (proportional hazards[PH]). However, MAIC are time-varying by nature and therefore violate the PH assumption.<sup>57, 58</sup> The

direction of any bias that may have been introduced by the potential violation of the PH assumption is unclear.

Across all MAICs, follow-up duration was not balanced between the larotrectinib and comparator groups; restricted mean survival time was applied to all MAICs except EPI-VITRAKVI. The impact of follow-up imbalance in EPI-VITRAKVI is uncertain.

### 3.4.4 Selection of covariates for adjustment

Covariates selected for matching were informed by systematic reviews and the availability of data from the comparator sources. Table 21 presents a summary of covariates selected for matching. There was wide variation in the number and type of covariates that were matched. Clinical advice to the EAG indicated that key prognostic covariates across tumour types included age, line of therapy, tumour type, presence of brain metastases, and disease stage. All MAICs matched for age and line of therapy (although those were measured differently between MAICs). Tumour type/location was accounted for all MAICs, although in HMF, only in a sensitivity analysis. Disease stage was not matched for in HMF. The presence of baseline metastases, and ECOG performance status were accounted for in only two MAICs (VICTORIA and FLATIRON).

**Table 21 Covariates matched for in indirect comparisons of NTRK fusion positive patients**

|                                             | VICTORIA | FLATIRON | HMF  | EPI-VITRAKVI |
|---------------------------------------------|----------|----------|------|--------------|
| Age                                         | X        | X        | X    | X            |
| Line of therapy                             | X        | X        | X    | X            |
| Tumour location/type                        | X        | X        | X*   | X            |
| Brain metastases                            |          | X        |      |              |
| Disease stage/baseline metastases           | X        | X        |      | X            |
| ECOG PS                                     | X        | X        |      |              |
| Time from diagnosis to treatment initiation |          |          |      | X            |
| NTRK1-gene                                  |          | X        | X    |              |
| Smoking history                             |          | X        |      |              |
| Practice type                               |          | X        |      |              |
| Race                                        | X        |          |      |              |
| Year of treatment initiation                |          |          | X    |              |
| Others                                      | X**      |          | X*** | X****        |

Source: CS, pages 76, 77, 80; Brose (2025)<sup>50</sup> page 3, Bokemeyer (2023)<sup>51</sup> page 3, Orbach (2024)<sup>54</sup> page 3.

ECOG: Eastern Cooperative Oncology Group. IFS: Infantile Sarcoma. NTRK: Neurotrophic Tyrosine Receptor Kinase.

\* Only matched for in sensitivity analyses

\*\* Sex considered as additional covariate

\*\*\* Year of biopsy also included

\*\*\*\*Additional covariates were considered such as sex, disease history, and treatment-related information.

### 3.4.5 Calculation of propensity scores

Information on the calculation of propensity scores was very limited in the CS, the company response to clarification (Question A23) and the original papers.<sup>50-52, 54</sup> The optimal methodology for propensity scoring depends upon whether IPD is available for both the larotrectinib and comparator cohorts, or just the larotrectinib arm alone, and so critique of propensity score calculation has been considered for each of those scenarios separately.

#### 3.4.5.1 ITCs with full IPD

Two MAICs utilised IPD for both the larotrectinib and comparator cohorts. These were VICTORIA<sup>50</sup> and EPI VITRAKVI<sup>54</sup>.

In VICTORIA, IPTW was generated on the basis of the propensity score, but no details were given on the logistic regression upon which the propensity scores were based, and no details were provided of the propensity score calculations. The CS and VICTORIA MAIC publication<sup>50</sup> reported that initial exact matching of the two cohorts were performed on the basis of tumour type and treatment line number. Following Factual Accuracy Check, the company explained that initial exact matching meant that “larotrectinib-treated and comparator patients were identical on these variables within each matched set, and they did not confound the treatment comparison. Propensity scores and IPTW were therefore estimated in the pooled matched cohort rather than within tumour/line subgroups, avoiding instability from small sample sizes and limited overlap while preserving the exact-match structure.” The EAG considers this approach to be reasonable. The clarification question response (A23) confirmed that there was no reporting of the number or percentage of individuals with zero weight following IPTW and that there was no reported use of robust sandwich estimators or bootstrapping methods to quantify uncertainty in the weighted analyses.

In EPI-VITRAKVI, the IPTW method was used based on a propensity score model. The use of a logistic regression with “dependent variable: larotrectinib group (yes/no)” to generate the propensity score is mentioned,<sup>54</sup> but no details are given of the calculations used to generate the propensity scores. It is, however, clearly stated that each patient was weighted by the reciprocal of the probability of receiving the treatment they received. In response to clarification question A23, the company did not provide further information on propensity score calculation, but confirmed that there was no reporting of individuals with zero weight following IPTW, nor reporting of the use of robust sandwich estimators or bootstrapping methods.

#### 3.4.5.2 Studies where IPD was used for the larotrectinib cohort only

The remaining two MAICs - FLATIRON<sup>51</sup> and HMF<sup>52</sup> – used IPD for the larotrectinib arm but aggregate data for the comparator arm. Because IPD was only used for the intervention arm, the established ‘propensity score weighting’ approach is to weight participants in the arm with IPD, using

methods such as the generalised method of moments, such that selected overall baseline characteristics in the IPD group match those in the aggregate data group.<sup>59</sup> Because of the lack of IPD for the comparator group it is particularly important to assess the distribution of weights, which need to be clustered around one.<sup>60</sup> It is also important to ensure a higher estimated sample size (ESS) as a low ESS relative to the absolute sample size may indicate an unstable estimate.<sup>60</sup>

Flatiron<sup>51</sup> and the CS did not provide any details of methodology relating to such propensity score weighting. In the company response to clarification questions (A23), the company stated that inverse propensity score weighting was used, but no further details were given. However, the company clarified that although the number of individuals with zero weight was unknown, most weights were  $\leq 1$ , with few outliers. The company also confirmed that the ‘study employed robust statistical techniques, specifically the robust sandwich estimator’. Finally, the company reported that ESS was 13.1 for the base case, which is a substantially lower figure relative to the actual sample size of 85 in the larotrectinib cohort, indicating a potentially unstable estimate.

HMF used inverse propensity score weighting. ESS was reported as  $n=36$  for the base case, which was deemed small by the company, relative to the actual sample size of  $n=120$  in the larotrectinib cohort, suggesting an unstable estimate. A sensitivity analysis that accounted for tumour location reduced the ESS to  $n=12$ , which raises further concerns about the reliability of the HMF MAIC. The company also confirmed that although there was no reporting on the number with zero weights, “over 80% of patients had weights  $\leq 1$ , and around 20% had weights  $>1$ , with no concerns about outliers or excessive weighting”. Finally, the company stated there was no reporting on the use of robust methods such as ‘sandwich’ estimators or bootstrapping methods.

### **3.4.6 Assessment of overlap between trial evidence and comparator cohorts**

The level of overlap between trial evidence and comparator cohorts differed markedly between the MAICs. These are discussed separately below.

#### **3.4.6.1 VICTORIA**

Demographic and disease characteristics with and without weighting are presented in Appendix Table 49. The larotrectinib population was younger than the comparator group prior to weighting (mean 52.7 vs. 58.7 years). The measured baseline characteristics between larotrectinib and comparator arms were otherwise generally well matched both prior to and after IPTW weighting (Appendix Table 49). However, the percentage of patients with brain metastases at baseline, a key covariate, was not reported, therefore there is some uncertainty regarding the extent which the two groups overlap. Although other key variables were well matched, any unobserved difference in baseline brain metastases in this unanchored, non-randomised comparison may introduce bias in survival outcomes.



#### 3.4.6.2 FLATIRON

Overall, the overlap between the two groups prior to weighting was poor. Appendix Table 50 shows notable differences between the larotrectinib and FLATIRON comparator groups in age, NTRK1, brain metastases, ECOG status and tumour type prior to matching. Observed between-group imbalances were mostly resolved following weighted adjustments, although four rarer tumours (represented by one patient each) were only present in the comparator arm. It is unclear why these were not excluded from the analyses, and their inclusion may have introduced bias due to prognostic heterogeneity between tumour types. The ESS for larotrectinib following weighting was  $n=13.14$ , indicating limited overlap and a distribution of weights skewed towards a small number and proportion of patients.

#### 3.4.6.3 HMF

The overlap between the larotrectinib and SoC groups was poor, as indicated by the limited ESS in the main analysis ( $n=36$ ) and in the sensitivity analysis that included tumour location as an additional matched covariate ( $n=12$ ).

#### 3.4.6.4 EPI VITRAKVI

Overall, the overlap between the two groups prior to weighting was limited. Appendix Table 51 shows that prior to IPTW, larotrectinib patients were older, more heavily pre-treated, with higher rates of metastatic disease, and with a longer time since diagnosis. As these variables were not compared following weighting, the EAG could not assess the extent to which adjustments resolved these between-group imbalances.

### 3.4.7 Results

Three MAICs (VICTORIA, FLATIRON and HMF) reported a statistically significant improvement in OS favouring larotrectinib compared with comparator treatments, and one (EPI-VITRAKVI) found no statistically significant difference in OS between larotrectinib and chemotherapy in IFS patients. PFS HRs were statistically significant and favoured larotrectinib in VICTORIA, but was not statistically significant in EPI-VITRAKVI. Both VICTORIA and EPI-VITRAKVI reported a numerical difference in ORR favouring larotrectinib, although the difference was either not statistically significant, or significance testing was not reported. Further details are reported below.

#### 3.4.7.1 VICTORIA

Table 22 summarises results from VICTORIA. Unweighted ORR across all five tumour types was 73.8% (95% CI 62.7 to 83.0) for larotrectinib. This is more favourable to larotrectinib than the ePAS9 pooled analyses (65% [95% CI 59 to 70]) and the BHM main analyses (ORR [redacted] % [95% PredI [redacted] to [redacted]]). ORR was 53.8% (37.2 to 69.9) in the comparator cohort although this estimate is limited by significant missing data (52%). VICTORIA found a statistically significant difference in OS, PFS,

duration of treatment and time to next treatment favouring larotrectinib against the comparator group. Weighted and unweighted results were generally very similar, although median OS for larotrectinib was only reached in the unweighted analyses, indicating that matching somewhat favoured the intervention for this outcome. Kaplan-Meier curves for OS are reported in CS Figure 13; survival curves for PFS, treatment duration and time to next treatment are reported in Brose (2025).<sup>50</sup>

**Table 22 Comparative effectiveness estimates for larotrectinib vs comparator cohort with NTRK fusion solid tumours (VICTORIA)**

|                                              | Median value (95% CI), months |                                | HR (95% CI)*     |
|----------------------------------------------|-------------------------------|--------------------------------|------------------|
|                                              | Larotrectinib<br>n=82         | Comparator<br>n=82             |                  |
| <b>ORR</b>                                   |                               |                                |                  |
| Unweighted                                   | 73.8% (62.7-83.0)             | 53.8% (37.2-69.9) <sup>#</sup> | NR               |
| Weighted                                     | NR                            | NR                             | NR               |
| <b>Overall survival</b>                      |                               |                                |                  |
| Unweighted                                   | 63.4 (42.9-NE)                | 37.2 (17.4-NE)                 | 0.47 (0.26-0.88) |
| Weighted                                     | Not reached (42.9-NE)         | 37.2 (12.5-NE)                 | 0.44 (0.23-0.83) |
| <b>Progression-free survival<sup>^</sup></b> |                               |                                |                  |
| Unweighted                                   | 36.8 (19.2-55.7)              | 5.2 (3.7-6.2)                  | 0.29 (0.19-0.46) |
| Weighted                                     | 36.8 (25.8-58.2)              | 5.2 (3.5-6.8)                  | 0.29 (0.18-0.46) |
| <b>Duration of treatment</b>                 |                               |                                |                  |
| Unweighted                                   | 29.3 (15.7-38.6)              | 3.5 (2.8-4.7)                  | 0.24 (0.17-0.36) |
| Weighted                                     | 30.8 (18.2-47.6)              | 3.4 (2.7-4.7)                  | 0.23 (0.15-0.33) |
| <b>Time to next treatment</b>                |                               |                                |                  |
| Unweighted                                   | 58.1 (53.2-NE)                | 10.0 (6.7-17.7)                | 0.24 (0.14-0.40) |
| Weighted                                     | NE (53.2-NE)                  | 10.6 (6.1-17.7)                | 0.22 (0.13-0.38) |

Source: CS Table 20, Brose (2025)<sup>50</sup> supplement page 5,

CI: Confidence Intervals. HR: Hazard ratio. NE: Not estimated. NR: Not Reported. ORR: Objective Response Rate

\*Except for ORR, for which no relative estimates were reported. Values below 1 favour larotrectinib over the comparator cohort. <sup>#</sup>52% had missing response data.

<sup>^</sup> Radiologist assessment. Based on RECIST v1.1 criteria for larotrectinib, and defined as the time from index date to the date of progression (for patients with progression confirmed by imaging or oncologist assessment) or death (within 30 days after last assessment or within 30 days after index line end date) for the comparator cohort.

### 3.4.7.2 FLATIRON and HMF

Results for FLATIRON and HMF are reported in Table 23 and Table 24 respectively. Both FLATIRON and HMF found a statistically significant difference in OS favouring larotrectinib against non-NTRK inhibitor comparators. Weighting had a significant impact on the precision and magnitude of FLATIRON results, although both unweighted and weighted estimates favoured larotrectinib.

**Table 23 Comparative overall survival estimates for larotrectinib vs comparator cohort with NTRK fusion solid tumours (FLATIRON)**

|            | Median value (95% CI), months |                           | HR (95% CI)*      |
|------------|-------------------------------|---------------------------|-------------------|
|            | Larotrectinib<br>n=85         | Comparator cohort<br>n=28 |                   |
| Unweighted | Not reached                   | 10.2 (7.2, 14.1)          | 0.09 (0.05, 0.19) |
| Weighted   | 39.7 (16.4, NE)               | 10.2 (7.2, 14.1)          | 0.22 (0.09, 0.52) |

Source: Bokemeyer (2023) <sup>51</sup>Table 3, and page 5

CI: Confidence Intervals. HR: Hazard ratio. NE: Not estimated.

**Table 24 Comparative overall survival estimates for larotrectinib vs comparator cohort with NTRK fusion solid tumours (Hartwig Medical Foundation)**

|            | Median value (IQR), months |                             | HR (95% CI)*     |
|------------|----------------------------|-----------------------------|------------------|
|            | Larotrectinib<br>(n=120)   | Comparator cohort<br>(n=24) |                  |
| Unweighted | 60.1 (23.3-NE)             | 13.0 (6.4-18.3)             | 0.18 (0.10-0.34) |
| Weighted   | 50.3 (23.3-NE)             | 13.0 (6.4-18.3)             | 0.16 (0.07-0.36) |

Source: CS, page 81 and Figure 14

CI: Confidence Intervals. HR: Hazard ratio. IQR: Interquartile Range. NR: Not reported.

### 3.4.7.3 EPI-VITRAKVI

Table 25 summarises the results of EPI-VITRAKVI. The weighted analysis found no statistically significant difference between larotrectinib and chemotherapy in ORR. Median OS was not reached in either arm both before and after weighting. EPI-VITRAKVI found no statistically significant difference in OS between the two groups (weighted HR 0.21, 95% CI 0.02 to 2.84). However, these results are based on very immature OS data, where over 90% of patients were alive at follow-up in both arms (results presented in Orbach (2024)<sup>54</sup> with wide confidence intervals, and are therefore very uncertain. Median PFS was not estimable in the larotrectinib arm and was reached at 16.0 months in the comparator arm. Weighted PFS results showed no statistically significant difference between the two groups (HR 0.80, 95% CI 0.41 to 1.58), although the immaturity of the larotrectinib data and imprecision mean this estimate is uncertain.

**Table 25 Comparative effectiveness estimates for larotrectinib vs comparator cohort with NTRK fusion solid tumours (EPI-VITRAKVI)**

|                       | Median value (months) or % (95% CI) |                        | HR (95% CI)*        |
|-----------------------|-------------------------------------|------------------------|---------------------|
|                       | Larotrectinib<br>(n=51)             | Chemotherapy<br>(n=42) |                     |
| ORR                   |                                     |                        |                     |
| Unweighted            | 90.2% (78.6-96.7)                   | 76.2 (60.5-87.9)       | NR                  |
| Weighted <sup>†</sup> | NR                                  | NR                     | OR 1.77 (0.52-5.97) |
| Overall survival      |                                     |                        |                     |

|                                                    |                    |                      |                                 |
|----------------------------------------------------|--------------------|----------------------|---------------------------------|
| Unweighted                                         | NR                 | NR                   | 0.32 (0.03 - 3.06)              |
| Weighted                                           | NR                 | NR                   | 0.21 (0.02 - 2.84)*             |
| <b>PFS</b>                                         |                    |                      |                                 |
| Unweighted                                         | NR                 | NR                   | NR                              |
| Weighted                                           | NE                 | 16.0 (16.0-NE)       | 0.80 (0.41-1.58)*               |
| <b>Event-free survival/Time to medical failure</b> |                    |                      |                                 |
| Unweighted                                         | NE (NE- NE)        | NE (57.1- NE)        | 0.21 (0.07 - 0.63) <sup>#</sup> |
| Weighted                                           | NE (NE- NE)        | 24.0 (3.0-NE)        | 0.20 (0.06 - 0.63) <sup>+</sup> |
| <b>Event-free survival at 24 months</b>            |                    |                      |                                 |
| Unweighted                                         | 94.3% (84.8- 99.3) | 79.2% (38.5 to 99.8) | NR                              |
| Weighted                                           | NR                 | NR                   | NR                              |
| <b>Time to subsequent systemic treatment</b>       |                    |                      |                                 |
| Unweighted                                         | NR                 | NR                   | 0.23 (0.05 - 1.13)              |
| Weighted                                           | NE                 | 24.0 (3.0-NE)        | 0.14 (0.03 - 0.63)*             |
| <b>Mutilating surgery</b>                          |                    |                      |                                 |
| Unweighted                                         | NR                 | NR                   | 0.23 (0.05 - 1.12)              |
| Weighted                                           | NR                 | NR                   | 0.35 (0.06 - 2.24)*             |
| <b>Radiation therapy</b>                           |                    |                      |                                 |
| Unweighted                                         | NR                 | NR                   | NC                              |
| Weighted                                           | NR                 | NR                   | NC                              |

Source: Orbach (2024)<sup>54</sup> Figure 2, page5

CI: confidence interval. HR: Hazard Ratio. IRS: Intergroup Rhabdomyosarcoma Study. IPTW: Inverse Probability of Treatment Weighting. NE: value cannot be estimated due to censored data. NC: Not collected. NR: Not Reported. ORR: Objective Response Rate. PFS: Progression Free Survival.

Time to medical treatment failure, defined as the time (months) from the start of treatment to the date of the earliest event from: subsequent systemic treatment, radiation therapy, mutilating surgery, or death due to any cause.

\*HR was weighted by stabilized IPTW (adjusted for IRS group classification, age at index, and time from locally advanced/metastatic disease diagnosis to treatment initiation) and stratified by IRS groups.

~ Weighted logistic regression (no further details)

<sup>#</sup> Cox proportion hazards model with treatment status as indicator variable

<sup>+</sup> Cox proportion hazards model Weighted by stabilized IPTW and stratified by IRS groups

### 3.4.8 Points for critique

Reporting of the MAIC methods was limited in the CS, therefore the EAG's summary and critique relied largely on publications. In all indirect comparisons, the company attempted to identify relevant comparator data from NTRK fusion positive patients, to match IPD from larotrectinib trial evidence against comparator evidence according to covariates identified from systematic reviews. Where available, IPD was obtained for the comparator in two of the indirect comparisons. However, all MAICs have significant internal and external validity limitations. These are detailed below.

#### 3.4.8.1 Applicability to NHS practice

The distributions of tumour types in the MAIC populations are not reflective of NHS practice. MAICs included between one and 10 tumour types/locations; no indirect evidence was presented for primary CNS patients (35% of NHS patients in the SACT), or for paediatric patients other than those with IFS.

Although larotrectinib is tumour agnostic, the CS showed evidence of significant heterogeneity in response, prognostic variability and variations in SoC treatments between tumour types (see Section 3.2). Therefore, the applicability of the MAICs to most NTRK fusion positive solid tumours is unknown.

#### *3.4.8.2 Selection bias*

As larotrectinib is licensed for all advanced and metastatic solid tumour types harbouring a NTRK fusion, the company did not provide a satisfactory rationale for excluding most solid tumour types. Overall, tumour types with more favourable ORR with larotrectinib were over-represented (e.g. IFS and STS), and conversely, tumour types with lower ORR were excluded (notably primary CNS and all other tumour types with ORR estimated below █% in ePAS9). ORR from the subset of larotrectinib patients included in VICTORIA was numerically higher than in ePAS9 and the BHM. The EAG is therefore concerned that the MAICs are at high risk of patient selection bias. The magnitude and direction of this bias are difficult to assess, notably because this will depend on the efficacy of relevant SoC therapies, although the EAG consider it likely to favour larotrectinib.

#### *3.4.8.3 Residual confounding*

Unanchored MAICs require that observed and unobserved prognostic factors and treatment effect modifiers are accounted for and matched between the intervention and control groups, and that the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and effect modifiers.<sup>61</sup> Due to limited data availability, this strong assumption is not met for any of the MAICs. Since the cohorts were only balanced on the basis of an incomplete list prognostic and effect modifiers, the possibility of residual confounding cannot be ruled out. Baseline CNS metastases, a key prognostic factor, were only accounted for in FLATIRON. Matching was necessarily simplistic and did not account for all tumour specific prognostic factors.

Overlap in baseline characteristics between intervention and comparator groups varied between the MAICs. Baseline characteristics that were measured were generally well matched in VICTORIA, except for age prior to weighting. There was poor overlap between groups in FLATIRON MAIC, which significantly limits the precision and reliability of its estimates. Due to reporting limitations, the impact of baseline imbalances on MAIC results is uncertain for EPI-VITRAKVI and HMF.

#### *3.4.8.4 Analytical limitations*

FLATIRON and HMF did not account for propensity score outliers, and VICTORIA and HMF did not account for excessive matching. Only FLATIRON reported using robust sandwich estimators. Only VICTORIA explored impact of delayed entry bias (using truncation analysis). EPI-VITRAKVI did not adjust for the significant imbalance in follow-up between the larotrectinib and chemotherapy group, which may have introduced further bias. None of the MAICs explored the potential impact of

subsequent therapies on OS, which could be substantial particularly in treatment naïve patients, who were included in all MAICs.

Data from comparator cohorts were aggregated to generate weighted estimates, including where IPD was available for both groups (VICTORIA and EPI-VITRAKVI). NICE methods guidance does not recommend conducting a MAIC when IPD is available for both the intervention and comparator arm, although it does not recommend suitable alternatives.<sup>61</sup> Since the publication of TSD18, alternative approaches to propensity-score matched unanchored indirect comparisons have been proposed, including doubly robust methods for time-to-event outcomes by Park (2024).<sup>62</sup> This approach can be applied with either individual patient or aggregate data and may yield more robust estimates. Where IPD is available for both arms, IPD meta-regression has been recommended as gold standard.<sup>58, 63</sup> However, these methods still rely on the strong assumption that all prognostic covariates have been included. This is not met for any of the MAICs.

#### *3.4.8.1 Historical bias*

Reporting was insufficient to assess the extent to which therapies in the comparator groups reflect NHS SoC. However, across the four MAICs, comparator evidence was retrospectively drawn from non-UK historical evidence ranging from 2000 to 2023, some of which may be outdated. It is likely that most patients included in the comparator groups, who were NTRK fusion positive, received systemic therapies prior to the licencing of NTRK fusion inhibitors. Improvements in practice in the SoC of several solid tumours (including in the 2L+ setting) have been observed during this period (e.g. NSCLC, melanoma), whilst progress in others such as IFS (the only tumour type in EPI-VITRAKVI) has been limited. The risk of historical bias cannot be quantified and will vary by tumour type, although overall, it is likely to favour larotrectinib relative to SoC in all MAICs except EPI-VITRAKVI.

#### *3.4.8.2 Other sources of uncertainty*

Given the rarity of NTRK fusions, the use of cut-offs older than ePAS9, and the population selection criteria, all MAICs included limited patient numbers. Therefore, many of the reported outcome estimates are imprecise. The nature of the study design and small sample sizes across the tumour types precluded exploration of clinical efficacy by disease characteristics such as tumour type and NTRK gene.

As all MAICs comparator evidence is from retrospectively collected data from multiple ‘RW’ sources outside of a trial context, there is a risk that the quality of comparator data may be more variable and not directly comparable with outcomes measured in a highly controlled clinical trial context.

FLATIRON and HMF only reported OS, and none of the indirect comparisons reported quality of life or safety outcomes. Relative estimates for time-to-event may not be informative as they are pooled from a variety of tumour types with different prognoses and different SOC therapies (except for EPI-VITRAKVI, which only included one tumour type, and where the SOC was chemotherapy).

### ***3.5 Additional work on clinical effectiveness done by the EAG***

No additional work on clinical effectiveness was performed by the EAG.

### ***3.6 Conclusions of the clinical-effectiveness section***

The CS clinical evidence has additional strengths compared with the original CS for TA630. The pooled trial evidence had an updated data cut from July 2024 and included a larger number of patients (including for primary CNS) and tumour types. Observational evidence from several sources was presented, including data from patients who received larotrectinib in the NHS through the CDF (SACT). Four MAICs comparing larotrectinib against NTRK fusion positive patients who received non-NTRK fusion inhibitors were conducted. Overall, the new evidence helps to address some of the uncertainties highlighted in the original EAG report.<sup>42</sup> However, the EAG considers that the CS trial evidence and MAICs have significant internal and external validity limitations.

Despite the updated data cut, OS trial data is still immature, with median OS not estimable in primary-CNS (SAS3) and non-primary CNS (ePAS9) populations. The durability of the survival benefit observed in the trial evidence is therefore uncertain. Post-progression outcomes are uncertain due to lack of maturity and there is potential confounding due to high rates of subsequent therapy use in the trial. HRQoL presented by the company is at high risk of bias and has limited applicability to the NHS population (notably primary CNS patients).

The SACT data directly reflects outcomes of patients who received larotrectinib in the NHS. However, the sample size (n=60) is small, therefore most solid tumours that may harbour an NTRK fusion were represented by few or no patients. This limited statistical power and the ability to detect differences across tumour types and other patient and disease characteristics.

There are significant differences between the larotrectinib trial evidence population and the SACT database; only 2% of SACT patient population were treatment naive, compared with ■% in ePAS9 and ■% in SAS3. Other notable differences between SACT and the trial evidence included the limited overlap in tumour types.

Results between SACT and the trial evidence differed. ORR rates were numerically higher in SACT than in ePAS9 and SAS3 (72%, 65% and ■% respectively), although rates of CR were numerically lower in SACT than ePAS9 and were ■ SAS3 (7%, 22% and ■% respectively). OS results

were less favourable to larotrectinib in SACT than in the trial evidence. In ePAS9, the median OS was not reached after a median duration of follow up of [REDACTED] months, and the 4-, 5- and 6-year OS rates were [REDACTED]%, [REDACTED]% and [REDACTED]%, respectively. In the SAS3 primary CNS tumour dataset, the OS rate at 4 years and 5 years was [REDACTED]%. In contrast, median OS in the SACT was reached at [REDACTED] months ([REDACTED] years). The comparability of these data sources is limited due to differences in study design, population characteristics, exposure to subsequent therapies, data maturity, and the lack of PFS data in SACT. Overall, the EAG is concerned that the trial evidence has limited applicability to NHS practice.

The CS showed clear evidence of heterogeneity in ORR from the pooled analyses of larotrectinib trials. An ORR that does account for this heterogeneity was estimated as [REDACTED]% (95% PredI: [REDACTED]% to [REDACTED]%) in the main analysis (which excluded primary CNS patients). This is numerically [REDACTED] [REDACTED] to larotrectinib and [REDACTED] than the unadjusted, main pooled analyses (ORR 65% [95% CI 59% to 70%]). BHM stratified by tumour type showed significant variation across tumour types, although most of the substantial heterogeneity found by the BHM was unexplained. The EAG considers the BHM analyses to be more robust than the company's unadjusted pooled analyses. However, the EAG is concerned that pooled ORR estimates across a wide range of patient and disease characteristics may not be reliable for decision making. Given the prognostic heterogeneity across multiple tumour types, and the limited applicability of the trial evidence, pooled PFS and OS estimates are unlikely to be reliable to inform decisions across tumour types in an NHS population.

The lack of control arm in the trial evidence meant that all comparisons between larotrectinib and standard of care therapies were based on unanchored MAIC comparing subsets of the trial evidence against 'RW' comparator evidence. All four MAICs presented by the company had significant internal and external validity limitations. The tumour types included in the MAICs represent a small subset of all solid tumour types that may harbour an NTRK fusion, therefore the applicability of the MAICs to most NTRK fusion positive solid tumours is unknown. Tumour types with more favourable ORRs with larotrectinib were over-represented, and conversely, tumour types with lower ORR (notably primary CNS) were excluded. The EAG is therefore concerned that the MAICs are at high risk of patient selection bias. The magnitude and direction of this bias are difficult to assess, notably because this will depend on the efficacy of relevant SoC therapies. None of MAICs were able to account for all observed and unobserved prognostic factors and treatment effect modifiers (a key assumption in unanchored MAICs), which limits their reliability. All MAICs had analytical limitations, imprecise results due to limited sample sizes, and potential limitations associated with comparing trial evidence against 'RW' data. Other concerns included the risk of historical bias, which may negatively impact outcomes of comparator cohorts.



Overall, the limitations of the trial evidence and MAICs, which inform the company's base case and scenario analyses, are likely to have significant implications for the cost-effectiveness model estimates. This is further discussed in Sections 4 and 5.

## **4 COST-EFFECTIVENESS**

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation.

### ***4.1 Critique of the review of cost-effectiveness evidence***

#### **4.1.1 Summary of company's SLR**

The company conducted an original SLR in 2019 and an updated search in 2025 to identify cost-effectiveness and healthcare cost and resource-use (HCRU) studies relevant to treatments for NTRK fusion-positive solid tumours. The detailed report of the methods and results of the SLRs can be found in Appendix E of the CS. The EAG considers the overall methods reasonable and consistent with standard guidance.

#### **4.1.2 Search strategy**

Appendix E of the CS included the search strategies to identify economic evaluations and HCRU studies relating NTRK fusion positive tumours. The searches were run on 7<sup>th</sup> May 2025. The searches were designed to update the original company searches undertaken for their previous submission in 2019.

Within Appendix E the company included details of the original searches for the previous submission in 2019. These searches were previously appraised by the EAG; therefore, the current appraisal relates to the 2025 update searches only.

The following issues were identified by the EAG which may have affected optimal retrieval of all relevant studies:

- Some relevant sources of health economics literature were not searched.
- As with the searches for the clinical effectiveness SLR, mistakes within the search syntax were apparent in the strategies. Although some of these mistakes were tested by the company following the EAG's clarification request [CQ6 – CQ9] and found not to affect retrieval, they did not test and correct all mistakes.
- The database searches were restricted to English language publications only and letters were removed from the search results.

### 4.1.3 Inclusion/exclusion criteria

The inclusion criteria followed a PICOST framework and were generally appropriate. The population was restricted to patients with NTRK fusion-positive solid tumours; no limits were placed on interventions, comparators or outcomes. Eligible study designs included cost-effectiveness and cost-utility analyses, budget-impact analyses, and costing studies reporting treatment-related costs or resource use. Studies focusing solely on NTRK fusion screening were excluded. The processes of screening, data extraction and quality assessment were clearly described and considered appropriate.

### 4.1.4 Identified studies

The original SLR identified no relevant economic evaluations. The updated SLR identified nine unique studies, including six cost-effectiveness studies and three reporting HCRU data.

Across the six cost-effectiveness studies, larotrectinib evaluated against standard of care or conventional chemotherapy. Studies were undertaken in a range of settings including the Netherlands, Canada, China, the United States and a multi-country analysis incorporating the UK. Various modelling approaches were applied, including partitioned survival, microsimulation and Monte Carlo simulation, with lifetime horizons in most cases. Perspectives differed between studies (healthcare payer, societal, or both), and discount rates ranged from 3.5% to 5%. Across studies, larotrectinib therapies produced higher QALYs and substantially higher costs than standard of care, with ICERs showing wide variability depending on country context, comparators and modelling assumptions. Detailed results are presented in Table 38 of the CS.

### 4.1.5 Interpretation of the cost effectiveness review

Overall, none of the identified studies directly assessed the cost-effectiveness of larotrectinib in the UK NHS setting. Consequently, the identified literature provides only limited directly applicable evidence to inform the current economic evaluation. The company used these findings mainly to confirm that partitioned survival models are widely applied in oncology and to inform the choice of model structure.

## 4.2 Critique of the submitted economic evaluation

### 4.2.1 NICE reference case checklist

Table 26 NICE reference case checklist

| Element of health technology assessment | Reference case                                                     | EAG comment on company's submission                 |
|-----------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------|
| Perspective on outcomes                 | All health effects, whether for patients or, when relevant, carers | QALY benefits to treated individuals were included. |

| Element of health technology assessment                                              | Reference case                                                                                                                                           | EAG comment on company's submission                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Perspective on costs                                                                 | NHS and Personal Social Services                                                                                                                         | NHS and PSS costs were accounted for.                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Type of economic evaluation                                                          | Cost–utility analysis with fully incremental analysis                                                                                                    | Cost-utility analysis                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Time horizon                                                                         | Long enough to reflect all important differences in costs or outcomes between the technologies being compared                                            | The economic model uses a lifetime time horizon, considering 80 years for all patients. This was more than sufficient to encompass the lifetime of adult patients, but ■■■ of paediatric patients on larotrectinib remained alive at the end of the modelled time horizon in the company's base case.                                                                                                                                                               |
| Synthesis of evidence on health effects                                              | Based on systematic review                                                                                                                               | Efficacy and HRQoL data for larotrectinib were based only on Study 20289 and 20290 for larotrectinib. Other efficacy data and HRQoL data for larotrectinib was identified but not used in the model. Separate searches for comparator data were performed, and supplemented by targeted reviews of previous NICE Technology Appraisals.                                                                                                                             |
| Measuring and valuing health effects                                                 | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.                             | <p>Health effects were expressed in QALYs. HRQoL for larotrectinib patients was assessed using EQ-5D-5L and was mapped to EQ-5D-3L using the algorithm developed by Hernández Alava (2023).<sup>64</sup></p> <p>HRQoL for the SoC arm was based on a range of sources, most of which used data derived directly from patients, but many used non-reference case methods such as time trade-off and standard gamble to elicit utilities from the general public.</p> |
| Source of data for measurement of health-related quality of life                     | Reported directly by patients, carers or both                                                                                                            | <p>HRQoL for larotrectinib was based on EQ-5D reported directly by patients.</p> <p>HRQoL for the SoC arm was based on a mixture of EQ-5D and non-reference case methods, with many utilities elicited from the general public.</p>                                                                                                                                                                                                                                 |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population                                                                                                               | Societal tariffs based on UK EQ-5D data.                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Equity considerations                                                                | An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances | QALYs were weighted for severity weighting at different levels across tumour types. The use of a single severity modifier based on pooled QALY shortfall is preferred.                                                                                                                                                                                                                                                                                              |
| Evidence on resource use and costs                                                   | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS                                           | Included costs were largely based on NHS National Cost Collection data, and relevant drug unit costs.                                                                                                                                                                                                                                                                                                                                                               |

| Element of health technology assessment | Reference case                                                          | EAG comment on company's submission                   |
|-----------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------|
| Discounting                             | The same annual rate for both costs and health effects (currently 3.5%) | Costs and benefits were discounted at 3.5% per annum. |

Abbreviations: QALY: quality-adjusted life year. NHS: National Health Service. PSS: Personal Social Services. HRQoL: health-related quality of life. EQ-5D: EuroQol 5-Dimension. EQ-5D-3L: EuroQol 5-Dimension 3-Level. EQ-5D-5L: EuroQol 5-Dimension 5-Level. SoC: standard of care.

#### 4.2.2 Model structure

The company developed a partitioned survival model (PSM) to estimate the cost-effectiveness of larotrectinib compared with SoC in patients with NTRK fusion-positive solid tumours. The model is consistent with the structure originally submitted in TA630, with modifications to reflect the updated decision problem and the availability of more mature trial data (ePAS9, SAS3) and new comparator evidence sources.

The company's base case is informed by two MAICs (VICTORIA<sup>50</sup> for the adult population, EPI-VITRAKVI<sup>54</sup> for paediatric patients), while alternative approaches including a responder/non-responder analysis, an intra-patient comparison, a naïve literature-based comparison and cure model, were explored as scenario analyses. All analyses share a common three-state PSM structure (progression-free, progressed disease, and death) but differ in how relative treatment effects for larotrectinib versus SoC are derived and applied, and the level of granularity with which the tumour types are modelled.

The underlying structure consisted of three mutually exclusive health states: progression-free, progressed disease, and death. Patients enter the model in the progression-free state and can remain progression-free, transition to progressed disease, or die. The proportion of patients in each health state at any time point was derived from the PFS and OS curves, with the difference between OS and PFS representing the proportion in the progressed-disease state. The model used a 7-day cycle length, reflecting the frequency of treatment administration and timing of outcome assessment in the clinical trials. Given the short cycle length, no half-cycle correction was applied. A lifetime time horizon of 80 years was adopted in the base case. Costs and QALYs were discounted at an annual rate of 3.5%.

The larotrectinib arm was modelled as tumour-agnostic, using pooled PFS, OS, and health-state utility values across all tumour types, which used data from the larotrectinib clinical trials (ePAS9 and SAS3 datasets). In the company's base-case model, separate adult and paediatric model engines were implemented, using demographic-specific outcomes for each engine, but assuming homogeneity of treatment response and outcomes within each respective population. Outcomes were combined from the adult and paediatric engines to produce a single combined ICER, using a weighting of ■■■% paediatric (STS/IFS) and ■■■% adult patients, derived from the distribution of tumour sites in the

ePAS9 and SAS3 pooled datasets. Survival was extrapolated from the pooled ePAS9 and SAS3 datasets using standard parametric models. The company's base-case PSM applies HRs derived from unanchored, population-adjusted MAICs (described in Section 3.4) to derive relative treatment effects for larotrectinib versus SoC.

In the SoC arm, stratification by tumour location was implemented to reflect differences in resource use and HRQoL across the tumour sites. The model therefore included 12 tumour-specific engines, including NSCLC, salivary gland carcinoma, melanoma, colorectal cancer, soft-tissue sarcoma (GIST and non-GIST), paediatric sarcomas/IFS, breast, cholangiocarcinoma, CNS/glioma, pancreas, and thyroid cancer. Health state residency was based on the pooled HR-derived curves, but SoC QALYs were calculated on the basis of tumour-specific health state utilities. Tumour site-specific cost inputs were applied within these engines, and comparator results were aggregated using weights based on selected tumour location prevalence in the larotrectinib trials (with some grouped into proxies).

The company's model adopts a lifetime time horizon (80 years) in the base case. In adult tumour sites, there are largely less than ■ of patients remaining alive at the end of the time horizon. In the paediatric cohort in the company's base case, ■ of patients remain alive at the end of the model time horizon. The model adopts an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% per annum.

### ***Points for critique***

The company retained the three-state partitioned survival model (progression-free, progressed, death) with tumour-specific sub-models per their preferred approach in TA630. While this framework is transparent and consistent with precedent in oncology, it remains limited in capturing the possibility of heterogeneity of treatment effect across tumour types. The Committee in TA630 previously concluded that, given the single-arm and histology-independent evidence, the most appropriate model structure remains uncertain. The EAG considers a single PSM unable to capture the high level of heterogeneity in natural history, treatment response, and overall treatment outcomes, in a way that allows decision uncertainty to be appropriately characterised and considered in decision making across this diverse population. It is likely that this approach introduces bias, if response and survival outcomes differ across tumour sites, particularly when coupled with the company's preferred approach to the application of the QALY multiplier. The EAG considers there to be sufficient data for a number of distinctive sub-populations to be modelled independently in this modelling framework, in terms of both sample size and duration of follow-up.

The EAG consider a model structure which more granularly captures heterogeneity to be more informative for decision making, though there may be multiple plausible alternatives to the structure as presented. This may allow comparisons of larotrectinib with a relevant SoC in a number of more

common tumour types, based on data directly derived from a given tumour site. A decision on rarer histologies may then be made on the basis of pooled outcome data.

The EAG considers the time horizon largely appropriate, but that it is likely to underestimate QALYs generated in paediatric patients modelled to achieve a near-general population life expectancy.

Although it is unclear whether this would account for a large proportion of patients in NHS practice given uncertainties around modelled post-progression survival (PPS). It is, however, likely to be a conservative choice, if larotrectinib is substantially more effective than SoC in paediatric patients and can generate cure-like outcomes in some patients.

#### *Weighting of paediatric and adult patients*

The calculation of a single ICER for adults and paediatric patients, despite their very different modelled treatment outcomes, means the model is likely to overestimate the cost-effectiveness of larotrectinib.

The EAG prefer the use of a model structure that presents ICERs separately for adult and paediatric patients to allow more a transparent assessment of cost-effectiveness and the impact of alternative assumptions. The EAG would also prefer the independent modelling of larotrectinib for histologies with sufficient data, to more granularly reflect costs and benefits (including QALY weighting) and permit changes in population composition to be reflected in the overall model outcomes, i.e. even if cost-effectiveness results are then pooled across histologies to inform a single decision.

#### *4.2.2.1 Responder / non-responder model*

In this scenario, patients in the ePAS9/SAS3 datasets were stratified by best objective response (complete or partial response versus stable or progressive disease). Separate PFS and OS curves were fitted for responders and non-responders. Larotrectinib outcomes were generated as a weighted combination of these curves, weighted according to an ORR representing response in selected tumour types derived from the BHM (see Section 3.2.4). SoC outcomes were assumed equivalent to non-responders, that is, those who did not achieve a partial or complete response.

Although the company used a BHM to estimate a pooled ORR that statistically accounts for variation in response across tumour types, this heterogeneity was not structurally represented in the model. The model essentially remained tumour-agnostic, applying a common response rate across all tumour sites and within the adult and paediatric populations. Separate PFS and OS curves were fitted for adults and paediatric patients within the responders and non-responder strata, but tumour-specific response or survival differences were not explicitly modelled.

The company did not adopt the response-based model as its preferred approach, arguing that equating non-responders with SoC outcomes misattributes the value of larotrectinib in achieving 'stable

disease', especially in those with primary CNS tumours. They argue that this model structure therefore systematically underrepresents the relative effectiveness of larotrectinib.

### ***Points for critique***

The EAG maintains that the response-based model structure remains informative. As discussed in Section 3.2.4, there is clear and substantial heterogeneity in response across NTRK fusion-positive solid tumours, which undermines the assumption of a homogeneous treatment effect implicit in the pooled PSM structure. This assumption is central to the validity of the company's base-case analysis as a single tool for decision making. The limited overlap in tumour-type distributions between the populations in the trials and the NHS necessitates the assumption that treatment effects are fully generalisable and independent of tumour site. In the presence of marked heterogeneity of response, this assumption is unlikely to hold, and the MAIC-adjusted PSM therefore provides a weak basis for extrapolating cost-effectiveness to the NHS population.

The clinical implausibility of PPS estimates generated in paediatric patients further demonstrates the limited capacity of this model structure to inform meaningful decisions in the whole population. The EAG considered a response-based model using BHM-derived response estimates to be informative for decision making, consistent with the committee's previous preferences (TA630) and the methodological recommendations of Murphy et al. (2021).<sup>46, 65</sup>

The EAG acknowledges that the response-based framework has limitations. Differences in underlying natural history across tumour types, and the potential for larotrectinib to achieve durable stable disease in a subset of non-responders, means that the results from this model structure should be considered informative but not definitive. Nevertheless, the EAG considers the response-based a methodologically plausible and for exploring heterogeneity in treatment effects, and that it may underrepresent the outcomes of patients on SoC who in the present appraisal are in largely receipt of potentially effective systemic therapies at an earlier treatment line than considered in TA630. The EAG's preference is that tumour site-specific response rates from the BHM are applied directly in the model, allowing outcomes to be reweighted to reflect the distribution of tumour sites in the NHS population and appropriate severity weighting of QALYs gained.

The EAG requested that the company provide an updated response-based model which uses BHM analyses accounting for the different levels of response in adults and children separately (CQ B6). The company declined to provide this analysis.

The MAIC-informed model is the company's primary analysis, but key uncertainties persist around the unanchored indirect comparisons and survival extrapolations (discussed in Section 3.4 and 4.2.5.1). The response-based model estimates survival conditional on treatment response within the

trial population itself and thereby mitigating the issues inherent to a reliance on the MAIC, which the EAG considers flawed as a means to producing a generalisable comparative treatment effect. The EAG therefore considers that the response-based model structure be considered alongside, rather than subordinate to, the MAIC-based analysis.

#### *4.2.2.2 Intra-patient comparison (GMI analysis)*

The intra-patient model used the growth modulation index (GMI), where each patient's time-to-progression on prior therapy served as a proxy for SoC PFS. SoC OS was inferred by applying the relative OS/PFS relationship observed for larotrectinib.

#### ***Points for critique***

In TA630, the committee noted that while such analyses provide some indication of treatment activity, they are subject to substantial bias and structural uncertainty, and that the previous line of therapy may not represent current NHS practice. The EAG agrees that these limitations persist in the current submission, as the assumptions underlying the GMI framework remain unverified and the relationship between PFS and OS on larotrectinib is unlikely to generalise to SoC. The intra-patient comparison is therefore considered exploratory and not as a plausible alternative structure.

#### *4.2.2.3 Naïve literature-based comparison*

The company also presented an alternative model structure which compares pooled larotrectinib outcomes with unadjusted OS and PFS data from published literature and previous NICE technology appraisals to directly model outcomes for each tumour site. For tumour types with low NTRK fusion prevalence, the company applied HRs from the VOYAGER 1 and 2 studies to adjust for increased mortality risk associated with NTRK fusion (Section 2.1.3).

#### ***Points for critique***

The committee in TA630 recognised the difficulty in identifying appropriate comparators across multiple rare tumour types but concluded that naïve literature-based comparison introduced bias and failed to account for heterogeneity and the presence of other important prognostic factors. The EAG considers that these concerns remain applicable to the current submission and is furthermore concerned that the identified sources of efficacy data may be poorly representative of outcomes on current NHS care. The EAG therefore agrees with the committee's previous assessment that the naïve literature-based comparison should be considered exploratory and not as a plausible alternative structure.

#### *4.2.2.4 Mixture-cure model*

The company implemented a mixture-cure model for paediatric patients only, assuming a cure fraction among those treated with larotrectinib. The adult cohort was modelled per the base-case PSM.



### ***Points for critique***

In TA630, the committee considered the potential for cure among paediatric patients but concluded that this was highly uncertain and unlikely to be generalisable to clinical practice. The paediatric PFS data are now sufficiently mature and do not show any clear evidence of a survival plateau consistent with cure. The mixture-cure framework necessarily assumes that a substantial cure fraction exists amongst progressed patients, which the EAG considers clinically implausible. Given the lack of empirical evidence supporting a curative effect and the maturity of follow-up, the EAG does not consider the mixture-cure model to be an appropriate structure for decision-making, as it is likely to overestimate long-term survival and QALY gains.

### **4.2.3 Population**

The CS states that the population considered in the economic model reflects patients enrolled in the larotrectinib clinical trials, and the marketing authorisation granted by the MHRA, i.e. patients with NTRK fusion cancer that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

#### ***4.2.3.1 Larotrectinib population***

Larotrectinib is assessed in the model as a tumour-agnostic treatment option. The model implicitly assumes that treatment outcomes are the same regardless of tumour type and thus does not explicitly consider histology in the larotrectinib arm. Paediatric patients with STS and IFS tumours are modelled in a separate engine. The outcomes of paediatric patients with primary CNS tumours are included in the paediatric engine, but the comparator, HRQoL, and resource use is assumed to be equivalent to STS.

The baseline characteristics of the modelled population for larotrectinib is therefore aligned with the ePAS9 and SAS3 datasets, as described in Section 3.2.4. Baseline patient age and sex distribution in the larotrectinib and stratified comparator arms vary according to tumour site (CS Table 41, Page 141), reflecting the larotrectinib trials. Outcomes were combined from the adult and paediatric engines to provide a single combined ICER, using a weighting of [REDACTED] % paediatric (i.e. STS/IFS) and [REDACTED] % adult patients. The model uses OS and PFS data notionally derived from the full distribution of tumour sites in the ePAS9 and SAS3 pooled datasets, but paediatric patients with primary CNS tumours contribute to the primary CNS weighting, which is only explicitly modelled as an adult tumour location. However, OS and PFS data on paediatric primary CNS patients was included in the modelled paediatric OS and PFS curves.

The company considered the modelled population to be reflective of NHS clinical practice and in the data collected in SACT.

#### 4.2.3.2 Comparator population

The comparators are defined according to tumour location and are thus modelled separately for each of the selected tumour types. As discussed in Sections 4.2.2 and 4.2.5, these engines consider only tumour-site specific utilities and resource use, and the outputs are weighted according to the selected population composition in the cost-effectiveness results. The modelled population comprises the 12 most frequently observed tumour types across the ePAS9 and SAS3 datasets, with less common tumour types redistributed amongst other tumour locations (per CS Table 42, Page 143).

The adult comparator population considered in the company's base case is that included in Brose *et al.*<sup>50</sup>, compared through the VICTORIA MAIC, which adjusts the Brose *et al.*<sup>50</sup> SoC population to be more similar to that recruited to the larotrectinib trials. The VICTORIA MAIC is discussed in further detail in Section 3.4. The EPI VITRAKVI retrospective observational study comprises the comparator population in the base case paediatric comparison, again via a MAIC described elsewhere. This study included only those with locally advanced or metastatic IFS.

#### **Points for critique**

The generalisability of the patient population in the trial evidence to the NHS has been previously discussed in Section 3.2.3. In brief, the EAG is concerned that the ePAS9 and SAS3 datasets are poorly reflective of the SACT population in terms of the number of previous lines of therapy, and of the distribution of primary tumour location. The EAG considers it highly likely that this mismatch will impact on the generalisability of the cost-effectiveness results for larotrectinib, particularly given the observed heterogeneity in treatment response across tumour locations, and the clear differences in tumour site distribution between the trial and SACT datasets. The composition of the trial and SACT population is compared in Table 9, which demonstrates that primary CNS tumours in particular are underrepresented in the trial evidence. As is discussed elsewhere, the EAG does not consider the population adjustment undertaken in the MAIC to produce a generalisable comparison of relative treatment effectiveness to the NHS setting, as neither the larotrectinib study populations, nor the comparator study populations, resemble the NHS clinical population in terms of tumour type distribution (amongst other characteristics). The comparator population for paediatric patients is particularly limited, being focused entirely on IFS, whose outcomes are unlikely to represent those of all paediatric solid tumour types. The model did not account for paediatric primary CNS as a separate tumour location, with their own outcomes, resource use, or HRQoL. This is an important source of uncertainty, given the size of the primary CNS tumour population.

As described in Section 3.2, the EAG expressed a preference for generalisability of the modelled population to the NHS, requesting analysis from the company which used population adjustment methods, or directly integrated data from SACT into the model (CQ A3, B11). The company declined to present any synthesis or economic analysis inclusive of data collected in SACT. The EAG present a

scenario analysis in which SACT is used to directly inform population characteristics and treatment outcomes in Section 5.2.

The EAG also considered a response-based model which used tumour-specific response rates and weighted outcomes according to the NHS population to provide another more informative alternative to the company's base-case analysis, requesting a range of re-analyses in CQ A13, B6, and B7. In their clarification response, the company again declined to provide any of the requested analyses (discussed further in Section 4.2.5). In Section 5.2.3 the EAG present an alternative response-based model which allows for tumour-specific response rates and thus the alignment of the population by tumour location to that observed in SACT.

As discussed in Section 3.2 and 4.2.5, the high level of heterogeneity in outcomes and uncertainty between the adult population and paediatric populations means the use of a single pooled ICER to represent cost-effectiveness in these populations is not meaningful for decision making, increasing decision uncertainty in the adult population, whilst artificially decreasing the ICER. In response to CQ B2 the company provided ICERs for the base case and other scenarios separately for adult and paediatric populations (although paediatric primary CNS resource use and HRQoL was not represented in paediatric population ICERs). However, the company declined to provide the additional subgroup analyses requested by the EAG (CQ A3, A13). The EAG considers this a key area of uncertainty, and that the present analysis may be unsuitable for decision making.

The EAG also considers the grouping of primary CNS patients with the other tumour types potentially inappropriate and likely misleading with regards to the cost-effectiveness of larotrectinib. Given the distinctiveness of this population with regards to natural history and treatment response, it may be more appropriate to generate separate cost-effectiveness results for patients with primary CNS tumours directly, as with other tumour types with sufficient available data as previously described in Section 4.2.2. This is a key area of uncertainty.

#### **4.2.4 Interventions and comparators**

Larotrectinib is an oral TRK inhibitor used to treat adult and paediatric patients with NTRK fusion-positive solid tumours. The marketing authorisation states that larotrectinib should only be used in patients who have exhausted all satisfactory treatment options, as response rate and duration may be quantitatively different depending on tumour type. In TA630 it was therefore assumed that larotrectinib would be used as a last-line treatment option, but data collected during its time in the CDF indicate that clinicians have typically used larotrectinib earlier in the treatment pathway (See CQ Response Table 20, Page 71), with included patients having received an average of ■■■ prior lines of therapy, and ■■■ having received only one prior line of therapy. This reflects in part the increased prevalence of genetic testing, which in some tumour types allows NTRK status to be known before

the point at which patients would otherwise be considered for treatment with larotrectinib. The EAG was advised that in a patient whose fusion status is known, the only satisfactory treatment option would be a targeted therapy, particularly if the alternative is associated with higher toxicity.

As larotrectinib is specifically indicated for patients with solid tumours harbouring an NTRK gene fusion, diagnostic testing to identify patients eligible for treatment forms an essential component of the intervention. The company considered diagnostic testing to be part of routine practice in the NHS and therefore did not include this component in the economic modelling. This is discussed in further detail in Section 4.2.7.

The company's model compared larotrectinib with SoC relevant to 12 tumour types which represent the most common (individually or categorised) tumour types observed in the larotrectinib trial population. Comparator treatments were selected based on the assumption that larotrectinib is generally used in practice as a second-line treatment option, unless there is a clear indication that TRK inhibitors should be used later in the treatment pathway. This contrasts with the original submission, in which the comparator was based on a mixed basket of last line SoC. Relevant comparators in each tumour type were therefore identified on the basis of guidelines and through expert elicitation. This broadly aligns with its use in data collected in SACT, although these data were not available for specific tumour types. Table 27 presents a list of comparator therapies by tumour site, along with the data sources and company's justification for their selection.

**Table 27 List of comparator therapies by tumour site**

| <b>Tumour site</b>                              | <b>Comparator treatment</b>                                                | <b>Data source (for treatment cost)</b>                     | <b>Details / Evidence base</b>                                                                                       | <b>Company justification (from submission)</b>                                                                                                                 |
|-------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NSCLC                                           | Nintedanib + docetaxel                                                     | NICE TA347 <sup>66</sup>                                    | Used as second-line therapy for metastatic NSCLC without actionable mutations; based on phase III LUME-Lung 1 trial. | Recommended by UK lung cancer specialist and consistent with ESMO 2025 guidelines for non-oncogene-addicted NSCLC. <sup>13</sup>                               |
| Salivary gland cancer                           | Cisplatin + vinorelbine                                                    | Airoldi et al., 2017 <sup>67</sup>                          | Phase II study in recurrent or metastatic salivary gland malignancy.                                                 | Reflects real-world UK practice per advisory board; consistent with ESMO 2022 guidelines where platinum-based chemotherapy is commonly used. <sup>18</sup>     |
| Melanoma                                        | Pembrolizumab                                                              | NICE TA357 <sup>68</sup>                                    | Based on Keynote-002 trial in advanced melanoma post-immunotherapy.                                                  | Selected as second-line standard in clinical practice; endorsed by UK advisory board.                                                                          |
| Colorectal cancer (incl. appendix proxy)        | Trifluridine-tipiracil                                                     | Mayer et al., 2015 <sup>68</sup>                            | RECOURSE phase III trial in metastatic CRC after $\geq 2$ prior lines.                                               | ESMO 2023 guidelines recommend TRK testing after $\geq 2$ lines; <sup>15</sup> thus larotrectinib modelled vs third-line comparator, validated by clinicians.  |
| STS (adult, GIST)                               | Regorafenib                                                                | NICE TA488 <sup>69</sup>                                    | GRID phase III trial in GIST post-imatinib.                                                                          | Reflects ESMO 2021 guidelines <sup>20</sup> and validated by advisory board as second-line comparator after sunitinib.                                         |
| STS (adult, non-GIST; incl. bone sarcoma proxy) | Trabectedin                                                                | NICE TA185 <sup>70</sup> Demetri et al., 2016 <sup>71</sup> | Approved for advanced soft-tissue sarcoma post-anthracycline.                                                        | Recommended by the ESMO 2021 guidelines <sup>19</sup> and clinicians as representative of second-line STS; used as proxy for bone sarcoma due to limited data. |
| STS (paediatric; incl. IFS proxy)               | Irinotecan + vincristine + temozolomide (VIT)                              | VIT-0910 trial <sup>72</sup>                                | European standard for progressive/relapsed paediatric rhabdomyosarcoma.                                              | Only effective option available; advised by paediatric oncologists as appropriate comparator for paediatric STS and IFS.                                       |
| Breast cancer                                   | Vinorelbine (IV and oral), Gemcitabine, Docetaxel, Paclitaxel, Doxorubicin | NICE TA423 <sup>73</sup>                                    | Standard chemotherapy options for metastatic breast cancer post targeted therapies.                                  | Modelled as best supportive care mix of real-world chemotherapies; supported by ESMO 2021 guidelines <sup>10</sup> and UK clinical practice.                   |
| Cholangiocarcinoma / biliary tract cancer       | 5-fluorouracil + oxaliplatin + folinic acid (FOLFOX)                       | ABC-06 trial <sup>74</sup>                                  | Phase III trial in advanced BTC post-cisplatin/gemcitabine failure.                                                  | Consistent with ESMO 2023 guidelines; <sup>9</sup> advisory board recommended FOLFOX as second-line SoC.                                                       |
| CNS / Glioma                                    | Lomustine                                                                  | Batchelor et al., 2013 <sup>75</sup>                        | Phase III study in recurrent glioblastoma after temozolomide and radiation.                                          | Recommended by neuro-oncologists on advisory board as relevant UK practice.                                                                                    |

|                   |             |                                   |                                                                                                       |                                                                                                                                                  |
|-------------------|-------------|-----------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Pancreatic cancer | Gemcitabine | Conroy et al., 2022 <sup>76</sup> | ESMO 2023 guidelines support gemcitabine as second-line therapy for ECOG 0–1 patient post FOLFIRINOX. | In line with the ESMO 2023 guidelines <sup>17</sup> and validated by advisory board as appropriate comparator for second-line pancreatic cancer. |
| Thyroid cancer    | Lenvatinib  | SELECT trial (2015) <sup>77</sup> | Phase III trial in radioiodine-refractory differentiated thyroid cancer.                              | Aligned with ESMO 2022 guidelines <sup>12</sup> and UK advisory board recommendations.                                                           |

Abbreviations: ABC: Advanced Biliary Tract Cancer. BTC: Biliary Tract Cancer. CNS: Central Nervous System. CRC: Colorectal Cancer. ECOG: Eastern Cooperative Oncology Group performance status. ESMO: European Society for Medical Oncology. FOLFOX: 5-fluorouracil: folinic acid and oxaliplatin. GIST: Gastrointestinal Stromal Tumour. IFS: Infantile Fibrosarcoma. IV: Intravenous. NSCLC: Non-small-cell Lung Cancer. SoC: Standard of Care. STS: Soft-tissue Sarcoma. TA: Technology Appraisal. TRK: Tropomyosin Receptor Kinase. VIT: Vincristine: Irinotecan and Temozolomide regimen.

### ***Points for critique***

Real-world use of larotrectinib in NHS England may differ from the positioning assumed in the company's model for some tumour types. In some tumour types where NTRK fusion status is already known, larotrectinib has been used earlier than second line as assumed in the model. Misalignment between modelled and actual placement in the treatment pathway may mean incorrect comparisons are made, biasing against SoC for some tumour types. As has been discussed elsewhere, the EAG considers it appropriate to explore scenarios accounting for part of the cost of diagnostic testing in some tumour types.

The EAG heard from its clinical experts that some comparators (e.g. regorafenib, trabectedin for STS) are typically used *after* larotrectinib if this is used early. While the company positions larotrectinib after at least one prior therapy, inconsistent comparator selection across tumour types may misalign the treatment options being compared and may fail to capture the costs of the use of these treatments following progression on larotrectinib.

As the model no longer focuses on a last-line comparison, it may be appropriate to account for the use of subsequent active treatments and other interventions such as surgery and radiotherapy. The company's model assumes that all patients receive best supportive care following progression, but as discussed in Sections 3.2, 4.2.3, and 4.2.4, a large proportion of patients in the larotrectinib trial received further lines of systemic therapy (amongst other treatments), see Table 14 for ePAS9 and Table 15 for subsequent therapy use in SAS3. Around 13% of patients in SACT received other treatments after discontinuing larotrectinib. The model may therefore not fully capture the intervention and comparator regimens appropriately at this treatment line.

#### **4.2.5 Treatment effectiveness and extrapolation**

As previously described in Section 4.2.2, the company propose five alternative model structures, which explore different means of both implementing the efficacy data collected in the single arm larotrectinib trials, and constructing a comparator arm, reflecting costs and outcomes on the standard of care for each tumour site. This reflects the uncertainty in the optimal modelling approach expressed by the EAG and Appraisal Committee in TA630, and around the wider best practice in value assessment of histology independent technologies.

As previously discussed in Section 3.2, there was evidence of substantial heterogeneity of treatment response across the tumour sites included in the ePAS9 and SAS3 datasets. The pooling of evidence on all adult tumours to estimate a site-agnostic treatment effect is therefore subject to considerable uncertainty. Notably, adult primary CNS patients had an ORR of [REDACTED], and only [REDACTED] months median PFS. Given that primary CNS patients comprised the largest population in the SACT dataset,

the efficacy of larotrectinib in this group is particularly pertinent for NHS practice. However, there is no means by which the OS/PFS data for larotrectinib specifically in primary CNS patients (or indeed other specific tumour sites) can be up-weighted appropriately using the evidence or the model structures provided by the company.

#### *4.2.5.1 MAIC modelling approach*

The primary effectiveness inputs included in the company's MAIC-based company base-case model were PFS and OS. The MAIC approach assumes that the treatment effect for larotrectinib across all tumour types can be captured in a single curve for each outcome, and due to the way in which costs and benefits are aggregated across tumour types, implies that patients are represented precisely according to their baseline prevalence for the duration of the modelled time horizon. That is, the distribution of response and survival outcomes across tumour types is homogeneous – in both the larotrectinib and SoC arms. The application of a static HR from the unanchored MAIC necessarily assumes that an assumption of proportional hazards holds for all tumour types across larotrectinib and all comparator regimens.

The company fitted a range of standard parametric survival distributions to PFS and OS KM data independently for the adult cohort from the ePAS9 and SAS3 datasets, and paediatric patients from the ePAS9 and SAS3 datasets. SoC outcomes were modelled through the application of HRs derived from the MAICs described in Section 3.4 to the larotrectinib reference OS and PFS curves. The general approach to derivation of SoC curves in this model structure was through the multiplication of cycle-specific hazards by the reciprocal HR from the relevant MAIC to estimate cycle-specific hazards on SoC. Per cycle hazards were subsequently restricted to be equal to or greater than general population mortality using the latest Office for National Statistics (ONS) Life Tables for England and Wales, with starting age based on that of the tumour site-specific population in the larotrectinib trials.

The company's base case fits survival curves to OS and PFS data from paediatric patients separately, allowing the model to estimate the accrual of costs and QALYs independently in this group, allowing for a lower model starting age to that of the adult and mixed primary CNS cohort. The model then weights the outputs of the paediatric engine with that of the other tumour types in the generation of results. The company also provide functionality to model the two populations in the same engine, with baseline characteristics based on the overall population means, and survival models fitted pooled OS and PFS data.

#### ***Points for critique***

Whilst the MAIC analysis allows some degree of comparison with a population not treated with larotrectinib, it does not allow a robust comparison with SoC in an NHS-relevant population, nor does it address the clear heterogeneity in treatment effect across tumour sites or allow trial data to be



appropriately reweighted according to reflect the tumour site distribution observed in NHS practice. The assumption that PH holds following population adjustment is also unlikely to be valid. As MAIC reweights trial data to match marginal baseline characteristics in another population, the use of a static HR to adjust survival curves necessarily assumes that the relative treatment effect is constant overtime and invariant across clinically distinct subgroups, whose prevalence in the population changes over time due to differences in natural history and the treatment effect. This approach will generally underrepresent uncertainty and can introduce bias into long-term survival estimates and thus incremental QALYs, although the direction of any bias is unclear here.

As previously discussed in Section 3.2.3, there are substantial differences between the population composition of the trials and SACT dataset, which mean that trial outcomes are unlikely to be directly transferrable to an NHS context. The pooled result generated using the company's base-case MAIC model structure is also extremely sensitive to the separate survival analysis of paediatric OS extrapolations, which are subject to a high degree of uncertainty (discussed further below), and inflate the apparent QALY gain in the population as a whole. Furthermore, as is described elsewhere, the potentially extensive and non-generalisable use of subsequent systemic therapies in the larotrectinib trials may be a significant source of confounding in these OS data. The EAG requested analyses incorporating SACT data, either through an updated MAIC or other population adjusted indirect comparison methods (CQ A3), or through the direct integration of these data into the model. Acknowledging the limitations of the SACT data provided, which also do not allow the disaggregation of outcomes by tumour site or age group (though this analysis was requested in CQ A17 and A18), the EAG consider analyses including SACT to be informative for decision making, as a source of absolute outcomes on larotrectinib which are generalisable to the NHS in terms of population characteristics and the use of subsequent therapies. The EAG present scenario analysis in Section 5.2.2 exploring the implications for cost-effectiveness of the use of data collected in SACT.

The EAG considers the generation of a single ICER to be generally inappropriate given the very high degree of heterogeneity between several prospectively identifiable groups, which appear to have very different treatment outcomes and natural history, including the paediatric IFS/STS population, the adult primary CNS tumour population, and the paediatric primary CNS population. The EAG would prefer to produce results separately for the primary CNS cohort at least, which, as stated by the company, is associated with an intrinsically poorer prognosis than other tumour sites. However, as discussed previously, it may be more appropriate to provide results for the most common tumour sites based on directly observed data.

Given the issues discussed in Section 3.4, and below with the EPI VITRAKVI MAIC and the separate survival analysis for paediatric patients, where a single ICER is used to represent the full population eligible for larotrectinib, the EAG prefers the use of the fully pooled survival analysis set (i.e. curves

are fitted to the full population), rather than to separately model adults and paediatric patients followed by reweighting. This allows the more robust VICTORIA MAIC to be used to estimate SoC outcomes for all patients.

### ***Overall Survival – Adult patients***

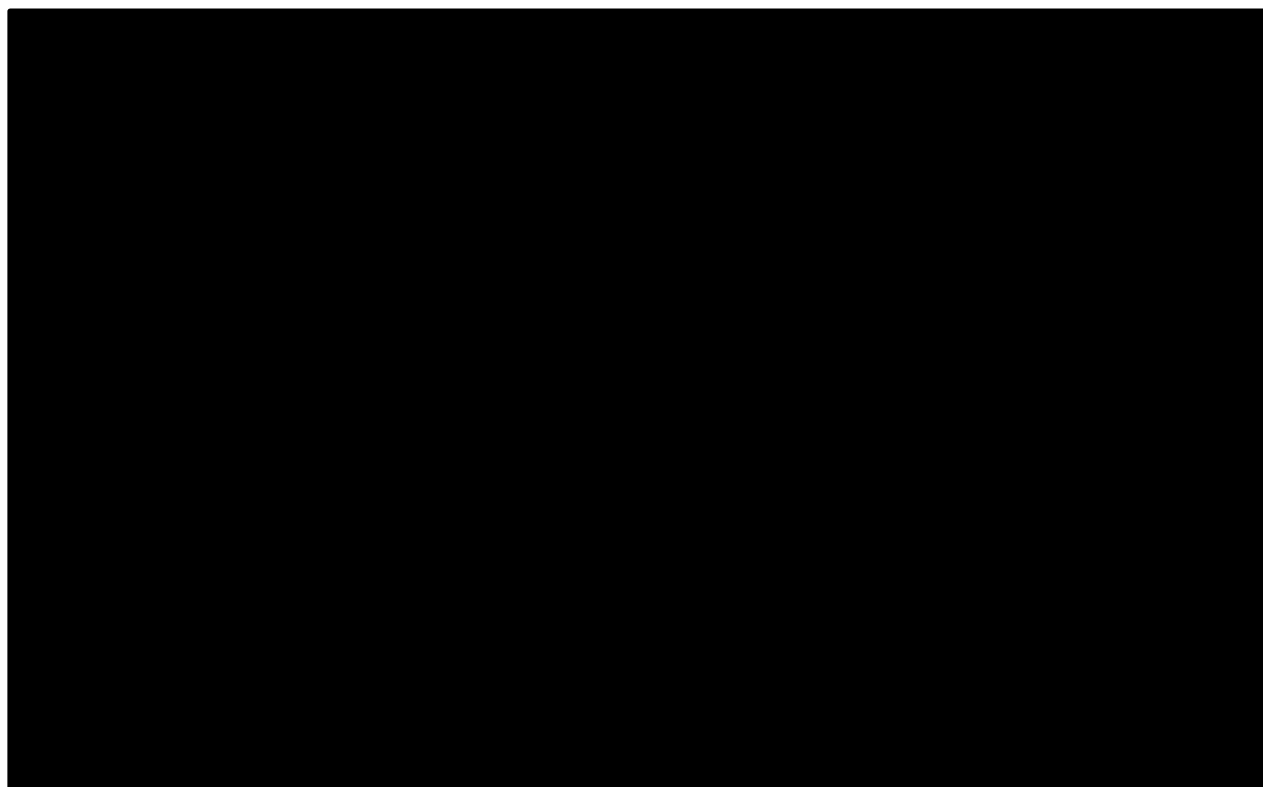
Overall survival data in adults were substantially more mature than in TA630, although median OS had still not been reached, with [REDACTED] deaths observed in the ePAS9 dataset and [REDACTED] deaths observed in the SAS3 dataset. Parametric model fits therefore presented a range of more plausible extrapolations than in the previous appraisal, where only [REDACTED] deaths had been observed.

The company selected the Weibull distribution to model OS for adult patients on larotrectinib in the base case. The Weibull model was ranked fifth in terms of statistical fit (based on AIC and BIC) but was considered more clinically plausible than the better-fitting models, which predicted significant long-term survival in a proportion of patients. It is also mathematically compatible with the application of HRs to generate the SoC curve. A visual comparison of the alternative parametric model fits for OS can be found in Figure 23 of the CS (Page 148), with statistical goodness-of-fit presented in CS Table 44 (Page 147).

The company applied the HR of 0.44 (95% CI 0.23 to 0.83) derived from the VICTORIA MAIC (i.e. reciprocal HR of 2.27) to produce the SoC OS curve (per the general method described above), which was then adjusted for general population mortality.

A comparison of OS and PFS on larotrectinib and SoC predicted through the MAIC approach in adults is presented in Figure 4 below.

**Figure 4 MAIC approach: Modelled adult OS (Weibull) and PFS (Weibull) curves (adapted from company's economic model)**



***Progression-free survival – Adult patients***

A total of [REDACTED] and [REDACTED] of patients experienced a PFS event in the ePAS9 and SAS3 datasets respectively. As with the fits of the extrapolations of OS data, the Weibull represented the best fitting model amongst those extrapolations most clinically plausible in terms of long-term PFS projections, despite ranking 5<sup>th</sup> in AIC and BIC. Comparisons of the visual and statistical fits of the alternative parametric models can be found on Page 152 of the CS.

The company applied the HR of 0.29 (95% CI 0.18 to 0.46) derived from the MAIC based on the VICTORIA study (i.e. reciprocal HR of 3.45) to produce the SoC OS curve (per the general method described above). A comparison of OS and PFS on larotrectinib and SoC in the model is presented in Figure 4.

***Points for critique***

The EAG is generally satisfied that the Weibull model represents the most appropriate distribution for modelling OS and PFS. As discussed above the assumption that proportional hazards is highly unlikely to hold, which is fundamental to the use of the summary effect generated by the MAIC (See also Section 3.4). The degree of heterogeneity in prognosis across different tumour sites on and off larotrectinib means that treatment effects are very likely to be time-varying - the assumption of a constant treatment effect across all tumour types and comparator treatment regimens appears clinically unsound, but the direction of any bias introduced through this assumption is unclear.

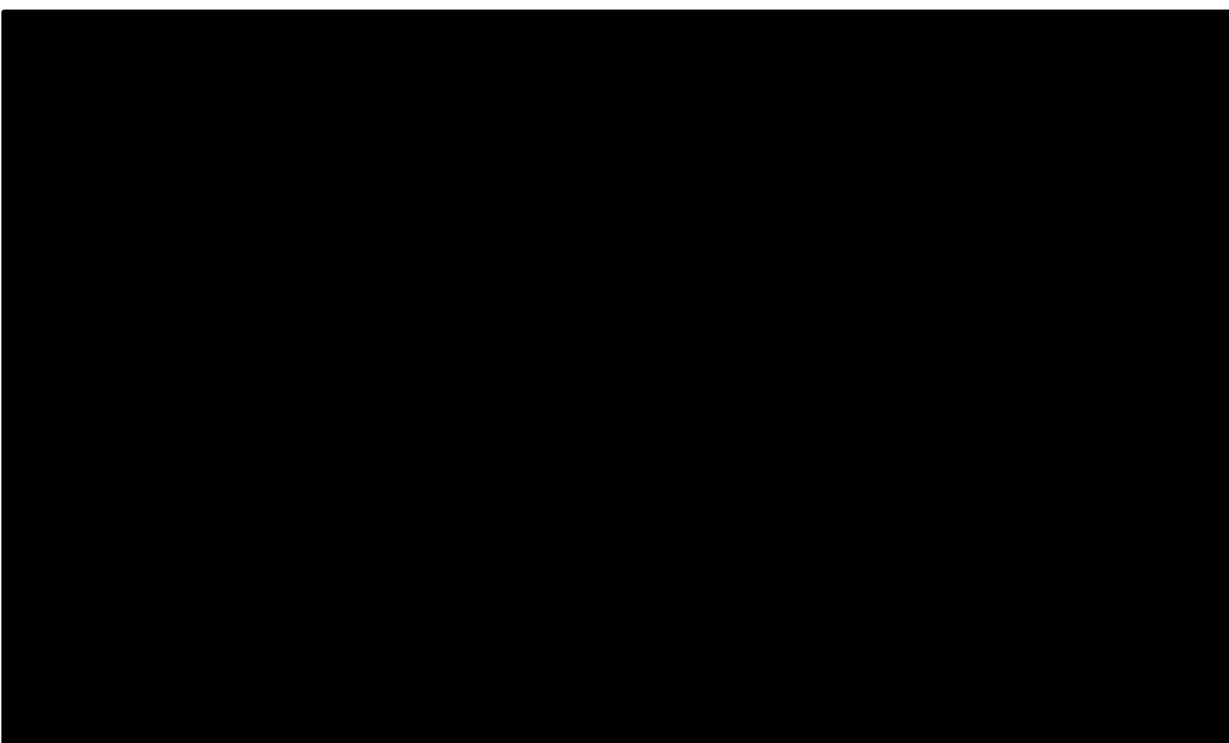
The EAG is also concerned that the extensive use of subsequent systemic therapies after progression on larotrectinib, particularly in adult patients, may introduce substantial confounding to OS outcomes. The company submission states that only [REDACTED] of patients received subsequent therapies after treatment with larotrectinib, however, in their clarification response (CQ B9), it appeared that up to [REDACTED] adult patients in ePAS9 received further systemic therapy (i.e. there were [REDACTED] initiations of subsequent systemics in this population), and a further [REDACTED] underwent radiotherapy or surgery. Other systemic therapies were used in [REDACTED] adult patients in SAS3 following progression, with radiotherapy, radioactive iodine therapy, and a combination of systemic and radiotherapy used in a further [REDACTED] patients [REDACTED]. These figures may include patients more than once, as some patients received combination therapy. Absolute numbers of adult patients in receipt of subsequent systemic therapies were not provided, but the overall proportion of adult and paediatric patients in receipt of subsequent therapies was [REDACTED] in ePAS9, and [REDACTED] in SAS3. These patients were not censored from the survival data informing the model. Furthermore, such high rates of subsequent systemic therapy use may belie differences in the underlying population, as this use does not represent NHS practice, per the data collected in SACT. More sophisticated methods to account for the use of subsequent treatment may be necessary to account for the likelihood of informative censoring in this setting, that is, it is more likely that fitter patients received a further line of systemic therapy after progression, and thus censoring alone could underestimate survival outcomes on treatment.

### ***Overall Survival – Paediatric patients***

Parametric models were fitted to the pooled paediatric populations in the ePAS9 and SAS3 datasets. These data remain very immature, with only [REDACTED] events ([REDACTED]) in the SAS3 cohort (n=[REDACTED]), and [REDACTED] events ([REDACTED]) in the ePAS9 cohort (n=[REDACTED]), i.e. [REDACTED] in the pooled cohort. This results in widely distributed predictions about long-term survival in these patients. The statistical fit of the parametric models can be found in CS Table 45 (Page 149), and a visual comparison up to 20 years is presented in CS Figure 24 (Page 150). The company again selected the Weibull as their preferred distribution, which had the second-worst statistical fit, but was again one of the more pessimistic extrapolations and allowed the application of the MAIC HR. The Weibull predicted OS of [REDACTED] at 20 years, and [REDACTED] at 50 years. The Gompertz and generalised gamma, the models with the best statistical fits to the observed data, predicted [REDACTED] and [REDACTED] survival at 50 years respectively. The EAG notes that the company report that their clinical experts recommended the exponential or gamma curves as acceptable options for extrapolation of OS – the former generating the most pessimistic predictions of long-term survival. A comparison of OS and PFS predictions at key milestones is presented in Table 28. As will be discussed below, even under the more pessimistic survival extrapolations, the model predicts that a large proportion of patients will survive for many decades with progressed disease. This compares to OS immediately following (or occurring very shortly after) progression on SoC.

The company applied the HR of 0.21 (95% CI 0.02 to 2.84) derived from the EPI VITRAKVI MAIC (i.e. reciprocal HR of 4.76) to produce the SoC OS curve. This is a substantially larger effect than observed for PFS in EPI VITRAKVI, for which a HR of 0.8 (reciprocal 1.25) was applied. Note that this is a non-significant point estimate subject to a very high degree of uncertainty. The use of this HR results in survival estimates lower than PFS for the first 6 months of the model, meaning a cap on PFS has to be applied. A comparison of modelled OS and PFS on larotrectinib and SoC in paediatric patients is presented in Figure 5.

**Figure 5 MAIC approach: Modelled paediatric OS (Weibull) and PFS (Weibull) curves (adapted from company's economic model)**



#### ***Progression-free survival - Paediatric patients***

The PFS data on paediatric patients in the ePAS9 and SAS3 dataset were somewhat more mature than the data for OS, with [REDACTED] progression events observed in ePAS9 and [REDACTED] in SAS3. This results in better agreement between the alternative model fits, but again these diverged into groups of more and less optimistic extrapolations, reflecting the differences in long-term hazards trends implied by these distributions. The Weibull was again chosen, with the company citing its reasonably pessimistic predictions about long-term outcomes, and its amenability to the application of a HR to estimate SoC outcomes.

The company applied the HR of 0.80 (95% CI 0.41 to 1.58) derived from the MAIC based on the EPI VITRAKVI study (i.e. reciprocal HR of 1.25) to produce the SoC OS curve. As noted above, this meant that PFS and OS on SoC follow one another very closely, with PFS being in excess of OS for

the first six months of the model. A comparison of OS and PFS at 10, 20, and 50 years on both larotrectinib and SoC is presented in Table 28.

**Table 28 MAIC approach: Paediatric OS and PFS milestones on larotrectinib and SoC**

| Distribution                   | OS – 10 yrs | PFS – 10 yrs | OS – 20 yrs | PFS – 20 yrs | OS – 50 yrs | PFS – 50 yrs |
|--------------------------------|-------------|--------------|-------------|--------------|-------------|--------------|
| <b>Larotrectinib arm</b>       |             |              |             |              |             |              |
| Exponential (most pessimistic) | ████        | ████         | ████        | ████         | ████        | ████         |
| Weibull (base-case)            | ████        | ████         | ████        | ████         | ████        | ████         |
| Gompertz (most optimistic)     | ████        | ████         | ████        | ████         | ████        | ████         |
| <b>SoC arm</b>                 |             |              |             |              |             |              |
| Exponential (most pessimistic) | ████        | ████         | ████        | ████         | ████        | ████         |
| Weibull (base-case)            | ████        | ████         | ████        | ████         | ████        | ████         |
| Gompertz (most optimistic)     | ████        | ████         | ████        | ████         | ████        | ████         |

OS: Overall Survival. PFS: Progression-free Survival. SoC: Standard of Care

### ***Points for critique***

The EAG considers the MAIC-adjusted survival analysis in paediatric patients to be subject to a very high degree of uncertainty. Key aspects of this analysis lack clinical face validity, and the resulting outputs appear implausible given the clinical context. In the company’s base-case analysis, these uncertainties appear to systemically favour larotrectinib through the weighting of inflated paediatric outcomes in the overall ICER.

A major concern is the divergence between OS and PFS in the trial data, which generates post-progression survival (PPS) outcomes on larotrectinib that are not credible. The company’s preferred models predicts █████ survival at 20 years, yet only █████ of these patients are progression free. This implies that paediatric patients on larotrectinib spend an average of █████ years in PFS but survive for a further █████ years following disease progression. In contrast, patients in the SoC arm, patients spent an average of █████ years in the PFS health state but survived for an average of only █████ months following progression. There is no clear biological or clinical mechanism for a persistent treatment effect of this magnitude following progression. These predictions are also inconsistent with the company’s naïve literature comparison analysis, which suggested 2.27 years in PFS and 10.34 months survival post-progression. The issue arises in part because of the substantially larger HR for OS than for PFS arising from the MAIC with EPI VITRAKVI, which as discussed in Section 3.4, the

EAG considers inappropriate, and results in almost overlapping OS and PFS curves for SoC. This in turn yields an implausibly large modelled treatment effect upon PPS, implying a 56-fold prolongation of PPS with larotrectinib relative to SoC, far beyond what could be inferred from the HRs produced by comparison using the EPI VITRAKVI MAIC, which themselves have serious limitations. Despite the large inverse treatment effect applied to SoC, life-year gain was substantially higher on SoC using the MAIC (██████) compared to the naïve literature-based comparison (3.13 years). This provides further evidence that the survival data from the larotrectinib trials are flawed, and may be subject to confounding due to the use of subsequent therapies.

The EAG asked that the company justify this magnitude of post-progression benefit, which the committee previously deemed implausible in TA630 (CQ B8). The company argued that paediatric STS tumours, particularly IFS, are associated with a favourable prognosis, and that some tumours may remain controlled indefinitely. However, the model does not predict prolonged disease control; it predicts disease progression followed by long-term survival, which the EAG's clinical advisers considered implausible. The EAG's clinical advisers suggested that larotrectinib may downsize tumours sufficiently to allow curative treatments such as surgery, meaning patients may be cured despite at one point experiencing progression. However, the EAG requested further evidence on the use of subsequent non-palliative treatments in ePAS9 and SAS3 (CQ A10 and B9), which showed that in ePAS9, only ████ (██████) paediatric patients received subsequent surgery, and ████ received radiotherapy, ████ received other systemic therapies (including NTRK inhibitors) after larotrectinib. Following progression in SAS3, ████ of patients received other systemic therapies, whilst ████ underwent radiotherapy, and ████ had surgery. Some of these patients may have received combinations of these options and are thus counted twice – a total of 22 adult and paediatric patients combined (36.7%) received a subsequent therapy. This suggests that enabling the use of other curative therapies after progression is unlikely to be a key driver of extended PPS in the STS/IFS population but may be more important in patients with primary CNS tumours. This supports the need for separate analyses on the primary CNS tumour population. As noted above, subsequent therapies were used much less frequently in the SACT cohort (13% - with ████ accessing these options through clinical trials), suggesting that any benefit generated by subsequent treatment options in the trials and model are unlikely to be observed in NHS practice.

It is likely that the PPS predicted by the model is largely an artefact of extrapolating immature OS data with better developed PFS data, compounded by inappropriate pooling of the primary CNS patients with other tumour types with a more favourable prognosis. The rate of progression amongst primary CNS patients in SAS3 is much higher than that observed for other paediatric tumour types in ePAS9, inflating early PFS hazards and distorting survival model fits for the overall cohort. As in the adult population, the EAG considers the prognostic and treatment response heterogeneity between the

primary CNS population and other tumour types too great to meaningfully pool these populations. Indeed, the assumption of equivalent progression and mortality risk across tumour types produces misleading long-term predictions in the population as a whole. The EAG therefore would prefer that the paediatric primary CNS tumour cohort is modelled separately to those with STS/IFS.

In order to mitigate the impact of the highly uncertain EPI VITRAKVI HRs, and to avoid the impact of explicitly modelling clearly implausible PPS outcomes on cost-effectiveness estimates, the EAG considers analyses based on fully pooled adult/paediatric survival data potentially informative, particularly as a comparison against the EAG's SACT-based analyses presented in Section 5.2. This allows the use of the more robust VICTORIA MAIC, which predicts a less extreme post-progression treatment effect with less uncertainty around the point estimate.

#### *4.2.5.2 Time-to-treatment discontinuation*

The company assumed time-to-treatment discontinuation (TTD) was equivalent to PFS, in alignment with advice received by the company that clinicians were likely to provide treatment only until the point of progression. The company also argue that small patient numbers and heavy censoring in the tail, with no equivalent data on SoC, means it is appropriate to assume that TTD is equal to PFS for larotrectinib. The company present observed TTD data in their submission (Figure 29, Page 156), but do not present any analyses which model TTD using the observed TTD data.

#### ***Points for critique***

The EAG notes that there are no prescribed stopping rules for larotrectinib in the marketing authorisation. The EAG's clinical advisers suggested that as a last-line systemic option with tolerable toxicity, it is likely that they would treat for as long as patients are receiving some benefit of treatment – even beyond the point of radiological progression.

The EAG consider it likely that the model underrepresents treatment costs on larotrectinib and note that any benefits arising from the post-progression use of larotrectinib in the ePAS9 and SAS3 datasets are not reflected in the modelled treatment costs. The EAG was unable to implement scenario analyses based on a separately modelled TTD curve in the time available but considers such a scenario informative for decision making. The EAG notes that the assumption that PFS is equivalent to time on treatment is explicitly made in the SACT scenario analyses presented in Section 5.2, although this scenario assumes ongoing benefit of continued treatment. Total treatment costs in this scenario may therefore be more representative of NHS practice.

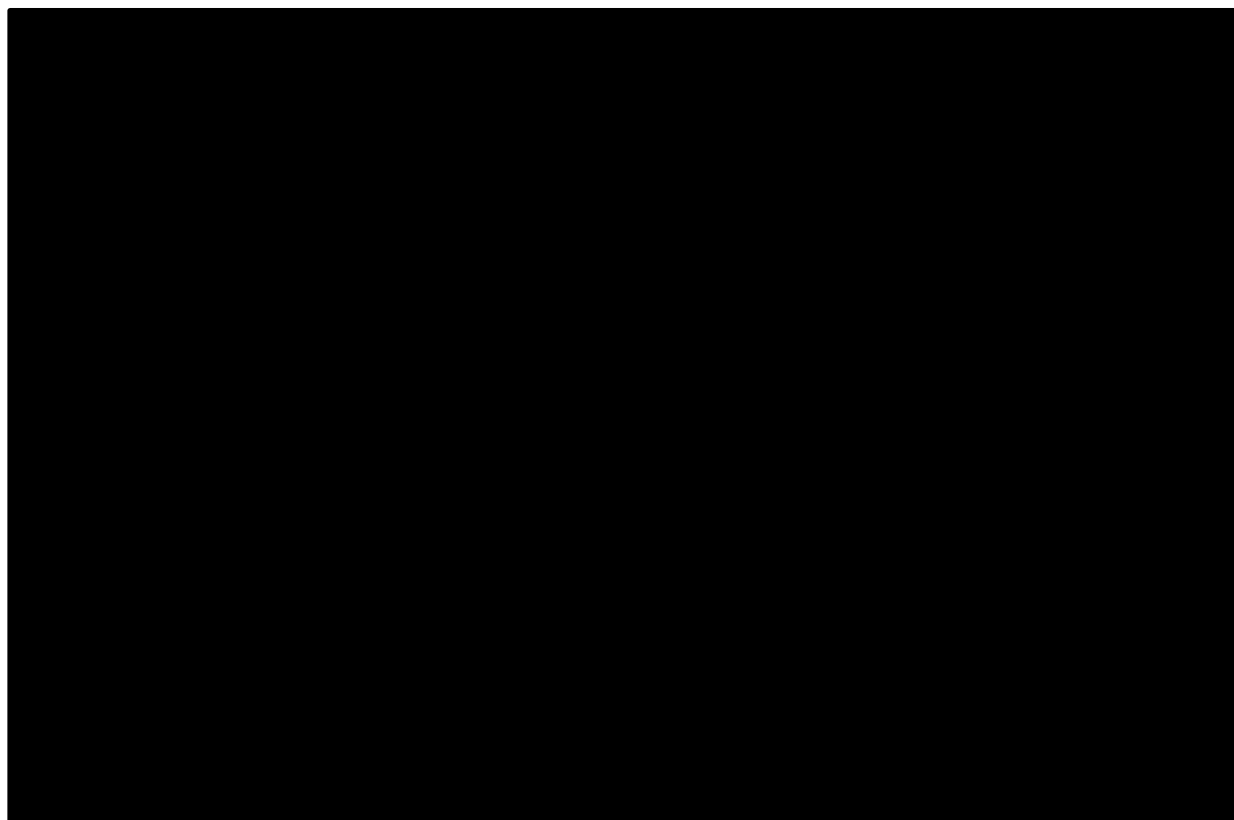
#### *4.2.5.3 Mixed adult and paediatric population*

In the economic model, the company provide the results of survival analysis conducted on the full pooled population of adults and paediatrics. The model fitting process is described in CS Appendix



M. The company again selected the Weibull distribution for OS and PFS, which was ranked 5<sup>th</sup> in terms of AIC and BIC for both outcomes. The baseline age of the mixed cohort is [REDACTED] years. The company then uses the VICTORIA MAIC HRs for PFS and OS to generate SoC outcomes. The selected curve fits can be seen in Figure 6Figure 6.

**Figure 6 MAIC approach: Modelled mixed adult and paediatric population OS and PFS curves (Weibull) (adapted from company's economic model)**



#### 4.2.5.4 Response-based model

The company present an alternative scenario which adopts the response-based model structure proposed by the ERG in TA630 (and described in detail in Murphy *et al.*).<sup>65</sup> In the company's original submission, survival models are fitted separately to OS and PFS data for patients achieving a complete or partial response in the ePAS9 and SAS3 datasets, and those with stable or progressive disease. Outcomes on larotrectinib are then modelled according to a mix of the responder and non-responder OS and PFS curves, weighted according to a single ORR derived from the various BHM approaches described in Section 3.2.4. Outcomes on SoC are assumed to be equivalent to patients who did not experience a treatment response in the larotrectinib trials.

Details of the company's separate survival curve fits to OS and PFS data for adult and paediatric responders and non-responders are presented in CS Appendix M. The EAG considers the company's approach to curve selection largely appropriate but notes issues with long-term survival in paediatric patients with progressed disease as previously discussed in the critique of the MAIC approach.

This approach allows the effect of heterogeneity of response between different tumour types to be explicitly captured in the model and improves the internal comparability of the intervention and comparator arm, particularly in terms of NTRK fusion status and study entry criteria. The company argues that the response-based model structure ignores the differential benefits of larotrectinib in achieving disease stability, which the company's clinical experts argue holds strong clinical value, particularly in patients with a primary CNS tumour. In the response-based model, the outcomes of patients achieving stable disease as their best response are also attributed to SoC. In this way, the company argues that the value of larotrectinib is systematically underestimated, and thus the response-based analysis should be disregarded.

In response to a request for further justification of the rejection of the response-based model (CQ B5), the company also argued that the 'instability' in BHM ORR when using different inclusion rules around tumour type rarity undermined its reliability. They also argue that the existence of observational evidence directly collected in patients with NTRK fusions on means there is no longer a need to construct a SoC arm from within the larotrectinib trial population.

The EAG also requested an updated response-based model which uses the ORR predicted for each tumour site to separately model outcomes on larotrectinib (CQ B7), to more easily allow the distribution of tumour types to be adjusted to that of the NHS population, and more appropriately weight QALY gains for tumour type severity using the company's preferred method of calculating individual weights by tumour type. Furthermore, the EAG requested a scenario in which BHM response rates were calculated separately for paediatric patients and adults (CQ A13 and B6). The company declined to provide either of the requested analyses. The EAG present the results of a tumour site specific response-based model (as implemented by the EAG) in Section 5.2.2, which likewise does not separately account for differences between adult and paediatric treatment response, but uses group-specific survival outcomes.

### ***Points for critique***

The EAG acknowledges the expert advice received by the company, suggesting that stable disease is a clinically valuable outcome, and that attributing this outcome to SoC could overestimate its effectiveness in some contexts. The EAG notes that it was the company's choice to classify stable disease as non-response in the BHM, and it would have been possible to produce sensitivity analysis in which non-response outcomes were represented only by those who continued to progress. However, whilst this argument may be valid in the context of a last-line comparison against likely ineffective or inactive treatment options (as in TA630), the present appraisal largely compares larotrectinib to second-line systemic therapies, which it can be assumed will be more efficacious than the hypothetical SoC considered in TA630. It may therefore be considered conservative to assume non-response in all patients on SoC.

The EAG also considers that the inclusion of stable disease benefits in the SoC arm may be counterbalanced somewhat by the method of construction of the response-based comparator arm. That is, it is plausible that patients predisposed to achieve better outcomes on larotrectinib would also have had better outcomes on SoC, thus by systematically excluding these patients from the comparator arm, which allocates only those patients with the worst outcomes to SoC, thereby underestimating SoC outcomes. Stable disease as a best response appeared to be far more common in patients with primary CNS tumours, with ■■■ of patients in SAS3 achieving this outcome, compared to only ■■■ in ePAS9. This means that potential bias against larotrectinib would be largely confined to this tumour type. However, the efficacy of SoC in achieving stable disease is unclear given the potential efficacy of the systemic therapies included as comparators, and it may be appropriate to include some benefit of treatment for this arm. This issue also supports the EAG's wider position that primary CNS patients should be modelled separately to other tumour types. The EAG acknowledges that the stable disease issue as a limitation of the responder-non-responder framing of treatment effect. However, it does not consider this to invalidate the potential benefits of the response-based model, particularly in its capacity to explore the impact of particular structural assumptions, especially tumour type distribution and the application of QALY multipliers.

The EAG does not consider the company's claim of 'instability' in BHM-derived ORRs, arising when rarer tumour types are included, to provide evidence that the method itself is unreliable. Rather, the observed variation is consistent with genuine differences in efficacy between tumour types, with some more common tumour types exhibiting higher response probabilities than others. The observed changes in ORR therefore may be considered to reinforce the conclusion that larotrectinib does not exhibit a truly tumour-agnostic treatment effect.

The EAG considers this modelling framework to remain informative for decision making for a number of reasons. Firstly, both the ERG and committee in TA630 previously concluded that an assumption of equal response rates across all histologies was inappropriate. The more extensive data collected since TA630 reinforces the position that larotrectinib is unlikely to be equally effective in all tumour types harbouring NTRK fusions. Secondly, real-world evidence collected in SACT highlights substantial generalisability concerns regarding the relevance of the case mix in the larotrectinib trial. These issues indicate the need for a modelling structure capable of explicitly capturing tumour-specific response rates in order to reflect an NHS-appropriate population distribution with respect to tumour type in predicted treatment outcomes. Thirdly, for the reasons described in Section 5.3.1, the accurate attribution of QALY gains to specific tumour types is necessary for the appropriate application of QALY weighting under the company's preferred approach to applying a severity modifier. Tumour types with high severity but low response rates should not be assumed to accrue QALYs equivalent to tumour types with a higher probability of response, nor should these

inappropriately attributed QALYs be subject to a severity-based up-weighting. A model applying a uniform ORR across all tumour types cannot meet this requirement.

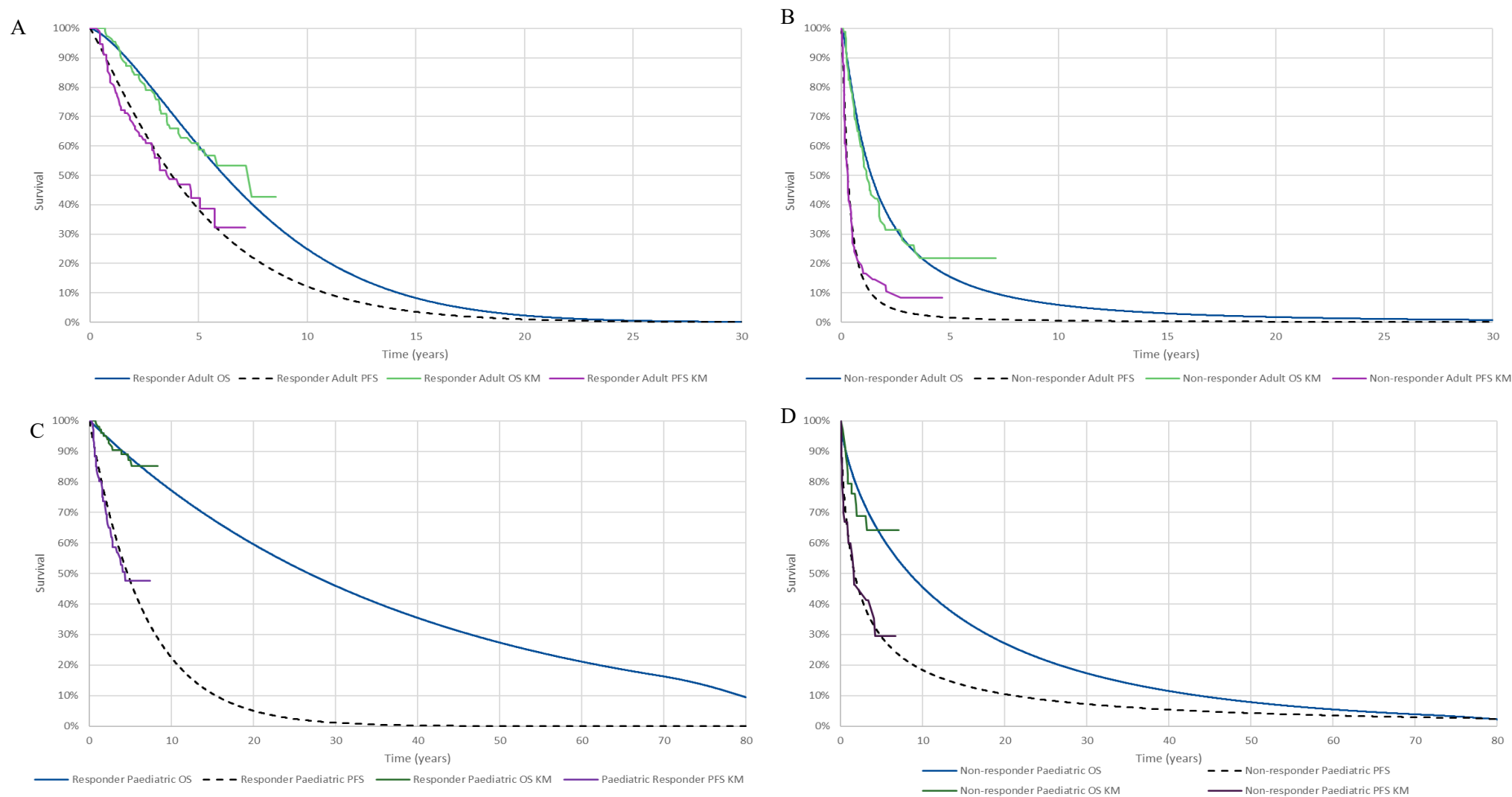
In the absence of the analyses requested from the company, the EAG implements an approximation of the tumour-site-specific response-based model in Section 5.2, using the site-specific predicted response rates generated by the company's BHM (Table 29) Plots of OS and PFS for adult and paediatric responders and non-responders are presented in Figure 7. As can be seen in these figures, this approach still generates substantial post-progression survival benefit in paediatric patients, with cure-like outcomes experienced by a significant proportion of responders despite disease progression.

**Table 29 Tumour-specific BHM predicted response rates applied in EAG scenario (company data on file)**

| Tumour site           | Predicted response rate | Credible interval |     | Notes                                                  |
|-----------------------|-------------------------|-------------------|-----|--------------------------------------------------------|
|                       |                         | 5%                | 95% |                                                        |
| NSCLC                 |                         |                   |     |                                                        |
| Salivary              |                         |                   |     |                                                        |
| Melanoma              |                         |                   |     |                                                        |
| Colorectal            |                         |                   |     |                                                        |
| STS adults (GIST)     |                         |                   |     | Adult STS assumed comprise whole population            |
| STS adults (non-GIST) |                         |                   |     |                                                        |
| STS paediatrics       |                         |                   |     |                                                        |
| IFS                   |                         |                   |     | IFS assumed to account for all non-primary CNS tumours |
| Appendix              |                         |                   |     |                                                        |
| Breast                |                         |                   |     | Assumed to all be secretory                            |
| Bone sarcoma          |                         |                   |     |                                                        |
| Cholangiocarcinoma    |                         |                   |     |                                                        |
| CNS/Glioma            |                         |                   |     | All patients - adults and children                     |
| Pancreas              |                         |                   |     |                                                        |
| Thyroid               |                         |                   |     |                                                        |

Abbreviations: BHM: Bayesian hierarchical model. NSCLC: non-small-cell lung cancer. STS: soft-tissue sarcoma. GIST: gastrointestinal stromal tumour. IFS: infantile fibrosarcoma. CNS: central nervous system.

**Figure 7 Plots of modelled and observed adult responder OS and PFS [A]; adult non-responder OS and PFS [B] paediatric responder OS and PFS [C]; paediatric non-responder OS and PFS [D] (adapted from company's economic model)**



#### *4.2.5.5 Intra-patient comparison (GMI) modelling approach*

As in the submission for TA630, the company also presented a model using a growth modulation index (GMI) analysis to approximate SoC outcomes, in which patients act as their own control by using outcome data from their previous line of therapy. This allows PFS on SoC to be modelled from the larotrectinib trial population for whom time to progression data were available. OS on SoC is modelled using the relative difference in hazards between the OS and PFS outcomes for the larotrectinib arm, i.e. it assumes the same relationship exists between progression and mortality as in larotrectinib patients. The larotrectinib arm is modelled as in the company's base-case analysis.

#### ***Points for critique***

The EAG considers the GMI analysis to be unreliable for a number of reasons. As described by the company, the assumption of an equivalent relationship between the timing of progression and mortality relative to larotrectinib is likely to be conservative. Basing SoC outcomes on a patient's previous unsuccessful line of therapy could also potentially underrepresent the effectiveness of the SoC at the present treatment line. This approach as implemented by the company also assumes no heterogeneity in treatment effect. The EAG does not consider this approach informative for use in decision making and it is therefore not discussed further.

#### *4.2.5.6 Naïve literature-based comparator modelling approach*

As in TA630, the company attempt to construct the SoC arm on the basis of OS and PFS identified in the literature for the selected comparator in each tumour location included in the larotrectinib trials. NICE TAs are identified for each This approach represents an unanchored and unadjusted naïve comparison. Costs and QALYs on SoC are accrued in model engines specific to each tumour location and are subsequently weighted according to the distribution of tumour types recruited to the larotrectinib trials.

The company consider this approach to bias against larotrectinib, in particular due to the patients in the selected NICE TAs and trials not comprising entirely those with NTRK fusions. The company presents scenarios which adjust OS for the purported negative prognostic effect of NTRK fusions, per the VOYAGER1/2 studies (Section 2.1.3).

Importantly, SoC QALYs generated using this approach are used in the company's original base-case analysis to estimate QALY shortfall by tumour type. These analyses therefore influence the QALY gain multipliers applied in the company's base case.

#### ***Points for critique***

The EAG again notes that the studies cited by the company (VOYAGER 1 and VOYAGER 2) to support the existence of a prognostic effect of NTRK fusions on mortality risk found no association

between presence of an NTRK fusion and risk of death (VOYAGER 1: HR 1.44 [95% CI 0.61 – 3.37]; VOYAGER 2: 1.47 [95% CI 0.39 – 5.57]). Although, the EAG acknowledges the Lassen *et al.* study cited in the company's clarification response, which found a statistically significant relationship between NTRK gene fusions and mortality (1.51 [95% CI 1.01 to 2.29]).

#### *4.2.5.7 Mixture cure modelling approach*

The company explore a scenario which fits mixture cure models to investigate the assumption that treatment with larotrectinib could be potentially curative in paediatric patients (excluding those with primary CNS tumours). Whilst the Committee in TA630 considered cure modelling to be potentially informative for decision making at the time of the original appraisal, there is now little evidence that larotrectinib could offer potential cure-like benefits in adult patients, and mixture cure modelling would be unlikely to be successful in adults. This modelling approach applies the methods used in the company's base case for adult patients on larotrectinib and SoC. Outcomes for paediatric patients on SoC are modelled per the company's base case.

#### ***Points for critique***

CS Appendix M describes the company's approach to the fitting of mixture cure models. The cure fractions estimated using each approach for PFS and OS were redacted by the company for unclear reasons. Due to the high level of immaturity of OS data in the paediatric STS/IFS population, all mixture cure models estimated a cure fraction of approximately [REDACTED] (precise figures are redacted). The cure fraction from the models fitted to PFS, however, ranged from [REDACTED] to [REDACTED], meaning that all of the company's mixture cure models assumed a substantial proportion (in some cases almost all) patients were cured despite having experienced disease progression. As larotrectinib is modelled as the last line of therapy, the only plausible clinical explanation for a disparity between PFS and OS cure fractions of this magnitude, i.e. larotrectinib could allow patients to be downstaged to receive curative resection despite progression, seems unlikely.

As discussed previously, the EAG asked the company to comment on the use of potentially curative options in these patients in the larotrectinib trials, and whether this was representative of NHS practice. This showed that the use of potentially curative options such as surgery [REDACTED] or radiotherapy [REDACTED] were used in only a very small number of paediatric patients in ePAS9, which is unlikely to be an important driver of curative outcomes in this population. Whilst a higher proportion of patients received subsequent therapy in the SAS3 population, it remains unlikely that this would occur to the extent modelled in NHS clinical practice. The EAG therefore does not consider this scenario further.

## 4.2.6 Health related quality of life

### 4.2.6.1 Systematic review of HRQoL studies

Appendix F of the CS included the search strategies to identify HRQoL studies relating to NTRK fusion positive tumours. The original searches were run on 6th August 2020 and were updated for the current review on 7th May 2025, with additional sources searched in June 2025.

The systematic literature search identified 16 unique HRQoL publications across both the original and updated searches. These comprised six HTA reports, five empirical HRQoL studies, and five utility or cost-effectiveness modelling studies.

The SLR methods were clearly described and generally appropriate. However, the relevance of the identified evidence to the company's cost-effectiveness model was limited. None of the empirical HRQoL studies reported EQ-5D-based utility values suitable for direct use in the model; instead, they provided non-preference-based outcomes such as EORTC QLQ-C30, PedsQL and EQ-5D-5L domain scores. However, the SLR did identify several published economic modelling studies that reported utility values, which allow comparison with the utilities applied in the company's base case, presented in Table 30 below.

### *Points for critique*

The EAG appraisal of the HRQoL searches identified several issues. As with the searches for the clinical effectiveness SLR, some mistakes within the search syntax were apparent in the 2025 update strategies. Although some of these mistakes highlighted by the EAG were tested by the company and found not to affect retrieval, the company did not test and correct all mistakes. The EAG also noted that the 2025 database updates were limited to records in the English language, and that different search strategies were used for the original and update searches.

In addition to Appendix F, further targeting literature searching for tumour location specific utilities and mapping were mentioned in Sections 3.4.1 and 3.4.3 of the CS. The search strategies were not provided; however, the company clarified these searches were pragmatic desk research rather than formal searches (see company response to CQ C12 and C13). These issues may have affected optimal retrieval of all relevant studies for the SLR.

The utility values applied in the company base case (■■■■ PFS; ■■■■ PD) were compared with the utility evidence identified in the SLR (CS Appendix F, Table 11), collected from patients treated with NTRK inhibitors (larotrectinib, entrectinib, repotrectinib). Published utilities for PFS health states ranged between 0.43-0.83 for patients on treatment, while PD utilities range between 0.30–0.73 across relevant tumour types.



In particular, the company's PD utility estimate of [REDACTED] appears higher than most other published evidence on NTRK inhibitors, and the utility decrement between PF and PD is considerably smaller than those reported in the literature ([REDACTED] vs typical decrements of 0.15–0.35). The EAG notes in Sections 4.2.4 and 4.2.5 that a reasonably large proportion of patients in the larotrectinib trials went on to receive further lines of systemic therapy, amongst other non-palliative treatment options which do not see such frequent use in NHS practice. This may mean that PD utilities collected in the larotrectinib studies may be more representative of PFS2 HRQoL, or otherwise slowed progression, which would not be representative of NHS practice. This suggests that the company's assumptions may underestimate the reduction in quality of life associated with disease progression. As discussed below, the EAG considers a PD utility more aligned with those identified in the company's SLR, and those applied to SoC, to be more appropriate.

#### *4.2.6.2 Health State Utilities*

Health state utilities were based on the a priori assumption that HRQoL in the larotrectinib arm is always higher than that on SoC, regardless of whether patients are on- or off- treatment. HRQoL is also assumed to be subject to a site-agnostic homogeneous treatment effect, i.e. utility for a larotrectinib-treated patient is independent of the site of their tumour. Utility data for larotrectinib were derived directly from HRQoL data collected in the clinical trials, whereas comparator utilities were sourced from previous NICE TAs and targeted literature searches to provide tumour-specific utility estimates. The company adjusts utilities for age using the general-population EQ-5D-3L norms from the Health Survey for England 2014, following the multiplicative approach recommended in NICE DSU TSD 12<sup>78</sup>.

##### **4.2.6.2.1 Larotrectinib**

Utility values for larotrectinib were based on HRQoL data collected from patients in Study 20289 (patients aged  $\geq 12$  years) and Study 20290 (patients aged 1 month to 21 years). Study 20288 was excluded as HRQoL data were not collected.

In Study 20289, HRQoL was measured using the EQ-5D-5L instrument on Day 1 of every other 28-day cycle during the first year, and every 12 weeks thereafter. In Study 20290, paediatric HRQoL was assessed using the Paediatric Quality of Life Inventory (PedsQL), specifically the Infant Scales (PedsQL IS) for patients aged 1–24 months and the Generic Core Scales (PedsQL GCS) for children older than 2 years. Assessments were performed on Day 1 of each 28-day cycle until treatment discontinuation. The analysis presented reflects the ePAS9 and SAS3 datasets, including a total of [REDACTED] patients, [REDACTED] of whom were paediatric patients and [REDACTED] were adults.

The company reported that all HRQoL data were mapped to EQ-5D-3L utilities using validated approaches consistent with the NICE reference case. EQ-5D-5L data from Study 20289 were mapped

to EQ-5D-3L using the NICE Decision Support Unit (DSU) mapping framework developed by Hernández Alava et al. (2022)<sup>64</sup>. For paediatric data, the company applied the mapping algorithm published by Khan et al. (2014)<sup>79</sup>, which was developed in a UK sample of children aged 11–15 years. No mapping algorithm was available for PedsQL IS; therefore, patients younger than two years were excluded from the derivation of utilities. Detailed information on the timing of data collection (including relative to progression), and mapped EQ-5D-3L scores by cycle in CS Appendix J. These data showed that both paediatric and adult populations contributed utility data for an extended period post-progression.

The company analysed all HRQoL data using a mixed-model repeated-measures (MMRM) approach to generate a single utility for each health state, which it considered preferable to ordinary least-squares regression based on model fit. The company commented that utilities were generally [REDACTED] in paediatric patients (i.e. Study 20290) relative to the adult utilities from Study 20289. Mean pre-progression utility in Study 20289 was [REDACTED] and mean post-progression utility was [REDACTED]. In Study 20290, mean pre-progression utility was [REDACTED], whereas post-progression utility was [REDACTED]. It should be noted that these utilities do not map strictly onto the adult and paediatric tumour site groupings in the company's base-case analysis, as Study 20290 included a substantial proportion of paediatric patients with primary CNS tumours, who were instead grouped with adult patients in the model. Equivalent utilities for all adult and paediatric patients from the MMRM analysis were not made available, but these data would be informative for future subgroup-based models.

The company generated a single utility for each health state based on the combined adult and paediatric HRQoL data. The resulting utilities are presented in Table 30 below.

In addition to the base case, the company included one scenario testing the impact of removing any PD HRQoL advantage for larotrectinib. CS Scenario 7 assigns both larotrectinib and the comparator a common progressed-disease utility of 0.53, the weighted average of literature derived PD utilities across tumour sites. This scenario assumes that post-progression quality of life does not differ between treatments. The company also explored a scenario in which HRQoL assessments collected in the first cycle after treatment initiation were excluded (Appendix J). The resulting utilities were similar to the base case MMRM estimates and the company therefore not carried through to the main analysis.

#### **4.2.6.2.2 Comparator**

The tumour-site specific utilities for the comparator were identified by the company using previous NICE TAs. Where a relevant NICE TA was unavailable, the company sourced values from published literature or assigned proxy estimates. The company stated that EQ-5D-3L analyses were prioritised where available but did not list the derivation method for each health state utility.

Based on the company's submission and its response to CQ B14, the majority of tumour sites use SoC utilities that broadly align with the NICE reference case. For common adult solid tumours including NSCLC, melanoma, colorectal, GIST, breast, pancreatic, and thyroid cancer, utilities EQ-5D based or mapped appropriately, and are generally acceptable.

The remaining tumour sites rely on non-reference case or otherwise outdated sources. Salivary gland cancer uses proxy utilities from a head-and-neck economic evaluation, derived from standard gamble (SG) and time trade-off (TTO) exercises completed by clinicians or the unaffected general public rather than patients. Adult non-GIST STS relies on SG-based utilities originally elicited in NSCLC patients. CNS/glioma utilities come from TA23, which reported only QLQ-C30 scores; the company did not explain how these were converted into utilities, and no updated sources were identified. The paediatric STS utility includes no paediatric HRQoL data, and adult STS utilities were applied to these patients without justification or adjustment. For cholangiocarcinoma, no utility data were identified, so the company applied a weighted average of other tumour sites as a proxy. A detailed summary of utility inputs, including data sources and measurement methods, is provided in Table 30.

**Table 30 Tumour site- and treatment-specific health state utilities identified in the SLR compared to those applied in the model REF TO ADD**

| Tumour location                        | Progression-free utility (95% CI) | Progressed disease utility (95% CI) | Source reported by company                                                | Description of source                                                                                                                                      | Measurement method                                                                                                                                                                                                          |
|----------------------------------------|-----------------------------------|-------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Utilities identified in the SLR</b> |                                   |                                     |                                                                           |                                                                                                                                                            |                                                                                                                                                                                                                             |
| NSCLC                                  | 0.653 (0.61-0.70)                 | 0.473 (0.41-0.51)                   | Roth 2020 <sup>80</sup> ; Suh 2024 <sup>81</sup> ; Suh 2025 <sup>82</sup> | Roth 2020: metastatic TRK-positive NSCLC, second line ; other Suh studies provide tumour-specific utilities for NSCLC patients eligible for larotrectinib. | Standard gamble (UK general public)                                                                                                                                                                                         |
| Thyroid / DTC                          | 0.80 (0.77-0.84)                  | 0.50 (0.45-0.56)                    | Suh 2024 <sup>81</sup> ; Suh 2025 <sup>82</sup>                           | Utilities derived using TRK fusion–positive thyroid patients receiving larotrectinib                                                                       | Time Trade-Off (UK general public)                                                                                                                                                                                          |
| Colorectal                             | 0.82 (0.78-0.86)                  | 0.64 (0.55-0.75)                    | Suh 2022 <sup>83</sup> ; Suh 2025 <sup>82</sup>                           | Utilities derived using TRK fusion–positive colorectal patients receiving larotrectinib                                                                    | EQ-5D (patient-reported)                                                                                                                                                                                                    |
| STS adults                             | 0.43 (0.39-0.47)                  | 0.3 (0.26-0.34)                     | Suh 2022 <sup>83</sup> ; Suh 2025 <sup>82</sup>                           | Utilities from metastatic NTRK-positive STS patients receiving larotrectinib                                                                               | Time Trade-Off (UK general public)                                                                                                                                                                                          |
| Larotrectinib tumour agnostic          | 0.67                              | 0.47                                | Suh 2025 <sup>82</sup>                                                    | Prevalence-weighted average across NSCLC, CRC, thyroid and STS                                                                                             | Mixed sources (EQ-5D, TTO, SG; prevalence-weighted)                                                                                                                                                                         |
| <b>Utilities applied in the model</b>  |                                   |                                     |                                                                           |                                                                                                                                                            |                                                                                                                                                                                                                             |
| Larotrectinib tumour agnostic          | ████ (0.75 – 0.80)                | ████ (0.73 – 0.75)                  | ePAS9 and SAS3                                                            | Data were collected in Study 20289 (patients aged ≥12 years) and Study 20290 (patients aged 1 month to 21 years)                                           | Mean EQ-5D-5L utilities pooled across all tumour sites                                                                                                                                                                      |
| <b>SoC tumour location specific</b>    |                                   |                                     |                                                                           |                                                                                                                                                            |                                                                                                                                                                                                                             |
| SoC pooled                             | 0.633                             | 0.529                               | Mixed                                                                     | Weighted average of all literature health states                                                                                                           | Mixed sources                                                                                                                                                                                                               |
| NSCLC                                  | 0.74                              | 0.46                                | NICE TA347 <sup>66</sup>                                                  | Chouaid 2013 <sup>84</sup>                                                                                                                                 | EQ-5D data from NSCLC patients.                                                                                                                                                                                             |
| Salivary                               | 0.75                              | 0.60                                | Liberato 2012 <sup>85</sup>                                               | No relevant NICE TA; model used head-and-neck cancer proxy. Representativeness uncertain.                                                                  | PFS utility derived from standard gamble responses on advanced breast cancer by oncology nurses, adjusted using expert opinion. PD utility derived from TTO responses on advanced head and neck cancer by resident doctors. |

|                        |      |      |                                                        |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                  |
|------------------------|------|------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Melanoma               | 0.75 | 0.69 | NICE TA357 <sup>68</sup>                               | KEYNOTE-002 trial                                                                                                                                                                                     | EQ-5D utility values from melanoma patients.                                                                                                                                                                                                                                                     |
| Colorectal             | 0.73 | 0.59 | NICE TA405 / Grothey 2013 <sup>86</sup>                | ERG-recommended EQ-5D from CORRECT trial.                                                                                                                                                             | EQ-5D data from metastatic colorectal cancer patients                                                                                                                                                                                                                                            |
| STS (adult GIST)       | 0.77 | 0.65 | NICE TA488 Demetri 2013 (GRID trial) <sup>69</sup>     | GIST-specific; correct for GIST subgroup.                                                                                                                                                             | EQ-5D assessment in patients with metastatic and/or unresectable GIST                                                                                                                                                                                                                            |
| STS (adult non-GIST)   | 0.65 | 0.47 | TA185 <sup>70</sup> ; Nafees 2008 <sup>87</sup>        | Incorrectly linked to adult GIST in the CS; corrected in the CQ response B14.                                                                                                                         | In the absence of STS-specific data, TA185 implemented standard gamble utility values from NSCLC patients                                                                                                                                                                                        |
| STS (paediatric + IFS) | 0.68 | 0.43 | Delea 2014 <sup>88</sup> ; Shingler 2012 <sup>89</sup> | Both studies include adult STS patients (Olaratumab and PALETTE trials). No rationale for applying adult EQ-5D utilities to infant populations. IFS was merged into this group without justification. | Combined EQ-5D and mapped QLQ-C30 utility data from adult patients with advanced STS for PFS. For PD, post-progression utilities from this dataset were combined with an estimate of utility in the terminal phase of the disease from a vignette study in the UK general public, employing TTO. |
| Breast                 | 0.71 | 0.50 | NICE TA423 <sup>73</sup>                               | Kaufman 2015 <sup>90</sup> ; Lloyd 2006 <sup>91</sup>                                                                                                                                                 | PFS utility derived from QLQ-C30 data in patients with locally advanced or metastatic breast cancer, mapped to EQ-5D values. PD utility values obtained from the UK general public using the standard gamble method and descriptions of metastatic breast cancer.                                |
| Cholangiocarcinoma     | 0.63 | 0.53 | No source                                              | No relevant NICE TA; HRQoL estimated as weighted mean across other cancers. Proxy assumption increases uncertainty.                                                                                   | Weighted average of other tumour sites                                                                                                                                                                                                                                                           |
| CNS / Glioma           | 0.60 | 0.60 | NICE TA23 <sup>92</sup>                                | Osoba 2000 <sup>93</sup> ; Osoba 2000 <sup>b 94</sup>                                                                                                                                                 | EORTC QLQ-C30 utility data from patients with malignant gliomas. no                                                                                                                                                                                                                              |

|                    |      |      |                                                    |                                                                           |                                                                                                                                                                                                                                |
|--------------------|------|------|----------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    |      |      |                                                    |                                                                           | information on how these were converted into utility values.                                                                                                                                                                   |
| Pancreas           | 0.67 | 0.60 | NICE TA440 <sup>95</sup>                           | Romanus 2012 <sup>96</sup> ; Al-Batran 2016 <sup>97</sup>                 | PFS utility derived from EQ-5D data in patients with advanced pancreas cancer. For PD utility, EQ-5D index scores were elicited using the TTO method derived from patients with locally advanced or metastatic gastric cancer. |
| Thyroid (RAIR DTC) | 0.72 | 0.64 | TA535 <sup>98</sup> ; DECISION trial <sup>99</sup> | Bayer RAIR DTC NICE model Internal model reference; transparency limited. | EQ-5D data from patients with locally advanced or metastatic thyroid cancer                                                                                                                                                    |

Source: Based on CS Table 49, 50 and 51, CQ Table 30 and 31.

Abbreviations: NSCLC: non-small-cell lung cancer. DTC: differentiated thyroid cancer. CRC: colorectal cancer. STS: soft-tissue sarcoma. GIST: gastrointestinal stromal tumour. IFS: infantile fibrosarcoma. CNS: central nervous system. SoC: standard of care. HRQoL: health-related quality of life. EQ-5D: EuroQol 5-Dimension. EQ-5D-5L: EuroQol 5-Dimension 5-Level. EQ-5D-3L: EuroQol 5-Dimension 3-Level. TTO: time trade-off. SG: standard gamble. PFS: progression-free survival. PD: progressed disease. QLQ-C30: EORTC Quality of Life Questionnaire-C30. ERG: Evidence Review Group. TA: Technology Appraisal. RAIR: radioiodine-refractory.

## ***Points for critique***

### **Larotrectinib utilities**

The EAG agrees in principle that larotrectinib may generate benefit above and beyond that defined by the health state alone. However, the average magnitude of this treatment benefit within each health state is likely to be too large in the company's analysis. A comparison with the sources of HRQoL data on TRK inhibitors identified in the company's SLR suggests that the larotrectinib trials may either be systematically overestimating HRQoL across all patients, or that the average HRQoL of the population recruited to the trial may not be representative of all tumour sites.

Although the company highlights the large number of post-progression HRQoL assessments in the larotrectinib trials, most measurements were collected within the first six months after progression, and it remains uncertain whether patients with more severe symptoms or rapid decline are fully represented in these data. The company investigated missingness patterns and reported no systematic relationship between completion rates and baseline characteristics. Patients with a higher number of HRQoL assessments tended to have longer post-progression and overall survival, which is expected given their longer observation time. This also implies that patients with shorter survival who may experience greater deterioration in HRQoL contribute fewer measurements, particularly at later time points.

Long-term post-progression utilities are also disproportionately informed by paediatric patients, who report higher HRQoL overall. Overall, these limitations mean it is uncertain whether the pooled utility values meaningfully reflect HRQoL in the NHS population, given differences in tumour types, patient severity and earlier treatment setting of larotrectinib in practice.

As has been discussed previously, the high rate of systemic therapy use in patients who progressed on larotrectinib is likely to have influenced utility, with patients who continue to provide responses after progression more likely to represent those who have achieved disease stability or a response to a new line of therapy. Patients who initiated another systemic therapy (or indeed received other interventions) after progression were not censored from the utility analysis. The data collected in patients with PD are likely to be inflated by individuals who achieved disease stability or response to a subsequent therapy, who are in turn more likely to continue to complete EQ-5D responses. As this use of subsequent therapies is unlikely to be replicated in NHS practice, the EAG considers the PD utility unlikely to represent the HRQoL of patients who have progressed on larotrectinib on the NHS. The EAG therefore explores a scenario in Section 5.2.2 in which the PD health state shares a common utility across treatments in better alignment with the data collected on NTRK inhibitors in the company's SLR.

### **Comparator utilities**

The EAG is concerned that the use of non-reference case PD utilities in five tumour sites may introduce bias in favour of larotrectinib. The use of time trade-off and standard gamble utilities derived from healthy members of the general public is not aligned with the NICE Reference case and is methodologically inappropriate where other modelled health state utilities are based on EQ-5D or other preference-based patient-reported outcomes. Healthy responders to vignette exercises tend to have a strong aversion to illness and undervalue any adaptation effects, leading to exaggerated decrements in HRQoL compared with valuations reported by patients living with the condition. Vignette-based descriptions of health states are often difficult for responders to interpret or distinguish from one another, especially when differences are subtle, resulting in internally inconsistent or poorly discriminating valuations.

Utilities in a single model should represent the same underlying construct of HRQoL and be derived on a consistent, common scale, in order to appropriately value the impact of modifying the disease course in a given population. Mixing TTO or SG values for only one treatment arm with patient-reported EQ-5D data introduces methodological heterogeneity that can bias incremental QALY estimates and distort apparent treatment effects. The EAG considers an approach that uses only reference-case derived HRQoL values more appropriate than that presented by the company.

Furthermore, the EQ-5D values applied for SoC are largely up to, or in excess of, 20 years old. This may mean that they do not adequately capture the HRQoL of current care on the NHS, particularly in tumour sites where more efficacious and less-toxic therapies have become available at earlier treatment lines. This could be seen to be supported by the company's argument that PD utilities after larotrectinib are higher than those post-SoC due to its superior efficacy and lower toxicity burden.

### **Paediatric utilities**

In the company's model, paediatric patients comprise those with STS, IFS, and CNS tumours, but paediatric CNS and STS utility data is not included in either the larotrectinib or SoC arm. In the comparator arm, CNS utilities come from adults, and paediatric STS and IFS utilities are taken from adult STS studies due to the absence of paediatric utility data. The EAG note that more appropriate sources for paediatric CNS utilities may be available. For example, NICE TA977 includes EQ-5D-based HRQoL data for paediatric CNS tumour populations and may provide a better source than the adult-derived values currently applied in the model.

In addition, pooling adult and paediatric utilities prevents appropriate adjustment for age-related changes in HRQoL and obscures potential differences between age groups. Given these limitations, the EAG would prefer to see utilities estimated separately for adults and children in a scenario using age-group-specific utilities to assess the impact on the cost-effectiveness results.



#### 4.2.6.3 *Adverse events utilities*

In the company's model, AE inputs indicate asymmetry in how AEs have been implemented across the larotrectinib and comparator arms. Disutilities were applied to the full cohort within the first model cycle, weighted by event rates from the relevant clinical trials. AEs were assumed to resolve within one week.

In the larotrectinib arm, only two AEs were included: anaemia (■) and neutropenia (■), based on ePAS9 adverse event rates. No other adverse events were included. The company assumed that the same disutility value would apply for a given type of AE across all tumour locations, irrespective of disease context or treatment.

The comparator arm includes between six and eight grade 3/4 AEs depending on the tumour type, including diarrhoea, febrile neutropenia, leukopenia, lymphopenia, thrombocytopenia and vomiting, in addition to anaemia and neutropenia. These events are applied using trial-specific event rates drawn from NICE TA and literatures.

#### ***Points for critique***

The EAG considers that the assumption that all adverse events resolve within one week is likely to underestimate their impact. And the effect of AE utility in the comparator arm is likely already partly captured within the treatment-specific utility values used by the company. If this is the case, applying additional AE-related disutility to the comparator may partly double-count the impact of toxicity, while the one-week duration assumption may understate the corresponding burden for larotrectinib.

#### **4.2.7 Resources and costs**

The company included only direct medical costs in the model, including drug acquisition, administration, follow-up and AE-related costs. Unit costs for resource use were based on the NHS National Cost Collection 2023/2024<sup>100</sup> and Personal Social Services Research Unit (PSSRU) Unit Costs of Health<sup>101</sup> and Social Care 2024 report<sup>102</sup>. Unit costs for medicines were based on the British National Formulary (BNF)<sup>103</sup> and the Drugs and pharmaceutical electronic market information tool (eMIT)<sup>104</sup>.

For healthcare resource use (HCRU) inputs, the company prioritised identifying data from relevant NICE technology appraisals, followed by evidence from the SLR, and finally targeted literature searches when required.

##### *4.2.7.1 Systematic review of resource use and costs*

The combined SLR of cost-effectiveness and HCRU studies identified three studies reporting resource-use or cost data in NTRK fusion-positive solid tumours (mainly NSCLC and thyroid cancer), findings were summarised in CS appendix G. These studies covered lung and thyroid cancer

populations in Brazil and the United States, and were based on heterogeneous data sources, including retrospective claims databases and national reimbursement models. Across all three studies, reported outputs were predominantly aggregate treatment costs rather than resource use units, and none provided UK-relevant estimates. As such, the evidence is not directly suitable in the economic model.

### ***Points for critique***

Although the SLR does not yield NHS-applicable resource use inputs, it offers indirect information relevant to the plausibility of the company's costing assumptions.

Firstly, the Brazilian and US studies suggest that real-world treatment pathways for patients with NTRK-positive NSCLC can be substantially more costly than standard chemotherapy-based pathways. However, these differences primarily reflect non-UK pricing structures and do not translate into resource data suitable for modelling.

Second, Grossman *et al.*<sup>105</sup> reported lower hospitalisation incidence and length of stay among Larotrectinib treated NTRK fusion-positive patients compared with matched SoC cohorts. The direction of effect suggests that HCRU may differ between larotrectinib and standard therapy.

The EAG notes that the company's economic model assumes no differential monitoring, hospitalisation, or other HCRU costs between treatment arms. This simplification may overestimate or underestimate cost offsets, depending on the extent to which real-world patterns differ between larotrectinib and SoC in NHS practice.

#### ***4.2.7.2 Drug acquisition and administration costs***

### ***Larotrectinib***

The treatment cost for larotrectinib includes only direct drug acquisition costs, with no administration costs applied. The company assumed that no cost for oral administration is incurred.

The company stated that larotrectinib is available in three formulations (100 mg capsules, 25 mg capsules, and an oral solution) for adult and paediatric patients. However, the model does not differentiate between the three formulations and instead implies that all patients are in receipt of the 100 mg capsule. The cost per cycle of larotrectinib was calculated based on the expected price and the average daily dose of larotrectinib in the integrated efficacy analysis (CS Table 54). The company applied weighted costs according to the assumed distribution of adult (████%) and paediatric IFS/STS (████%) patients. Wastage was not accounted for on larotrectinib in alignment with the previous appraisal.

### ***Points for critique***

## 1. Oral administration costs

In TA630, both the EAG and the Committee concluded that oral administration costs should be included in the model. In the current submission, the company again excluded these costs, arguing that because larotrectinib is a targeted therapy rather than a traditional oral chemotherapy, the SB11Z tariff does not reflect monitoring requirements associated with larotrectinib.

Whilst larotrectinib differs pharmacologically from standard oral chemotherapy, patients still require regular clinical monitoring within the NHS. Therefore, oral administration or monitoring costs still need be included. The EAG requested that this cost be included in the model (CQ B21). The EAG advised that this tariff is not applicable upon each administration but should be applied in alignment with dispensation.

In clarification response, the company added a model scenario which include oral administration costs. This scenario applies the SB11Z “deliver exclusively oral chemotherapy” tariff (£247 per attendance; National Cost Collection 2023/24) once for each treatment cycle for all orally administered therapies. NHSE provided advice to the EAG on the inclusion of the SB11Z tariff, stating that ‘the same checks and expertise are needed for dispensing of any oral systemic anti-cancer therapy so the same tariff would apply for each dispensing’. The EAG therefore prefers that this cost be included in alignment with the length of each treatment cycle for all included systemic anti-cancer therapies.

The EAG notes that the model indicates that the administration cost is only applied to the capsule formulation of larotrectinib (100 mg) for all patients and does not apply administration costs to the oral solution formulation. As the formulations are not differentiated between, any costs associated with the solution-based formulation, which has a higher cost per day of treatment, are excluded. Because the model does not capture the relative use of capsules versus solution, nor is this data readily available in the documentation available to the EAG, the EAG is unable amend the model accordingly. The company’s approach may underestimate the true administration costs associated with larotrectinib.

## 2. Paediatric CNS/glioma patients

In the model, all costs for CNS/glioma patients are based on a fully adult population. Paediatric patients are more likely to receive the oral solution formulation. This assumption may therefore underestimate treatment costs, as the oral solution has a higher unit cost per mg compared with capsules. Applying paediatric dosing and formulation costs to this subgroup may result in a small increase in the ICER for larotrectinib.

### 3. Costs of post-progression larotrectinib treatment

In TA630, the committee concluded that post-progression treatment costs should be included, preferably aligned with modelled survival benefits. However, the current model assumes that time on treatment is equal to PFS. As was discussed in Section 4.2.5.2, time-to-discontinuation data from the larotrectinib trials indicates that a number of patients continued to receive treatment beyond progression. Clinical advice to the EAG suggested that it is likely that patients will be treated for as long as the clinician considers that they are receiving some benefit – even beyond the point of progression. It is therefore likely that the company's model underestimates the costs of larotrectinib. The EAG notes that the SACT scenario presented in Section 5.2.2 assumes PFS equivalent to TTD, thereby better accounting for total treatment costs (but assuming ongoing PFS benefit).

#### ***Comparator/standard of care***

The company estimated drug acquisition and administration costs for comparators according to the treatment regimens used for each tumour site.

Unit costs were obtained from eMIT and the BNF. Dosing schedules were informed by relevant previous NICE TAs or other published sources (see CS Table 55). Where multiple pack sizes were available for the same drug, the company selected the lowest unit-cost formulation. The base-case analysis assumed no drug wastage.

For comparators with BSA-based dosing, average BSA values were taken from relevant NICE TAs or published sources. Where data were unavailable for specific tumour types (salivary, STS paediatrics, cholangiocarcinoma and pancreas), the company applied the mean BSA from the integrated ePAS9 and SAS3 trial.

Oral therapies were assumed to incur no administration costs, whereas intravenous therapies were assigned a cost of £255.49 per 7-day cycle (simple chemotherapy administration cost, NHS National Cost Collection data). Additional costs were included for cholangiocarcinoma: district nurse visits to remove the infusion pump after each cycle and complex intravenous chemotherapy administration at first attendance. Treatment duration was sourced from the same NICE TAs and published evidence. The company applied weighted averages based on the tumour site distribution observed in the integrated ePAS9 and SAS3 dataset to derive the overall comparator treatment costs.

#### ***Points for critique***

The EAG noted that the SoC drug costs in CS Table 55 did not match the costs implemented in the model (CQ B23). In their response, the company confirmed that the modelled values were correct and the accompanying documentation was updated accordingly (Clarification response Table 32, Page 101).

In addition, the EAG identified several out-of-date comparator drug prices sourced from eMIT in the company's model. The EAG corrects all affected unit prices within the model in accordance with the Price Tracker provided by NICE in Section 5.2.1.

#### *4.2.7.3 Subsequent treatment costs*

The company assumes that subsequent treatment costs do not need to be considered, stating that SACT data showing only 13% of patients received any further therapy (25% of whom accessed these treatments through clinical trials), and that only 7% continued on larotrectinib after progression. The company argue that subsequent therapies are rare in NHS practice and that any associated costs would “cancel out” between the larotrectinib and SoC arms. Consequently, the base-case assumes that all patients discontinue active therapy upon progression, and no post-progression treatment costs are applied.

#### ***Points for critique***

In TA630, the committee concluded that post-progression treatment costs for larotrectinib should be incorporated into the economic model, preferably in alignment with the modelled survival benefits. However, given that the type of treatments used in the trial and the extent to which they were used are unlikely to represent NHS practice, it is uncertain whether the costs (or effectiveness) of these treatments should be reflected in the economic model.

In response to CQ B9, the company provided ePAS9 data on subsequent treatments: ■ of patients received other systemic therapies and ■ received an NTRK-targeted treatment (see Table 14 and Table 15). It is unclear whether these categories are mutually exclusive; the combined proportion appears substantially higher than the 13% reported in SACT. Given this, the EAG considers that post-progression treatment costs should be reflected in the model, inasmuch as they represent NHS practice, particularly because the base case predicts extended PPS, particularly in the paediatric population. As discussed in Section 4.2.5, such long-term PPS is unlikely to be achievable without subsequent intervention. This is consistent with company's own clinical advice<sup>106</sup> which indicated that sustained remission or cure in paediatric patients requires subsequent active treatment, typically surgical resection enabled by larotrectinib-induced tumour shrinkage.

Excluding these associated costs while assuming near-cure outcomes is inconsistent and likely underestimates total costs in the larotrectinib arm. The company's justification that costs would cancel out between arms is implausible, as the larotrectinib group has longer survival and therefore greater opportunity for prolonged use of subsequent treatment options. This assumption conflicts with both clinical expert opinion and the model's implied cure like survival benefits, particularly in the paediatric population (STS and IFS). The EAG recommends exploring scenarios incorporating

reasonable costs for active post-larotrectinib treatment or otherwise adjusting the model to reflect crossover or subsequent treatment confounding.

#### *4.2.7.4 Health state unit costs and resource use*

The company did not identify any larotrectinib HCRU data in their literature searches and therefore assumed that HCRU in the larotrectinib arm is equal to a weighted average of the comparator tumour site health state costs, with weights based on the tumour distribution in the integrated efficacy dataset. This assumption was validated with UK clinicians and is considered by the company to be conservative, on the basis that resource use in terms of monitoring requirements for a targeted oral therapy may plausibly be lower than for SoC.

Health state costs for each tumour type were derived from relevant NICE TAs or published literature. Unit costs were primarily sourced from the National Cost Collection Data Publication (National Schedule 2023/2024 – Summary), NHS Reference Costs 2021/22 and 2017/18, the eMIT, BNF 2025. PSSRU 2024, and previous NICE guidance (see Table 5 in CS Appendix M). Health state costs were based on residence in the PFS and PD states, with a one-off cost for some tumour sites applied at the time of entering the health state, and a recurring per-cycle cost applied while patients remain in that state. A one-off end-of-life (EoL) cost was applied to patients transitioning to the death state.

#### ***Points for critique***

The EAG previously noted that the health state costs by tumour location in CS Table 57 did not match the costs implemented in the model. In response, the company confirmed that the modelled values were correct and updated the supporting documentation accordingly (presented in CQ B24 Table 33).

The EAG noted that for CNS/glioma, the company has included only a single MRI-based start-up cost (£516) in PFS, with £0 per-cycle PFS and PD costs. This approach appears overly simplified and does not align with modern economic modelling practice or the clinical management of CNS tumours, which typically require ongoing imaging and neurological follow-up. Moreover, the underlying source (NICE TA23) is over two decades old and does not provide health-state resource-use estimates consistent with contemporary NICE TAs. The EAG presents a scenario in Section 5.2.2 which applies costs based on TA977 in BRAF V600E mutation-positive glioma in children and young people, in which progression-free patients have a monthly oncologist visit, FBC, and ECG. Patients with progressed disease have a monthly multi-professional visit (£569.00 – Consultant Led (WF02A) - Paediatric Medical Oncology Service: Multi-professional Non-Admitted Face-to-Face Attendance, Follow-up), and a specialist cancer nurse visit (£277 – District Nursing Service (N10CF) - Specialist Nursing, Cancer related, child, face-to-face) related nursing N10CF, child, face-to-face).

#### 4.2.7.5 *Adverse events*

The company applied AE costs as a one-off cost in the first model cycle, weighted by corresponding AE incidence rates. In the base-case analysis, only anaemia and neutropenia (as AEs occurring in  $\geq 5\%$  of patients) were included for both larotrectinib and the comparator. The unit cost for anaemia was calculated as an activity-weighted average of multiple HRG codes from the NHS National Cost Collection Data (2023/24), whereas the unit cost for neutropenia was sourced from the NHS Reference Costs 2021/22.

#### ***Points for critique***

The company applied AE costs as a one-off up-front cost, weighted by incidence rates, and included only anaemia and neutropenia in the base case. This approach oversimplifies AE costing, does not reflect the timing of AE occurrence, and excludes relevant Grade  $\geq 3$  AEs reported in the evidence base for larotrectinib and the SoC comparators. Moreover, applying the same AE unit cost across paediatric and adult populations is unlikely to reflect true clinical practice. However, it is unlikely that this approach will have a significant impact on cost-effectiveness estimates, and may be unfavourable to larotrectinib, which is likely to have a more favourable AE profile than many SoC therapies.

#### 4.2.7.6 *NTRK fusion testing*

The company did not include the cost of NTRK gene fusion testing in the base-case analysis, stating that genomic testing at diagnosis is now routinely embedded in NHS care and funded centrally through the National Genomic Test Directory. NTRK fusions represent only a small subset of genes analysed within broader next-generation sequencing (NGS) panels, and testing was therefore considered part of standard NHS genomic practice rather than a cost specific to larotrectinib.

In the model, the company conducted a scenario analysis in which the full cost of all NTRK fusion testing was attributed to larotrectinib. Unit costs for NGS panels and IHC were based on unadjusted values in TA630, of £75 for IHC, and £350 for an NGS gene fusion panel. In its response to CQ B18 and B19, the company confirmed that testing unit costs were not updated due to the absence of a national NGS fusion panel tariff, noting that costs vary regionally. The model allows live updating of unit costs when a tariff become available.

#### ***Points for critique***

The EAG agrees that genomic testing is increasingly embedded in the NHS Genomic Medicine Service and is centrally funded through the National Genomic Test Directory. The EAG sought advice from NHSE who confirmed that testing can be considered standard practice and thus no additional cost should be applied to reflect testing for NTRK gene fusions in treated patients.

The EAG noted the Committee's preference in TA630 for the inclusion of testing costs, and that this assumption had a potentially substantial impact on the ICER. The EAG therefore considered scenario analysis exploring the inclusion of this cost potentially informative for decision making. The EAG received expert advice from a lead clinical scientist at an NHS Genomic Laboratory Hub, who highlighted the following points:

- NGS testing provision is not uniform across England: prioritisation varies by tumour type, prevalence, region, and local laboratory capacity.
- IHC screening is not widely used; most centres proceed directly to RNA-based NGS, contrary to the company's assumption that IHC + confirmatory NGS is routinely used in low-prevalence tumour types.
- WGS is not used for all paediatric cases as standard of care testing, thus a proportion of paediatric patients will receive NGS testing.
- RNA NGS panel performance varies between laboratories, and not all panels test the same number of fusions, meaning testing cost and accuracy are not as uniform as assumed, but all GLH labs will meet a minimum standard and will probably be a similar cost.

The EAG agrees that testing costs should not be applied uniformly across all tumour types. Instead, costs should reflect the most plausible counterfactual in each setting:

- *Tumour types where NTRK is the only relevant actionable fusion*  
In these cases, testing would not occur in the absence of TRK inhibitors. The full cost of an RNA-based fusion panel should therefore be attributed to larotrectinib (and entrectinib).
- *Tumour types with multiple actionable fusion targets*  
Where the same NGS panel informs eligibility for several targeted therapies (e.g., ALK, ROS1, RET, NTRK), the cost of testing should be shared across those targets. This means dividing the panel cost across all actionable fusions included in the assay.
- *Tumour types where NGS is already performed at an earlier line of therapy*  
If an actionable mutation requires genomic testing prior to the point at which larotrectinib would be used, a patient's NTRK fusion status may reasonably be assumed to be already known. In such cases, testing costs may be excluded.

The EAG asked the company to adopt a more granular, tumour site-specific approach to attributing testing costs. In its response, the company stated that it had implemented a revised "new testing cost scenario" within the updated model to reflect the EAG's feedback (CQ B19). The scenario did not work as intended in the submitted model but was made functional in the EAG-amended version.



The testing strategy the company applied by tumour type in this scenario is reproduced in Table 31. The EAG is satisfied the company's judgement of whether or not NTRK status has already been established at this clinical decision point is broadly appropriate. However, the company assume that IHC is used, followed by confirmatory NGS in 9% of cases (i.e. representing equivocal IHC results). In light of the advice above, the EAG explore the assumption that where IHC is currently listed, all patients receive NGS at first line. The EAG also considers it reasonable to divide the cost of NTRK fusion testing between it and entrectinib, which whilst is only currently available through the CDF, represents another technology which can be used after establishing positive NTRK fusion status.

The EAG undertook adjustments to the company's scenario analysis to better represent the appropriate counterfactual in the absence of larotrectinib, where testing costs considered applicable. Table 31 below presents the EAG's preferred site-specific testing costs, which assume NGS is used as a first line screening tool (rather than confirmatory post-IHC), that testing costs where applicable are split evenly with entrectinib, and that the unit cost of an NGS panel is £400. Note that these costs are weighted according to the selected tumour site distribution in the model.

**Table 31 Testing strategies by tumour type (adapted from company clarification response Table 32, Page 98 and company executable model)**

| <b>Tumour locations</b> | <b>Prevalence of NTRK fusion</b> | <b>Testing strategy</b>                                                        | <b>Total cost per patient (company scenario)</b> | <b>Total cost per patient (EAG)</b> |
|-------------------------|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------|
| NSCLC                   | 0.09%                            | No cost (testing in previous lines)                                            | £0                                               | £0                                  |
| Salivary                | 1.72%                            | No cost (already routinely tested)                                             | £0                                               | £0                                  |
| Melanoma                | 0.21%                            | WGS + 0.09*NGS (full NGS cost)                                                 | £15,000                                          | £17,143                             |
| Colorectal              | 0.12%                            | No cost (NGS testing in previous lines)                                        | £0                                               | £0                                  |
| STS adults (GIST)       | 1.28%                            | IHC + 0.09*NGS (full cost)                                                     | £8,320                                           | £31,250                             |
| STS adults (non-GIST)   | 0.56%                            | IHC + 0.09*NGS (1/3 price of NGS cost; 2 other targets [EWSR1-NR4A3 and EZH2]) | £15,268                                          | £23,810                             |
| STS paediatric          | 0.56%                            | WGS + 0.09*NGS (1/3 price of NGS cost; 2 other targets [EWSR1-NR4A3 and EZH2]) | £1,875                                           | £2,143                              |
| Breast                  | 0.07%                            | No cost (testing in previous lines)                                            | £0                                               | £0                                  |
| Cholangiocarcinoma      | 0.1%                             | IHC + 0.09*NGS (1/2 price of NGS cost; 1 other target [FGR2])                  | £90,750                                          | £200,000                            |
| CNS/Glioma              | 5.3% (paediatric)                | No cost (NGS testing in previous lines)                                        | £0                                               | £0                                  |
| Pancreas                | 0.26%                            | IHC + 0.09*NGS (full cost)                                                     | £40,962                                          | £153,846                            |
| Thyroid                 | 4.94%                            | IHC + 0.09*NGS (full cost)                                                     | £2,156                                           | £8,097                              |

Abbreviations: NTRK: neurotrophic tyrosine receptor kinase. NSCLC: non-small-cell lung cancer. STS: soft-tissue sarcoma. GIST: gastrointestinal stromal tumour. IHC: immunohistochemistry. NGS: next-generation sequencing. WGS: whole-genome sequencing. CNS: central nervous system.

## 5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions, and Section 5.3 explores decision modifiers including the company's and EAG's preferred approach to QALY weighting for severity.

### 5.1 *Company's cost effectiveness results*

#### 5.1.1 **Company's base case**

The cost-effectiveness results presented in the CS are based on a confidential PAS discount [REDACTED] off the list price of larotrectinib. Results do not include commercial arrangements available for the comparator treatment options, which can be found in the cPAS appendix to this report. Table 32 and Table 33 present the company's deterministic and probabilistic base-case results, respectively.

The company applied tumour-site-specific severity modifiers rather than a single severity weight for the indication. Each tumour type in the pooled larotrectinib population was assigned an independent severity weight based on the company's QALY-shortfall calculations. These site-specific severity weights are described in detail in Section 5.3.1. The company's approach is equivalent to the application of a severity weighting of 1.60x to incremental QALYs.

The EAG notes that this approach is inconsistent with NICE's guidance on the application of the severity modifier, which recommends that where there are differences in QALY shortfall across comparator treatments or subgroups, a single modifier should be calculated for a given population decision space. A population-level weighted average of QALY shortfall can be presented based on the proportion of patients in each subgroup, from which a single severity weight can be derived. The company's approach calculates a weighted average of severity modifiers applicable in each subgroup, rather than being based on a weighted average of the QALY shortfall. The applicable QALY weight for the company's preferred population composition, based on the outcomes of the naïve literature comparison and baseline characteristics of the larotrectinib trials is 1.2, based on an absolute QALY shortfall of [REDACTED] and a proportional shortfall of [REDACTED]. As discussed in Section 5.3.1, the EAG considers it appropriate to use an internally consistent source of population characteristics and SoC outcomes. The applicable QALY weight for the company's preferred population composition, based on the outcomes and baseline characteristics of the naïve literature comparison, is also 1.2, based on an absolute QALY shortfall of [REDACTED], and a proportional shortfall of [REDACTED]. The application of a single QALY weight to the adult and paediatric population may also be inappropriate, but appropriate and generalisable paediatric SoC data were not identified by the company. Considering the adult population only, a multiplier of 1.2 is always applicable under all approaches.

The EAG therefore presents the company's cost-effectiveness results using a severity modifier of 1.0, 1.2, and 1.7, and under the company's preferred approach which applies and weights tumour-site specific weights based on the characteristics of the larotrectinib trial population (i.e. a mean QALY weight of 1.6). Note that the results below do not account for the EAG's correction of the application of the severity modifier (described in Section 5.2.1), which applies the QALY multiplier to total QALYs on both treatments.

**Table 32 Company's deterministic base-case cost-effectiveness results (disease severity modifier of 1.0 / 1.2 / 1.7 / company mix)**

| Intervention                                                   | Total costs | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|----------------------------------------------------------------|-------------|-------------|-----------------------|-------------------|---------------|
| <b>Company base case - Mixed severity modifier (mean 1.60)</b> |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |
| Larotrectinib                                                  | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.0</b>                        |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |
| Larotrectinib                                                  | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.2</b>                        |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |
| Larotrectinib                                                  | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.7</b>                        |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |
| Larotrectinib                                                  | ■           | ■           | ■                     | ■                 | ■             |

ICER: Incremental Cost Effectiveness Ratio. QALY: Quality-adjusted life years.

**Table 33 Company's probabilistic base-case cost-effectiveness results (disease severity modifier of 1.0 / 1.2 / 1.7 / company mix)**

| Intervention                                                   | Total costs | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|----------------------------------------------------------------|-------------|-------------|-----------------------|-------------------|---------------|
| <b>Company base case - Mixed severity modifier (mean 1.60)</b> |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |
| Larotrectinib                                                  | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.0</b>                        |             |             |                       |                   |               |
| Comparator                                                     | ■           | ■           |                       |                   |               |

| Intervention                            | Total costs | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|-----------------------------------------|-------------|-------------|-----------------------|-------------------|---------------|
| Larotrectinib                           | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.2</b> |             |             |                       |                   |               |
| Comparator                              | ■           | ■           |                       |                   |               |
| Larotrectinib                           | ■           | ■           | ■                     | ■                 | ■             |
| <b>Disease severity modifier of 1.7</b> |             |             |                       |                   |               |
| Comparator                              | ■           | ■           |                       |                   |               |
| Larotrectinib                           | ■           | ■           | ■                     | ■                 | ■             |

ICER: Incremental Cost Effectiveness Ratio. QALY: Quality-adjusted life years.

### 5.1.2 Company's sensitivity and scenario analyses

The company presents results of the deterministic sensitivity analysis in Section 3.11.1 of the CS. The EAG was able to replicate these analyses except for those summarised in Table 34. The cause of these discrepancies is unclear, and the company's documentation of the parameter inputs for each scenario is insufficient to identify their source. These differences are largely relatively minor except for Scenario 9 (i.e. the use of a mixed adult-paediatric cohort in the MAIC) and Scenario 10 (i.e. the use of the older ePAS2 and SAS3 datasets). It should be noted that the EAG's scenarios presented in Section 5.2.2 which incorporate the functionality in company Scenarios 4.1 and 9 reflect the implementation in Table 34, rather than the company's implementation whose results are presented in the CS.

**Table 34 Cost-effectiveness results for scenario reported in the CS and EAG validation**

|                                                                                                     | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|-----------------------------------------------------------------------------------------------------|-----------------------|-------------------|---------------|--------------------------------|
| <b>Scenario 4.1 Naïve literature-based comparator (no adjustment for NTRK+ fusion prevalence)</b>   |                       |                   |               |                                |
| Company's results                                                                                   | ████                  | ████              | ████          | ████                           |
| EAG's validation results                                                                            | ████                  | ████              | ████          | ████                           |
| <b>Scenario 4.2 Naïve literature-based comparator with adjustment for NTRK+ fusions (VOYAGER 1)</b> |                       |                   |               |                                |
| Company's results                                                                                   | ████                  | ████              | ████          | ████                           |
| EAG's validation results                                                                            | ████                  | ████              | ████          | ████                           |
| <b>Scenario 4.3 Naïve literature-based comparator with adjustment for NTRK+ fusions (VOYAGER 2)</b> |                       |                   |               |                                |
| Company's results                                                                                   | ████                  | ████              | ████          | ████                           |
| EAG's validation results                                                                            | ████                  | ████              | ████          | ████                           |
| <b>Scenario 9 Mixed adult and paediatric cohort</b>                                                 |                       |                   |               |                                |
| Company's results                                                                                   | ████                  | ████              | ████          | ████                           |
| EAG's validation results                                                                            | ████                  | ████              | ████          | ████                           |
| <b>Scenario 10 Using more mature trial data (ePAS2 + SAS3)</b>                                      |                       |                   |               |                                |
| Company's results                                                                                   | ████                  | ████              | ████          | ████                           |
| EAG's validation results                                                                            | ████                  | ████              | ████          | ████                           |

EAG: External Assessment Group; ICER: Incremental Cost Effectiveness Ratio. QALY: Quality-adjusted life years.

## 5.2 EAG's additional analyses

### 5.2.1 Model validation and face validity check

The EAG reviewed the company's model in detail and applied the TECHNical Verification (TECH-VER) checklist for the company's base case model structure. There was insufficient time available to separately validate the model for each of the proposed model structures.

The EAG noted no substantive technical errors in the deterministic model logic with the exception of the application of the severity modifier. The company applied QALY weighting for severity to total QALYs gained in each tumour site for both interventions, rather than only to incremental QALYs gained on larotrectinib, per the NICE reference case. The EAG's corrected base case below applies the QALY weight multiplier to incremental QALYs on larotrectinib only, with the total QALYs presented based on the unadjusted values generated directly by the model engines. This had no impact on the ICER calculations as the incremental QALYs remain the same, but represents a significant presentational error, as total QALYs on both larotrectinib and SoC are misrepresented.

The EAG also corrects a number of drug unit costs according to the Price Tracker supplied by NICE. This represents the correct and current pricing based on eMIT and the Medicines Procurement and Supply Chain framework pricing (current as of 22<sup>nd</sup> October 2025). Together these corrections result in a small reduction in the ICER relative to the company base case.

During validation of the probabilistic sensitivity analysis (PSA), the EAG identified an issue with Excel's recalculation behaviour in the company's model whereby, after a number of iterations, the PSA began to repeatedly return identical results for the remainder of the probabilistic iterations. This behaviour indicates that the model failing sample and propagate random parameter values through the model, resulting in the reuse of 'stale' values rather than truly probabilistic draws. This issue is consistent with known limitations of Excel in very large models, where calculation chains can fail to refresh fully despite workbook recalculation being triggered. This occurs here due to the complexity of the executable model, which essentially samples and propagates random values for all possible model structures across 14 engines regardless of the selected assumptions in a given analysis. To address this, the EAG implemented a safeguard where a full recalculation of all dependency trees (*CalculateFullRebuild*) is forced at regular intervals during the PSA run. This ensured that all dependent cells were recalculated and that probabilistic sampling was correctly propagated through the model.

The PSA for the present model is particularly slow to complete – taking in excess of 3 hours to complete only 1,000 iterations. This constrained the number of iterations that could be feasibly run by the EAG and limited the extent to which parameter uncertainty could be characterised in the PSA results. Consequently, the PSA results may not fully characterise decision uncertainty, and estimates of cost-effectiveness derived from the PSA should be interpreted with caution. This issue may be mitigated in future through the use of multiple separate model files which are streamlined to provide analysis of a single model structure for generation of probabilistic results.

Table 35 presents the results of the EAG-corrected company base case. This analysis is presented both inclusive of the company's severity modifier calculation, and with a QALY multiplier of 1.0.

**Table 35 Results of EAG-corrected company base case (deterministic)**

| Analysis                           | Intervention  | Total costs | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER £/QALY |
|------------------------------------|---------------|-------------|-------------|-----------------------|-------------------|-------------|
| Company's base case (QALYs x 1.60) | SoC           | ■           | ■           |                       |                   |             |
|                                    | Larotrectinib | ■           | ■           | ■                     | ■                 | ■           |
| Company's base case (QALYs x 1.0)  | SoC           | ■           | ■           |                       |                   |             |
|                                    | Larotrectinib | ■           | ■           | ■                     | ■                 | ■           |

| Analysis                                       | Intervention  | Total costs | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER £/QALY |
|------------------------------------------------|---------------|-------------|-------------|-----------------------|-------------------|-------------|
| EAG-corrected company base case (QALYs x 1.60) | SoC           | ■           | ■           |                       |                   |             |
|                                                | Larotrectinib | ■           | ■           | ■                     | ■                 | ■           |
| EAG-corrected company base case (QALYs 1.0x)   | SoC           | ■           | ■           |                       |                   |             |
|                                                | Larotrectinib | ■           | ■           | ■                     | ■                 | ■           |

EAG: External Assessment Group. ICER: Incremental Cost Effectiveness Ratio. QALY: Quality-adjusted life years.

### 5.2.2 EAG's exploratory analyses using company's base case

Table 36 provides a summary of the EAG's exploratory analyses using the EAG-corrected company base-case. Table 37 presents the results of the EAG's exploratory analyses. Given potential uncertainty in the applicable severity modifier, these results are each presented using a consistent severity modifier of 1.0, 1.2, and 1.7. More information on the EAG's curve fitting process to pseudo-IPD from the SACT dataset and Brose *et al.* is provided in Appendix 3. Deterministic results are presented due to the substantial time required to run all analyses probabilistically.

**Table 36 Summary of EAG's exploratory analyses using company's base case**

| Scenario number | Company's base-case assumption                                                                                                                                                                | EAG scenario                                                                                                                  | Justification for EAG assumption                                                                                                                                                                                                                      | Section in EAG report |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 1               | Population tumour site distribution and baseline characteristics based on larotrectinib studies                                                                                               | Population tumour site distribution and baseline characteristics based on SACT                                                | Increases generalisability of population to NHS practice                                                                                                                                                                                              | 4.2.3, 4.2.5, 4.2.7   |
| 2               | Independent OS/PFS models fitted to adult and paediatric larotrectinib data. HR from EPI-VITRAKVI MAIC applied to paediatric curves to derive SoC. Adult curves adjusted using VICTORIA MAIC. | Single OS and PFS curve fitted to pooled adult and paediatric larotrectinib data. HR from VICTORIA used to derive SoC curves. | Separate curves fitted to immature (and potentially confounded) paediatric OS data implies implausible PPS. EPI-VITRAKVI MAIC flawed, subject to a high degree of uncertainty and in inappropriate population, resulting in implausible SoC outcomes. | 3.4, 4.2.2, 4.2.4     |

| Scenario number | Company's base-case assumption                                                                 | EAG scenario                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Justification for EAG assumption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Section in EAG report |
|-----------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 3               | VICTORIA and EPI-VITRAKVI MAICs used to generate SoC arm OS and PFS using ePAS9 and SAS3 data. | OS and PFS curve for larotrectinib based on overall weighted responder- and non-responder curves for each tumour site (Figure 7Plots of modelled and observed adult responder OS and PFS [A]; adult non-responder OS and PFS [B] paediatric responder OS and PFS [C]; paediatric non-responder OS and PFS [D] (adapted from company's economic model)). Predicted tumour site-specific response rates generated from BHM (Table 29). No response to SoC is assumed (i.e. SoC outcomes informed by non-responders to larotrectinib). Tumour site distribution based on larotrectinib trial. | Trial data suggests an assumption of equal response across tumour sites is inappropriate. The poor generalisability of the larotrectinib trial population relative to SACT in terms of tumour type distribution necessitates reweighting of outcome data (this scenario still applies larotrectinib distribution to explore effect of model structure only. Response-based model produces internally consistent comparison of outcomes in the trial population. This analysis may underrepresent the efficacy of SoC in current decision space, as all SoC patients assumed to be non-responders. | 4.2.2, 4.2.5.4        |
| 4               | VICTORIA and EPI-VITRAKVI MAICs used to generate SoC arm OS and PFS using ePAS9 and SAS3 data. | Efficacy of larotrectinib based on parametric models fitted by EAG to OS and treatment duration pseudo-IPD from SACT (representing PFS). Exponential modelled as best statistical fit to OS and PFS. See Appendix 3.<br><br>SoC efficacy based on parametric models fitted by company to OS and PFS derived from literature sources (naïve literature comparator).                                                                                                                                                                                                                         | Larotrectinib trial data is poorly generalisable to NHS practice in terms of patient characteristics, tumour site distribution, and use of subsequent therapies. Data collected in SACT provides NHS-relevant outcome data for larotrectinib. Treatment duration data from SACT may provide more NHS-relevant treatment cost estimates, given continued use of larotrectinib post-progression in some patients. Allows some continued benefit to be modelled.<br><br>Unanchored and unadjusted comparison with naïve literature comparator is subject to uncertainty.                             | 4.2.2, 4.2.5.1        |



| Scenario number | Company's base-case assumption                                                                                                                                                                      | EAG scenario                                                                                                                                                                                                                                                                                                                                                                                                                                           | Justification for EAG assumption                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Section in EAG report |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 5               | VICTORIA and EPI-VITRAKVI MAICs used to generate SoC arm OS and PFS using ePAS9 and SAS3 data.                                                                                                      | <p>Efficacy of larotrectinib based on parametric models fitted by EAG to pseudo-IPD for OS and treatment duration KM data from SACT (representing PFS). Exponential modelled as best statistical fit to OS and PFS.</p> <p>SoC efficacy based on unadjusted parametric models fitted by EAG to pseudo-IPD of OS and PFS Brose <i>et al.</i> (VICTORIA SoC population). Exponential modelled as best statistical fit to OS and PFS. See Appendix 3.</p> | <p>Larotrectinib trial data is poorly generalisable to NHS practice in terms of patient characteristics, tumour site distribution, and use of subsequent therapies. Data collected in SACT provides NHS-relevant outcome data for larotrectinib.</p> <p>Unanchored and unadjusted comparison with Brose <i>et al.</i> is subject to uncertainty. Represents an alternative source of outcome data in contemporary population of patients with NTRK gene fusions.</p>                              | 4.2.2, 4.2.5.1        |
| 6               | SoC health state utilities based on tumour site-specific values sourced from previous NICE appraisals and literature. Larotrectinib PFS/PD utilities based on larotrectinib trial.                  | SoC health state utilities based on weighted values excluding those derived using non-reference case methods (i.e. TTO, SG). Treatment specific PFS/PD utilities retained for larotrectinib.                                                                                                                                                                                                                                                           | Use of TTO and SG methods to elicit utilities for certain health states from the general public is likely to underestimate HRQoL. EQ-5D derived from affected patients should be used where possible.                                                                                                                                                                                                                                                                                             | 4.2.6                 |
| 7               | Larotrectinib PFS/PD utility based on data collected in larotrectinib trials. SoC health state utilities based on tumour site-specific values sourced from previous NICE appraisals and literature. | <p>Larotrectinib PD utility based on weighted average of SoC PD utility (excluding non-reference case values). Larotrectinib treatment-specific PFS utility retained.</p> <p>SoC health state utilities based on weighted values excluding those derived using non-reference case methods (i.e. TTO, SG).</p>                                                                                                                                          | <p>There is no reason to believe there should be a sustained and substantial treatment effect for those previously treated with larotrectinib patients with progressed disease. Company SLR identified much lower PD utilities on those treated with TRK inhibitors. Trial-derived PD values likely to be confounded by subsequent therapy use amongst other issues.</p> <p>EAG considers treatment-specific utility for PFS may be appropriate given efficacy and potential toxicity of SoC.</p> | 4.2.6                 |

| Scenario number | Company's base-case assumption                                                      | EAG scenario                                                                                                                                                                                                                                                                       | Justification for EAG assumption                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Section in EAG report |
|-----------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 8               | Genomic testing costs for identifying patients with NTRK gene fusions not included. | Cost of NGS panels is applied where NTRK gene fusion status not already established at earlier treatment line. Cost is split between number of alternative targeted therapies in a given tumour site.                                                                              | <p>The EAG and Committee in TA630 considered it appropriate to include testing costs, as genomic testing to assess eligibility comprises a core part of treatment with larotrectinib, and reflects real world commissioning cost to NHS where fusion status would not otherwise be tested for or known in absence of larotrectinib at a given treatment line.</p> <p>Testing costs should be split with other targeted therapies where testing occurs at the clinical decision point for larotrectinib</p> | 4.2.7                 |
| 9               | No ongoing health state resource use associated with CNS/glioma.                    | <p>The EAG source health state resource use estimates from TA977.</p> <p>PFS: Monthly Oncologist visit (£193 – HRG370), FBC (£3.31 – DAPS05), ECG (£75 – RD51A).</p> <p>PD: Monthly multiprofessional visit (£569.00 – WF02A) and specialist cancer nurse visit (£277 – N10CF)</p> | <p>Resource use for CNS/glioma was based on TA23, which used resource use estimation methods inconsistent with contemporary HTA practice.</p> <p>Resource use estimates from TA977 may better reflect NHS practice, and produce health state costs more in keeping with other modelled tumour sites.</p>                                                                                                                                                                                                   | 4.2.7                 |
| 10              | No cost associated with orally administered therapies                               | Include SB11Z tariff (£247) once per treatment cycle to account for dispensing.                                                                                                                                                                                                    | Aligns with Committee preference for inclusion of oral administration cost in TA630 and input from NHSE on inclusion of oral administration costs for systemic anti-cancer therapies.                                                                                                                                                                                                                                                                                                                      | 4.2.7                 |

CNS: Central nervous System. EAG: External Assessment Group. HR: Hazard Ratio. IPD: Individual Patient data. MAIC: Matching-Adjusted Indirect Comparison. NHS: National Health Service. NTRK: Neurotrophic Tyrosine Receptor Kinase. OS: Overall Survival. PD: Progressive Disease. PFS: Progression-free Survival. PPS: Post-progression Survival. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

**Table 37 Results of EAG's exploratory analyses using company's base case**

| Scenario number | Scenario applied to company's base case        | Incremental costs (£) | Inc. QALYs (x1.0) | ICER £/QALY (x1.0) | ICER £/QALY (x1.2) | ICER £/QALY (x1.7) |
|-----------------|------------------------------------------------|-----------------------|-------------------|--------------------|--------------------|--------------------|
|                 | Corrected company base case                    | ■                     | ■                 | ■                  | ■                  | ■                  |
| 1               | SACT tumour site distribution                  | ■                     | ■                 | ■                  | ■                  | ■                  |
| 2               | Structure: pooled population MAIC              | ■                     | ■                 | ■                  | ■                  | ■                  |
| 3               | Structure: Tumour-specific BHM responder model | ■                     | ■                 | ■                  | ■                  | ■                  |

| Scenario number | Scenario applied to company's base case                | Incremental costs (£) | Inc. QALYs (x1.0) | ICER £/QALY (x1.0) | ICER £/QALY (x1.2) | ICER £/QALY (x1.7) |
|-----------------|--------------------------------------------------------|-----------------------|-------------------|--------------------|--------------------|--------------------|
| 4               | Structure: SACT vs naïve literature comparator         | ■                     | ■                 | ■                  | ■                  | ■                  |
| 5               | Structure: SACT vs Brose comparator                    | ■                     | ■                 | ■                  | ■                  | ■                  |
| 6               | SoC utilities excluding non-reference case values      | ■                     | ■                 | ■                  | ■                  | ■                  |
| 7               | S6 + larotrectinib PD utility also based on Scenario 6 | ■                     | ■                 | ■                  | ■                  | ■                  |
| 8               | Diagnostic testing costs included                      | ■                     | ■                 | ■                  | ■                  | ■                  |
| 9               | Include CNS/glioma health state costs                  | ■                     | ■                 | ■                  | ■                  | ■                  |
| 10              | Include oral administration cost                       | ■                     | ■                 | ■                  | ■                  | ■                  |

BHM: Bayesian Hierarchical Model. CNS: Central nervous System. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

The EAG considers that a disease severity modifier of 1.2 is most likely to be appropriate, depending on the preferred source of SoC survival and baseline characteristics data. It may also be appropriate to weight incremental QALYs according to tumour site-specific QALY gain, but this approach can only be applied correctly at present using scenarios in which the EAG's version of the response-based model structure is adopted.

### 5.2.3 EAG's preferred assumptions

The EAG presents three alternative base-case analyses, which explore the effect of adopting the EAG's preferred assumptions in three model structures, each of which has respective strengths and weaknesses. The EAG considers these analyses together to be informative for decision making but does not consider any individual analysis to be a best representation of the cost-effectiveness of larotrectinib in the NHS.

All three of the EAG's base-case analyses adopt the following key changes to the base case already described in Table 36 above:

- Scenario 1: Tumour site distribution and baseline characteristics for larotrectinib based on SACT population. Impacts QALYs primarily through the ratio of adult to paediatric patients.
- Scenario 6: SoC health state utilities based on weighted values excluding those derived using non-reference case values.

- Scenario 7: Larotrectinib PD utility based on a weighted average of the SoC PD utilities (excluding non-reference case values). Larotrectinib PFS utility based on larotrectinib trials. (Scenario 6). Treatment-specific PFS utility assumed.
- Scenario 9: Health state resource use estimates for CNS/glioma based on TA977.
- Scenario 10: Oral administration costs included (SB11Z).

The above preferred assumptions are adopted in each of the following three base-case analyses.

Deterministic results with a QALY weight of 1.0, 1.2, and 1.7 are presented in Table 38, Table 39, and Table 40. Probabilistic results of all three base cases are compiled in Table 41.

- EAG base case 1: MAIC - OS and PFS curves fitted to pooled adult and paediatric larotrectinib trial data. SoC curves are derived using HRs from VICTORIA MAIC applied to larotrectinib curves. Results in Table 38
- EAG base case 2: BHM/response-based model - OS and PFS curve for larotrectinib based on adult- and paediatric-specific responder- and non-responder curves weighted according to PRR for each tumour site from the BHM. No response to SoC is assumed (i.e. SoC outcomes are informed by non-responders to larotrectinib). Tumour site distribution is based on SACT. Results in Table 39.
- EAG base case 3: SACT naïve comparison: Efficacy of larotrectinib based on parametric models fitted by EAG to OS and treatment duration pseudo-IPD from SACT (proxy relationship with PFS assumed). Exponential curves modelled as best statistical fit to OS and PFS. SoC efficacy based on parametric models fitted by company to tumour-specific OS and PFS derived from literature sources (naïve literature comparator). Results in Table 40.

**Table 38 Deterministic results using EAG’s preferred model assumptions [EAG base case 1 – pooled population MAIC]**

| Preferred assumption                           | Scenario no.             | Intervention         | Total |       | Incremental |       | Cumulative ICER £/QALY |      |      |
|------------------------------------------------|--------------------------|----------------------|-------|-------|-------------|-------|------------------------|------|------|
|                                                |                          |                      | Costs | QALYs | Costs       | QALYs | 1.0x                   | 1.2x | 1.7x |
| Company’s base case                            | N/A                      | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| EAG-corrected company base case                | N/A                      | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| SACT tumour site distribution                  | 1                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Structure: Pooled population MAIC              | 2                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| SoC utility excludes non-reference case values | 6                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Laro PD utility also based on Scenario 6       | 7                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Include CNS/glioma health state costs          | 9                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Include oral administration cost SB11Z         | 10                       | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| <b>EAG base case 1</b>                         | <b>1, 2, 6, 7, 9, 10</b> | <b>SoC</b>           | ████  | ████  |             |       |                        |      |      |
|                                                |                          | <b>Larotrectinib</b> | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |

CNS: Central nervous System. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

Absolute and proportional QALY shortfall in EAG base case 1 are █████ and █████ respectively using the site-specific baseline ages in the larotrectinib trials. A severity modifier of 1.2 is therefore applicable. The preferred ICER for larotrectinib in EAG base case 1 is thus █████ per QALY gained.

**Table 39 Deterministic results using EAG's preferred model assumptions [EAG base case 2 – response-based model]**

| Preferred assumption                                             | Scenario no.      | Intervention  | Total |       | Incremental |       | Cumulative ICER £/QALY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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|                                                                  |                   |               | Costs | QALYs | Costs       | QALYs | 1.0x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Company’s base case                                              | N/A               | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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|                                                                  |                   | Larotrectinib | ████  | ████  | ████        | ████  | ████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| EAG-corrected company base case                                  | N/A               | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| SACT tumour site distribution                                    | 1                 | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Structure: BHM/response-based model                              | 3                 | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| SoC utility excludes non-reference case values                   | 6                 | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Include CNS/glioma health state costs                            | 9                 | SoC           | ████  | ████  |             |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Inc. results using site-specific shortfall (mean weighting 1.39) |                   |               |       |       | ████        | ████  | 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|      |      |

CNS: Central nervous System. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

Absolute and proportional QALY shortfall in EAG base case 2 are █████ and █████ respectively using the site-specific baseline ages in the larotrectinib trials. A severity modifier of 1.2 is therefore applicable. The preferred ICER for larotrectinib in EAG base case 2 is thus █████ per QALY gained, although the EAG considers the ICER using site-specific QALY weighting of █████ a plausible alternative in this scenario.

**Table 40 Deterministic results using EAG's preferred model assumptions [EAG base case 3 – SACT naïve comparison]**

| Preferred assumption                           | Scenario no.             | Intervention         | Total |       | Incremental |       | Cumulative ICER £/QALY |      |      |
|------------------------------------------------|--------------------------|----------------------|-------|-------|-------------|-------|------------------------|------|------|
|                                                |                          |                      | Costs | QALYs | Costs       | QALYs | 1.0x                   | 1.2x | 1.7x |
| Company's base case                            | N/A                      | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| EAG-corrected company base case                | N/A                      | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| SACT tumour site distribution                  | 1                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Structure: SACT naïve comparison               | 4                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| SoC utility excludes non-reference case values | 6                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Laro PD utility also based on Scenario 6       | 7                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Include CNS/glioma health state costs          | 9                        | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| Include oral administration cost SB11Z         | 10                       | SoC                  | ████  | ████  |             |       |                        |      |      |
|                                                |                          | Larotrectinib        | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |
| <b>EAG base case 3</b>                         | <b>1, 4, 6, 7, 9, 10</b> | <b>SoC</b>           | ████  | ████  |             |       |                        |      |      |
|                                                |                          | <b>Larotrectinib</b> | ████  | ████  | ████        | ████  | ████                   | ████ | ████ |

CNS: Central nervous System. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. PD: Progressive Disease. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

Absolute and proportional QALY shortfall in EAG base case 3 are █████ and █████ respectively using the tumour site distribution of the SACT population, and baseline characteristics of the naïve SoC comparison sources, meaning a 1.2 multiplier is appropriate. However, if the mean baseline characteristics of the SACT population are used in a QALY shortfall calculation based on the mean QALYs of the SoC arm, absolute and proportional QALY shortfall are █████ and █████ respectively, meeting the criteria for a multiplier of 1.7. This is inconsistent with the source of efficacy data, however, and is unlikely to represent the shortfall of the equivalent SoC-treated population in NHS practice. The preferred ICER for larotrectinib in EAG base case 3 is thus █████ per QALY gained.

The probabilistic results of the three EAG base-case analyses is presented in Table 41 below. Each analysis was run over 1,000 probabilistic iterations.

In EAG base case 1, larotrectinib was cost-effective relative to SoC in [REDACTED] of model iterations at a threshold of £30,000 and with a QALY multiplier of 1.0 and 0.1% at 1.2. At a QALY multiplier of 1.7, larotrectinib had a [REDACTED] probability of cost-effectiveness versus SoC. The EAG's preferred ICER at a QALY multiplier of 1.2 is [REDACTED] per QALY gained.

In EAG base case 2, larotrectinib was cost-effective relative to SoC in [REDACTED] of model iterations at a threshold of £30,000 and with a QALY multiplier of 1.0 and 1.2. At a QALY multiplier of 1.7, larotrectinib had a [REDACTED] probability of cost-effectiveness versus SoC. The EAG's preferred ICER at a QALY multiplier of 1.2 is [REDACTED] per QALY gained.

In EAG base case 3, larotrectinib was cost-effective relative to SoC in [REDACTED] of model iterations at a threshold of £30,000 and with a QALY multiplier of 1.0 and 1.2. At a QALY multiplier of 1.7, larotrectinib had a [REDACTED] probability of cost-effectiveness versus SoC. The EAG's preferred ICER at a QALY multiplier of 1.2 is [REDACTED] per QALY gained.

**Table 41 Probabilistic results of EAG base cases 1 - 3**

| Preferred assumption   | Scenario no. | Intervention  | Total      |            | Incremental |            | Cumulative ICER £/QALY |            |            |
|------------------------|--------------|---------------|------------|------------|-------------|------------|------------------------|------------|------------|
|                        |              |               | Costs      | QALYs      | Costs       | QALYs      | 1.0x                   | 1.2x       | 1.7x       |
| EAG base case 1 (MAIC) | 1, 2, 6-10   | SoC           | [REDACTED] | [REDACTED] |             |            |                        |            |            |
|                        |              | Larotrectinib | [REDACTED] | [REDACTED] | [REDACTED]  | [REDACTED] | [REDACTED]             | [REDACTED] | [REDACTED] |
| EAG base case 2 (BHM)  | 1, 3, 6-10   | SoC           | [REDACTED] | [REDACTED] |             |            |                        |            |            |
|                        |              | Larotrectinib | [REDACTED] | [REDACTED] | [REDACTED]  | [REDACTED] | [REDACTED]             | [REDACTED] | [REDACTED] |
| EAG base case 3 (SACT) | 1, 4, 6-10   | SoC           | [REDACTED] | [REDACTED] |             |            |                        |            |            |
|                        |              | Larotrectinib | [REDACTED] | [REDACTED] | [REDACTED]  | [REDACTED] | [REDACTED]             | [REDACTED] | [REDACTED] |

BHM: Bayesian Hierarchical Model. . EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. SACT: Systemic Anti-Cancer Therapy data set.



## 5.2.4 Scenario analyses using EAG's preferred assumptions

A key uncertainty in the EAG's analysis which models the efficacy of larotrectinib using data collected in SACT is the applicability of the comparator population. EAG base case 3 is based on a naïve comparison with the sources of efficacy data identified by the company, which they consider to represent the effectiveness of SoC in the selected tumour sites. However, as discussed previously, many of these sources are old and may not represent the fitness of patients currently initiating this line of therapy on the NHS, and may also misrepresent the efficacy of current NHS care. Brose *et al.* was used as the basis of the SoC arm for the MAIC applied in the company's base case. As discussed in Section 3.4, this population has a substantially higher baseline mean age than the larotrectinib trials or the SACT population, as it did not recruit paediatric patients. This study also only included five tumour sites in the real-world control arm, but all patients did have tumours positive for an NTRK gene fusion.

The EAG fitted parametric models to OS and PFS data for the unweighted real-world control arm to be used as an alternative source of SoC outcomes for comparison with SACT. This represents a more contemporary population of patients with NTRK fusion-positive solid tumours treated with treatments other than a TRK inhibitor. This analysis is summarised in Table 42 and deterministic results are presented in EAG: External Assessment Group. IPD: Individual Patient Data. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

Table 43.

**Table 42 Summary of EAG's scenario analyses using EAG's preferred assumptions**

|   | EAG's base-case assumption                                                                                  | EAG's scenario                                                                                                                   |
|---|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 1 | SoC efficacy based on company's naïve literature comparison with tumour site distribution weighted to SACT. | SoC efficacy based on Exponential curves fitted by EAG to pseudo-IPD for unweighted real-world controls from Brose <i>et al.</i> |

EAG: External Assessment Group. IPD: Individual Patient Data. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

**Table 43 Deterministic results of EAG's scenario analysis using a naïve comparison of SACT with Brose *et al.***

| Scenario number                                       | Scenario applied to EAG's base case      | Incremental costs (£) | Inc. QALYs (x1.0) | ICER £/QALY (x1.0) | ICER £/QALY (x1.2) | ICER £/QALY (x1.7) |
|-------------------------------------------------------|------------------------------------------|-----------------------|-------------------|--------------------|--------------------|--------------------|
| EAG base case 3 (SACT vs naïve literature comparator) |                                          | ■                     | ■                 | ■                  | ■                  | ■                  |
| SoC based on EAG Scenario 5                           | SACT vs SoC based on Brose <i>et al.</i> | ■                     | ■                 | ■                  | ■                  | ■                  |

Absolute and proportional QALY shortfall in this scenario on EAG base case 3 are [REDACTED] and [REDACTED] respectively using the mean baseline characteristics of the SACT population, meaning a 1.2x modifier is applicable. Absolute and proportional shortfall based on the baseline characteristics of Brose *et al.* are substantially lower due to the mean age of the Brose population, at [REDACTED] and [REDACTED]%. The EAG therefore considers a 1.2x modifier to be appropriate in this scenario.

### 5.3 Decision modifiers

#### 5.3.1 QALY weighting for severity

The company presents the results of QALY shortfall analysis for each of the modelled tumour types in CS Section 3.6. In their base case, SoC QALYs for each tumour type were estimated using the naïve literature-based comparator efficacy and utility estimates. Starting age and distribution for each tumour type were taken from the larotrectinib trial population. Based on these inputs, the company calculated absolute and proportional QALY shortfall for each tumour type and assigned severity weightings to each independently.

All of the tumour sites, with the exception of primary pancreatic tumours, met the criteria for a 1.2x or 1.7x QALY weighting, reproduced in Table 44 below. The company then applied these tumour-specific severity weights to the pooled total QALYs accrued on larotrectinib and SoC, aggregating the severity-weighted QALYs from each tumour site according to their prevalence in the trial population. Under this approach, QALY gain is assumed to be homogeneous across tumour sites, ignoring heterogeneity in response rate and survival (i.e. the natural history of each tumour type) in both responders and non-responders.

The EAG requested that the company explore alternative approaches to applying severity weights. This included applying severity weights according to QALY gains generated within each tumour type, rather than to pooled QALYs weighted only by prevalence (CQ B25), and recalculating QALY shortfall dynamically so that it reflects the active assumptions regarding SoC efficacy, population characteristics, and utilities in each analysis (CQ B29). In response, the company implemented functionality allowing QALY shortfall to be recalculated conditional on selected scenarios but maintained that tumour-specific weighting of larotrectinib QALYs was not feasible within their preferred modelling framework. They also stated that the ‘instability’ of the BHM approach meant that weighting QALY gain via this means would introduce ‘significant uncertainty’.

The EAG also requested that the starting age and sex distribution of patients in each tumour site be based on the selected source of efficacy data, rather than the age of the population in the larotrectinib

trial, which tends to be younger than in the literature sources (thereby increasing apparent shortfall). This ensures alignment between the SoC QALYs applied in the shortfall calculation and the total QALYs expected in that same population. In this analysis, severity modifiers for STS adults and CNS/Glioma are revised from 1.7 to 1.2, and severity in thyroid tumours is revised from 1.2 to 1.0, relative to the company base case.

**Table 44 Company base-case QALY shortfall using naïve literature comparison QALYs and larotrectinib trial baseline characteristics by tumour type (CS Table 64, Page 180)**

| Tumour location                                        | Expected total QALYs for the general population | SoC QALYs | Absolute QALY shortfall | Proportional QALY shortfall | QALY weight |
|--------------------------------------------------------|-------------------------------------------------|-----------|-------------------------|-----------------------------|-------------|
| NSCLC                                                  | 14.39                                           | 0.73      | 13.66                   | 94.93%                      | 1.2         |
| Salivary                                               | 14.63                                           | 0.78      | 13.85                   | 94.67%                      | 1.2         |
| Melanoma                                               | 15.06                                           | 1.37      | 13.69                   | 90.90%                      | 1.2         |
| Colorectal (used as proxy for appendix)                | 10.32                                           | 0.48      | 9.84                    | 95.35%                      | 1.7         |
| STS adults (GIST)                                      | 15.56                                           | 1.4       | 14.16                   | 91.00%                      | 1.2         |
| STS adults (non-GIST) (used as proxy for bone sarcoma) | 18.66                                           | 0.71      | 17.95                   | 96.19%                      | 1.7         |
| STS paediatrics (used as proxy for IFS)                | 24.30                                           | 1.43      | 22.87                   | 94.11%                      | 1.7         |
| Breast                                                 | 15.99                                           | 0.61      | 15.38                   | 96.19%                      | 1.7         |
| Cholangiocarcinoma                                     | 14.43                                           | 0.41      | 14.02                   | 97.16%                      | 1.7         |
| CNS/Glioma                                             | 22.67                                           | 0.75      | 21.92                   | 96.69%                      | 1.7         |
| Pancreas                                               | 12.34                                           | 2.65      | 9.69                    | 78.53%                      | 1.0         |
| Thyroid                                                | 14.42                                           | 2.37      | 12.05                   | 83.56%                      | 1.2         |
| Mean QALY weight applied                               | 1.60                                            |           |                         |                             |             |
| Mean weighted QALY shortfall                           |                                                 |           |                         |                             |             |
| Implied overall severity weight                        | 1.2                                             |           |                         |                             |             |

CNS: Central Nervous System. GIST: Gastrointestinal stromal tumour. IFS: Infantile fibrosarcoma. NSCLC: Non-small cell lung cancer. QALY: Quality-adjusted life year. STS: Soft tissue sarcoma.

### ***Points for critique***

The EAG considers the company's QALY shortfall analysis and application of severity modifiers to be methodologically unsound in several important respects.

First, the company applied the QALY weighting for severity to total QALYs accrued on both larotrectinib and SoC, rather than applying the multiplier only to incremental QALYs generated by larotrectinib. QALY multipliers for severity should be applied to the additional health benefits

generated by the intervention, not to total or comparator QALYs. Applying the modifier to total QALYs therefore misrepresents absolute health outcomes on both treatments and inflates the reported total QALYs in a manner that is not informative to the decision-making process. The EAG corrected this error in Section 5.2 by applying severity weights exclusively to incremental QALYs on larotrectinib, with total QALYs presented using the unadjusted values generated directly by the model engines. While there is no impact of this correction on the ICER itself, the error is nevertheless material from a methodological and presentational perspective, as the total QALYs reported in the company's base case do not reflect the reference-case interpretation of severity weighting.

Second, as discussed in Section 4.2.6, the utilities selected by the company for the SoC arm are likely to underestimate HRQoL experienced by the relevant NHS populations. This is likely to overestimate QALY shortfall, increasing the probability that higher severity thresholds are met. In several tumour types, more realistic utility inputs are likely to result in a lower applicable severity modifier.

Third, the company calculates QALY shortfall using the age and sex distribution observed in the larotrectinib trials, which is generally younger than the populations underpinning the literature-based SoC estimates – particularly the primary CNS population, which is age 54 years in the literature comparison, compared to only [REDACTED] years in SAS3. Because a younger starting age increases expected lifetime QALYs, combining trial-derived baseline characteristics with survival data from an older cohort can systematically inflate estimated QALY shortfall. The EAG consider the use of internally consistent inputs to be more methodologically sound. As can be seen in Table 44 above, the company's base-case assumptions, i.e. use of the naïve literature comparison analysis to derive SoC QALYs, with baseline characteristics derived from the larotrectinib trials, produces a mean absolute QALY shortfall of [REDACTED] and absolute shortfall of [REDACTED]%, implying a QALY multiplier of 1.2.

Fourth, there is internal inconsistency between the data sources used to estimate severity and those used to calculate treatment outcomes. In the base case, SoC outcomes are derived from MAIC-adjusted survival curves, whereas QALY shortfall is calculated using naïve literature-based SoC estimates. This introduces contradictory assumptions regarding relative effectiveness - if the MAIC-adjusted survival curves are considered the appropriate representation of SoC in the cost-effectiveness comparison, then the QALYs generated from those curves should also be used to determine severity. The EAG prefers to base severity estimates on the selected efficacy data for a given analysis.

Importantly, the company's approach applies tumour-site-specific severity modifiers to pooled larotrectinib QALY gains, weighted by tumour prevalence rather than by the distribution of QALY gains across tumour types. This assumes that all tumour types, regardless of response rate, natural history, or prognosis on treatment, experience the same level of absolute QALY gain on larotrectinib. This approach is likely to substantially over-inflate QALY gain through inappropriate up-weighting of

QALYs generated in particular tumour types, particularly where severity is high and response to larotrectinib is low.

For example, this approach assumes that patients with primary CNS tumours, whose ORR in the SAS3 study was only █%, and have only 0.75 remaining QALYs in the company's naïve comparison, accrue █ total QALYs on larotrectinib, which are accordingly inflated to █ QALYs using a 1.7x QALY multiplier. These inflated gains comprise █ of the total QALYs generated by larotrectinib in the adult population, despite primary CNS tumour patients contributing only 18.0% of QALYs in the equivalent stratified naïve literature comparator population.

#### *Implications for the EAG's preferred analyses*

The EAG highlights that the company's approach applies different severity modifiers within a single decision space and aggregates upweighted QALYs into a single ICER. This means that a weighted average QALY multiplier of 1.60 is applied in the company's base case. This approach lacks transparency and is inconsistent with NICE's guidance on the application of the severity modifier, which indicates that a single severity modifier should be applied at the population level, even where differences in QALY shortfall exist across subgroups. Where SoC QALYs differs according to different comparators or sub-populations, NICE guidance suggests that a weighted shortfall for the whole population is calculated, from which a single severity modifier is calculated according to the usual thresholds. This distinction between a weighted average of severity modifiers versus one of QALY shortfall is non-trivial, and results in the application of a substantially higher effective weight. It may be more appropriate to calculate shortfall for the adult and paediatric populations separately. However, as no SoC efficacy data were identified by the company for paediatric patients with primary CNS tumours, it was not possible to calculate shortfall separately with any degree of confidence.

The EAG considers that if the severity modifier is to be applied on a tumour site-specific basis, QALY gains should be weighted according to the subgroup in which they are generated. The EAG does not consider it valid to approximate separate QALY weights by tumour site in analyses considering pooled efficacy data. The EAG therefore only explores the impact of applying separate QALY weights in the tumour site-specific response-based model (EAG base case 2). In all other analyses, a single severity modifier is applied according to mean QALY shortfall on SoC.

The EAG considers the SACT dataset to represent an appropriate distribution of tumour types and baseline characteristics from which to calculate the single SoC QALY shortfall (Table 45). The EAG's preferred approach to calculation of health state utilities is applied, i.e. non-reference case values are excluded. Across the alternative sources of SoC efficacy data, only when mean SoC QALYs derived from the naïve literature comparison approach are used *and* when baseline age and sex is based on SACT, is the threshold for a multiplier of 1.7 met.

**Table 45 Summary of EAG's preferred assumptions for general population QALY shortfall estimates**

| Factor                      | Value or source (reference to appropriate table or figure in submission)                       | Reference to section in submission or rationale |
|-----------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>EAG base case 1</b>      |                                                                                                |                                                 |
| Sex distribution (% female) | ePAS9 & SAS3 tumour-specific distribution                                                      | CS Table 41, Page 141                           |
| Starting age (years)        | ePAS9 & SAS3 tumour-specific distribution                                                      | CS Table 41, Page 141                           |
| Tumour type distribution    | SACT dataset                                                                                   | Table 46                                        |
| Expected years of life      | SoC arm (MAIC-adjusted) tumour-specific values                                                 | 4.2.5, 5.2.3                                    |
| Quality of life by age      | Age adjusted utilities                                                                         | 4.2.6.2                                         |
| Discount rate               | 3.5%                                                                                           | 4.2.2                                           |
| <b>EAG base case 2</b>      |                                                                                                |                                                 |
| Sex distribution (% female) | ePAS9 & SAS3 tumour-specific distribution                                                      | CS Table 41, Page 141                           |
| Starting age (years)        | ePAS9 & SAS3 tumour-specific distribution                                                      | CS Table 41, Page 141                           |
| Tumour type distribution    | SACT dataset                                                                                   | Table 46                                        |
| Expected years of life      | SoC arm (larotrectinib trial non-responders)                                                   | 4.2.5, 5.2.3                                    |
| Quality of life by age      | Age adjusted utilities                                                                         | 4.2.6.2                                         |
| Discount rate               | 3.5%                                                                                           | 4.2.2                                           |
| <b>EAG base case 3</b>      |                                                                                                |                                                 |
| Sex distribution (% female) | 43% (SACT)                                                                                     | SACT data on file                               |
| Starting age (years)        | 37.5 (SACT)                                                                                    | SACT data on file                               |
| Tumour type distribution    | SACT dataset                                                                                   | Table 46                                        |
| Expected years of life      | Naïve literature SoC arm weighted by SACT tumour types.                                        | 4.2.5, 5.2.3                                    |
| Quality of life by age      | Naïve literature SoC arm weighted by SACT tumour types. Non-reference case utilities excluded. | 4.2.6                                           |
| Discount rate               | 3.5%                                                                                           | 4.2.2                                           |

CS: Company Submission. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio. MAIC: Matching-Adjusted Indirect Comparison. SACT: Systemic Anti-Cancer Therapy data set. SoC: Standard of Care.

**Table 46 Weighted QALY shortfall by tumour site in alternative EAG scenarios**

| Tumour site                                                                                                             | Distribution           | Absolute QALY shortfall | Proportional QALY shortfall |
|-------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------|-----------------------------|
| All tumour sites share SACT baseline characteristics (age 37.5, 43% female), QALYs based on naïve literature comparison |                        |                         |                             |
| NSCLC                                                                                                                   | <div><div></div></div> | <div><div></div></div>  | <div><div></div></div>      |
| Salivary                                                                                                                | <div><div></div></div> |                         |                             |
| Colorectal                                                                                                              | <div><div></div></div> |                         |                             |
| STS adults (non-GIST)                                                                                                   | <div><div></div></div> |                         |                             |
| STS paediatric/IFS                                                                                                      | <div><div></div></div> |                         |                             |
| CNS/glioma                                                                                                              | <div><div></div></div> |                         |                             |
| Severity modifier                                                                                                       |                        | 1.7                     |                             |
|                                                                                                                         |                        |                         |                             |

| Tumour site                                                                                                                        | Distribution | Absolute QALY shortfall | Proportional QALY shortfall |
|------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------------------|-----------------------------|
| <b>SACT tumour site distribution, QALYs and tumour-specific age based on tumour-specific ORR responder model (EAG base case 2)</b> |              |                         |                             |
| NSCLC                                                                                                                              |              |                         |                             |
| Salivary                                                                                                                           |              |                         |                             |
| Colorectal                                                                                                                         |              |                         |                             |
| STS adults (non-GIST)                                                                                                              |              |                         |                             |
| STS paediatric/IFS                                                                                                                 |              |                         |                             |
| CNS/glioma                                                                                                                         |              |                         |                             |
| <b>Weighted QALY shortfall (laro trial baseline age/sex)</b>                                                                       |              |                         |                             |
| <b>Severity modifier</b>                                                                                                           |              | <b>1.2</b>              |                             |

CNS: Central Nervous System. GIST: Gastrointestinal stromal tumour. IFS: Infantile fibrosarcoma. NSCLC: Non-small cell lung cancer. QALY: Quality-adjusted life year. SACT: Systemic Anti-Cancer Therapy data set. STS: Soft tissue sarcoma.

A summary of the weighted QALY shortfall analyses along with implied QALY weighting in the company's base case, along with the three EAG base-case analyses is presented in Table 47 below. Using weighted absolute and proportional shortfall, all of the base case analyses meet the criteria for a QALY multiplier of 1.2. In the company's base case, an average severity weight of 1.60 is applied. In the EAG's BHM-based responder model, a weighted severity weight of 1.39 may be applicable.

**Table 47 Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting**

| Analysis               | Expected total QALYs for the general population | Expected total QALYs for people living with a condition on current treatment | Absolute QALY shortfall | Proportional QALY shortfall | Preferred QALY weight |       |
|------------------------|-------------------------------------------------|------------------------------------------------------------------------------|-------------------------|-----------------------------|-----------------------|-------|
| Company's base case    |                                                 |                                                                              |                         |                             | 1.2                   | 1.60* |
| EAG base case 1 (MAIC) |                                                 |                                                                              |                         |                             | 1.2                   |       |
| EAG base case 2 (BHM)  |                                                 |                                                                              |                         |                             | 1.2                   | 1.39* |
| EAG base case 3 (SACT) |                                                 |                                                                              |                         |                             | 1.2                   |       |

BHM: Bayesian Hierarchical Model. EAG: External Assessment Group. ICER: Incremental Cost-effectiveness Ratio.

MAIC: Matching-Adjusted Indirect Comparison. QALY: Quality-adjusted Life Year. SACT: Systemic Anti-Cancer Therapy data set

\* average QALY weighting when tumour-site specific severity modifiers applied

### 5.3.2 Uncaptured benefits

In Section 3.13 of the CS, the company highlights several benefits not directly captured in the QALY calculations, including the value of hope and reduced anxiety for emotional and psychological

wellbeing. Extended survival on larotrectinib may offer a bridge to future or alternative effective therapies, offering potential additional value beyond its immediate clinical benefit.

The company also highlights the advantage of larotrectinib as an oral treatment option, citing evidence that oncology patients prefer oral therapies over IV infusion for various reasons, including a reduced logistical and emotional burden of treatment, which may result in lower caregiver burden, which is particularly important when considering the paediatric population. The reduction in caregiver time requirements, stress, and potential income loss is not captured in the QALY framework but represents a meaningful benefit of larotrectinib. The company notes that any avoidance of chemotherapy toxicity can have lifetime benefits for paediatric patients, in whom chemotherapy and radiotherapy can impact growth, cognitive development, and organ function. The company concludes that their base-case ICER is thus a conservative estimate of the cost-effectiveness of larotrectinib.

### ***Points for critique***

The EAG notes the importance to patients of hope and option value, but considers these benefits to be subjective, and likely only to persist up to the point a patient initiates the drug itself. Such benefits are difficult to quantify and are outside the NICE reference case.

The impact of an oral therapy with a lower toxicity burden than the comparators on caregivers and family members could be represent an important uncaptured benefit; however, the company have not presented any quantitative evidence to show that larotrectinib is associated with a substantial effect on carers HRQoL.

The EAG notes that the impact of larotrectinib as a bridge to alternative effective therapies is already more than captured in the trial evidence, where many more patients than is seen in NHS practice received further lines of systemic therapies, surgery, and radiotherapy. The EAG therefore does not consider this to be an uncaptured benefit, indeed, the company's base case may overstate such benefits. The EAG also notes that the model includes a substantial increment associated with larotrectinib over SoC, well beyond that represented by the health state alone. This benefit persists for as long as patients remain free from progression and can be seen to represent in part the benefits of avoidance of chemotherapy. The EAG considers the benefits of larotrectinib over SoC beyond PFS and OS to be sufficiently captured in the model in this respect.

### **5.3.3 Health inequalities**

In CS Section 1.4, the company states that there may be inequalities which result from restricted access to TRK inhibitors in the NHS but provides no quantitative evidence that the availability of larotrectinib itself affects health inequalities. The company notes that regional variation in access to



NTRK testing may introduce health inequalities on the basis of a Sarcoma UK report, which highlights general equalities issues with access to genomic testing services.

The company also states that if larotrectinib were not made available in routine commissioning, access would depend on self-funding or through private healthcare, which would introduce socio-economic inequalities.

As no robust quantitative or qualitative evidence on the impact of larotrectinib upon health inequalities has been provided, the EAG does not consider larotrectinib to meaningfully address inequality or unfairness in the distribution of health across society.

#### ***5.4 Confidential comparator and subsequent treatment prices***

The confidential appendix to the EAR includes analyses using confidential pricing arrangements for lenvatinib, lomustine, nintedanib, pembrolizumab, regorafenib, trabectedin, and trifluridine and tipiracil hydrochloride.

The confidential appendix presents the results of the company base-case analysis, sensitivity and scenario analyses and the results of exploratory analyses conducted by the EAG, with results reflecting the application of confidential pricing arrangements. The prices applied in these analyses are correct as of 22<sup>nd</sup> October 2025.

#### ***5.5 Conclusions of the cost-effectiveness section***

The company submitted a partitioned survival model to evaluate the cost-effectiveness of larotrectinib across multiple tumour sites harbouring an NTRK gene fusion on the basis of data collected in the larotrectinib trials. The EAG considers the overall model structure to be consistent with that used in TA630 but notes that the general modelling approach remains subject to uncertainty. While data collected during the managed access period offers some clarity about the relevance of the trial to the NHS and long-term outcomes on larotrectinib, many of the key uncertainties identified in TA630 remain unresolved. As a result, the cost-effectiveness results remain subject to substantial structural, clinical, and methodological uncertainty.

A central concern is the assumption of a site-agnostic treatment effect, which is fundamental to the relevance of the trial evidence to the NHS setting. The company's model applies a single pooled treatment effect for larotrectinib across adult and paediatric patients to generate a single aggregated ICER despite clear evidence of heterogeneity in response rates, prognosis, and natural history between tumour sites. In particular, patients with primary CNS tumours, who represent the largest group in the SACT dataset, demonstrate markedly lower response rates than other tumour sites, while paediatric patients with STS/IFS appear to experience substantially more favourable outcomes. Combining these

populations obscures clinically meaningful differences and risks inflating the apparent cost-effectiveness of larotrectinib. The EAG therefore considers a single pooled ICER to be uninformative for decision-making unless disaggregated results demonstrate broad cost-effectiveness.

A further key issue is the lack of applicability of the modelled population to NHS practice. The company's analyses reflect the tumour-site distribution and baseline characteristics of the larotrectinib trials, which differ significantly from patients treated in the NHS. The EAG therefore conducted analyses using SACT-derived population characteristics, which led to higher ICERs for larotrectinib. This issue propagates through multiple components of the model, including survival extrapolations, comparator selection, health-related quality of life, and severity shortfall calculations. The EAG's implementation of SACT outcome data directly in the economic model demonstrated reduced QALY gain relative to the trial-based analysis.

There is also considerable uncertainty in the estimation of treatment effects. The company's preferred analyses rely on unanchored MAICs (VICTORIA for adults and EPI-VITRAKVI for paediatrics) and assume proportional hazards holds despite the use of population-adjustment methods and heterogeneous tumour types. Alternative naïve literature-based comparisons also have important limitations. The most internally valid comparison with any degree of applicability to NHS practice may therefore be generated using a response-based modelling approach. As a result, the magnitude and durability of any overall survival benefit relative to SoC remain highly uncertain.

Survival extrapolation further compounds this uncertainty. OS and PFS are extrapolated from pooled datasets despite limited follow-up and marked heterogeneity between tumour groups. In the paediatric population, the company's base-case extrapolations imply very long-term, cure-like survival for a large proportion of patients with progressed disease, generating significant QALY gains which have a large influence on QALY gain in the overall population, despite the clinical implausibility of such outcomes. Conversely, outcomes for adult patients with primary CNS tumours may be optimistic relative to available NHS-relevant data.

To better reflect heterogeneity in treatment response, the EAG explored a response-based model structure linking tumour-specific predicted response rates from a Bayesian Hierarchical Model to survival outcomes. This approach avoids the strong and unverifiable assumptions underpinning the unanchored MAICs and reduces the reliance on a pooled response rate that masks clinically important between-site variation. It also allows the reweighting of trial outcomes to better reflect the distribution of tumour types observed in the SACT dataset. This analysis produced materially higher ICERs than the company's base case.

The EAG also identified concerns regarding the choice of comparators, which vary substantially across tumour types and may not reflect real world NHS practice for the line of therapy at which larotrectinib is currently used. The model does not reflect differences in subsequent lines of active treatment, despite high use observed in ePAS9 and SAS3 relative to the SACT dataset, nor does it account for differences in resource use and HRQoL across certain tumour sites (particularly paediatric and adult). Paediatric comparators are particularly uncertain, as the MAIC analyses in many respects are restricted to STS and IFS patients, and thus do not represent the full paediatric population treated in NHS practice.

There is substantial uncertainty in the HRQoL inputs. The utilities used for larotrectinib imply minimal HRQoL loss following disease progression and remain high relative to both published evidence on TRK inhibitors and the utilities applied for SoC. These values are unlikely to be representative of NHS practice and likely reflect the extensive use of subsequent active treatments in the larotrectinib trial population. In contrast, comparator utilities are drawn from heterogeneous and in some cases outdated sources and include non-reference-case valuation methods and may underestimate HRQoL on the standard of care. These assumptions have a significant impact on incremental QALYs and are likely to bias the results in favour of larotrectinib.

The application of the severity modifier in the company's model was also inconsistent with NICE preferences. Severity multipliers were applied to total QALYs rather than incremental QALYs and separate modifiers were calculated and applied by tumour site rather than through the use of weighted QALY shortfall, resulting in an effective mean QALY weight of 1.60, despite no means of determining the provenance of QALY gain by tumour site in the company's model structure. The EAG found that a single severity modifier of 1.2 was appropriate across its preferred analyses but presents results on the tumour site-specific response-based model using individually calculated severity modifiers.

In addition, the EAG identified technical issues with the PSA, where Excel's recalculation behaviour resulted in identical parameter draws across iterations. Although a workaround was implemented, only a limited number of PSA iterations could feasibly be run, and the PSA results should be interpreted with caution.

Other secondary issues include uncertainty regarding subsequent treatment assumptions, comparator alignment, and lack of robust paediatric SoC evidence. While these issues individually have smaller effects, they contribute to uncertainty in the cost-effectiveness estimates.

After addressing errors and applying its preferred assumptions, the EAG's cost-effectiveness estimates are substantially higher than those reported by the company. Overall, the EAG concludes

that the company's base-case results are not a reliable basis for decision making. The EAG's preferred approaches allow a choice between a more internally consistent comparison or a more applicable estimate of effectiveness, as no single modelling approach presently available can offer a robust combined estimate of both effectiveness and comparative cost effectiveness for larotrectinib that are applicable to NHS practice.

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# APPENDICES

## APPENDIX 1. BASELINE CHARACTERISTICS OF PARTICIPANTS IN OBSERVATIONAL STUDIES

Table 48 Baseline characteristics of the four observational studies included in the company submission

| Characteristic                                                                         | Categories                                                   | SACT 2025 (n=60) | ON-TRK [SAF, non-CNS, n=■] | ON-TRK [SAF, CNS, n=■] | LAROTRACKING [N=26] | SACHA [n=■] |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------|------------------|----------------------------|------------------------|---------------------|-------------|
| Sex                                                                                    | Female                                                       | 43%              | ■                          | ■                      | 69.2%               | ■           |
| Age (yrs)                                                                              | 0 to <20 for SACT [0 to <18 for trials and ON-TRK]           | 37%              | ■                          | ■                      | -                   | ■           |
|                                                                                        | 20 to <50 for SACT [18 to 45 for trials, and ≥18 for ON-TRK] | 28%              | ■                          | ■                      | -                   | ■           |
|                                                                                        | ≥50 for SACT [≥45 for trials]                                | 35%              |                            |                        | -                   | ■           |
|                                                                                        | Median age                                                   | -                | ■                          | ■                      | 56.6                | ■           |
| ECOG Performance status at baseline [Performance status not specified as ECOG in SACT] | Performance status 0                                         | 39.3%*           | ■                          | ■                      | 33.3%*              | -           |
|                                                                                        | Performance status 1                                         | 50%*             | ■                          | ■                      | 50%*                | -           |
|                                                                                        | Performance status 2                                         | 10.7%*           | ■                          | ■                      | 16.7%*              | -           |
|                                                                                        | Performance status 3                                         | 0                | ■                          | ■                      | 0                   | -           |
|                                                                                        | Performance status 4                                         | 0                | ■                          | ■                      | 0                   | -           |
| Tumour types                                                                           | Primary brain tumour                                         | 25%*             | -                          | ■                      | 11.5%               | ■           |
|                                                                                        | Primary CNS tumour                                           | 5%*              |                            |                        |                     |             |
|                                                                                        | Sarcoma (STS)                                                | 20%*             | ■                          | ■                      | 0                   | ■           |
|                                                                                        | Infantile fibrosarcoma                                       | 7%*              | ■                          | ■                      | 0                   | ■           |
|                                                                                        | Lung adenocarcinoma                                          | 7%*              | ■                          | ■                      | 15.4%               | ■           |
|                                                                                        | Non-squamous NSCLC                                           | 7%*              |                            |                        |                     | ■           |
|                                                                                        | Lung (other)                                                 | 3%*              |                            |                        |                     | ■           |
|                                                                                        | Thyroid                                                      | 5%*              | ■                          | ■                      | 7.7% (anaplastic)   | ■           |
|                                                                                        | Papillary thyroid carcinoma                                  | 3%*              |                            |                        | 30.8%               | ■           |
|                                                                                        | Glioma                                                       | 5%*              | ■                          | ■                      | 0                   | ■           |
|                                                                                        | Colorectal                                                   | 3%*              | ■                          | ■                      | 0                   | ■           |
|                                                                                        | Forearm spindle cell sarcoma                                 | 2%*              | ■                          | ■                      | 0                   | ■           |
|                                                                                        | Head adenocarcinoma                                          | 2%*              | ■                          | ■                      | 0                   | ■           |

| Characteristic                   | Categories                                                      | SACT<br>2025<br>(n=60) | ON-<br>TRK<br>[SAF,<br>non-<br>CNS,<br>n=■] | ON-<br>TRK<br>[SAF,<br>CNS,<br>n=■] | LAROTRACKING<br>[N=26] | SACHA<br>[n=■] |
|----------------------------------|-----------------------------------------------------------------|------------------------|---------------------------------------------|-------------------------------------|------------------------|----------------|
|                                  | Oesophagus                                                      | 2%*                    | ■                                           | ■                                   | 0                      | ■              |
|                                  | Salivary gland carcinoma                                        | 2%*                    | ■                                           | ■                                   | 0                      | ■              |
|                                  | Salivary gland adenocarcinoma                                   | 2%*                    | ■                                           | ■                                   | 3.8%                   | ■              |
|                                  | Breast                                                          | 0                      | ■                                           | ■                                   | 7.7%                   | ■              |
|                                  | Melanoma                                                        | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Pancreas                                                        | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | GIST                                                            | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Cholangiocarcinoma                                              | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Bone sarcoma                                                    | 0                      |                                             |                                     |                        |                |
|                                  | Gastric                                                         | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Cervix                                                          | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | CMN                                                             | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Prostate                                                        | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Appendix                                                        | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Duodenal                                                        | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | External auditory canal                                         | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Hepatic                                                         | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Head and Neck                                                   | 0                      | ■                                           | ■                                   | 0                      | ■              |
|                                  | Ankle                                                           | 0                      | ■                                           | ■                                   | 3.8%                   | ■              |
|                                  | Parotid                                                         | 0                      | ■                                           | ■                                   | 11.5%                  | ■              |
|                                  | Caecum                                                          | 0                      | ■                                           | ■                                   | 3.8%                   | ■              |
|                                  | Cancer of unknown primary                                       | 0                      | ■                                           | ■                                   | 3.8%                   | ■              |
|                                  | Other                                                           | -                      | ■                                           | ■                                   | -                      | ■              |
| Type of disease)                 | Metastatic disease                                              | 41%*                   | ■                                           | ■                                   | 42.3%                  | ■              |
|                                  | Locally advanced with systemic therapy                          | 31%*                   |                                             |                                     | 57.7%                  | ■              |
|                                  | Locally advanced with surgical resection resulting in morbidity | 29%*                   |                                             |                                     |                        |                |
| Priori lines of systemic therapy | 0 (larotrectinib 1 <sup>st</sup> line)                          | 2%*                    | ■                                           |                                     | 23.1%                  | 23.1%          |
|                                  | 1                                                               | 80%*                   | ■                                           |                                     |                        | 76.9%          |

| Characteristic               | Categories                                            | SACT<br>2025<br>(n=60)             | ON-<br>TRK<br>[SAF,<br>non-<br>CNS,<br>n=■] | ON-<br>TRK<br>[SAF,<br>CNS,<br>n=■] | LAROTRACKING<br>[N=26]                                            | SACHA<br>[n=■]                                           |
|------------------------------|-------------------------------------------------------|------------------------------------|---------------------------------------------|-------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------|
|                              | 2                                                     | 8%*                                | ■                                           |                                     | 76.9%                                                             |                                                          |
|                              | ≥3                                                    | 10%*                               | ■                                           |                                     |                                                                   |                                                          |
|                              | Median lines                                          | -                                  | -                                           | -                                   | -                                                                 | ■                                                        |
|                              | Previous<br>Larotrectinib                             | -                                  | -                                           | -                                   | -                                                                 | ■                                                        |
| NTRK gene                    | NTRK1                                                 | 37%*                               | ■                                           | ■                                   | 46.2%                                                             | ■                                                        |
|                              | NTRK2                                                 | 31%*                               | ■                                           | ■                                   | 7.7%                                                              | ■                                                        |
|                              | NTRK3                                                 | 32%*                               | ■                                           | ■                                   | 46.2%                                                             | ■                                                        |
|                              | NTRK negative                                         | 0                                  | ■                                           | ■                                   | 0                                                                 | ■                                                        |
|                              | NTRK3<br>amplification                                | -                                  | -                                           | -                                   | -                                                                 | ■                                                        |
|                              | NTRK testing<br>method                                | Nucleic-<br>acid<br>based<br>assay | NR                                          | NR                                  | RNA-based<br>sequencing (n=20),<br>‘various<br>technologies’(n=6) | One<br>participant<br>diagnosed<br>by FISH,<br>others NR |
| Brain metastases             | None                                                  | 86%*                               | -                                           | -                                   | -                                                                 | -                                                        |
|                              | Brain metastases<br>with previous<br>cerebral surgery | 10%*                               | -                                           | -                                   | -                                                                 | -                                                        |
|                              | Brain metastases and<br>no cerebral surgery           | 3%*                                | -                                           | -                                   | -                                                                 | -                                                        |
| Race                         | White                                                 | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Asian                                                 | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Black or African<br>American                          | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | American Indian or<br>Alaska Native                   | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Native Hawaiian or<br>Pacific Islander                | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Multiple                                              | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Other                                                 | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
| Anthropometric               | Median body weight<br>kg                              | -                                  | ■                                           | ■                                   | -                                                                 | -                                                        |
|                              | Median height cm                                      | -                                  | -                                           | -                                   | -                                                                 | -                                                        |
|                              | BMI                                                   | -                                  | -                                           | -                                   | -                                                                 | -                                                        |
| Time from<br>diagnosis       | median (yrs)                                          | -                                  | -                                           | -                                   | -                                                                 | -                                                        |
| Tumour stage at<br>diagnosis | 0                                                     | -                                  | -                                           | -                                   | 4.2%                                                              | -                                                        |
|                              | I                                                     | -                                  | -                                           | -                                   | 4.2%                                                              | -                                                        |
|                              | II                                                    | -                                  | -                                           | -                                   | 8.3%                                                              | -                                                        |
|                              | III                                                   | -                                  | ■                                           | ■                                   | 41.7%                                                             | -                                                        |
|                              | IV                                                    | -                                  | ■                                           | ■                                   | 25%                                                               | -                                                        |

| Characteristic | Categories | SACT<br>2025<br>(n=60) | ON-<br>TRK<br>[SAF,<br>non-<br>CNS,<br>n=■] | ON-<br>TRK<br>[SAF,<br>CNS,<br>n=■] | LAROTRACKING<br>[N=26] | SACHA<br>[n=■] |
|----------------|------------|------------------------|---------------------------------------------|-------------------------------------|------------------------|----------------|
|                | NA         | -                      | -                                           | -                                   | 7.7%                   | -              |
|                | Tx         | -                      | ■                                           | ■                                   | 16.7%                  | -              |

Sources: Based on CS Tables 6, 25 and 28, Appendix N page 31, and the SACT,<sup>3</sup> ON-TRK,<sup>30</sup> Larotracking<sup>31</sup> and SACHA<sup>32</sup>) observational studies.

BMI: Body Mass Index. CNS: Central Nervous System. CMN: Congenital Mesoblastic Nephroma. ECOG: Eastern Cooperative Oncology Group. ePAS9: extended primary analysis set 9. GIST: Gastrointestinal Stromal Tumour. NA: Not applicable. NE: Not Estimable. NSCLC: Non-Small Cell Cancer. NR: Not Reported. NTRK: Neurotrophic Tyrosine Receptor Kinase. ON-TRK: Prospective non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib. SACHA: SACHAxLaro study. SACT: Systemic Anti-Cancer Therapy. SAF: Safety Analysis Set. SAS3: supplementary analysis set 3. STS: soft tissue sarcoma. Tx: stage cannot be assessed.

\*Where missing data were present across a set of categories, the percentage per category was adjusted by reducing the denominator by the number of missing participants. Therefore some values in this table may differ from those in the submission..

\*\* NR has been used rather than 0 for the ON-TRK NON-CNS tumour and SACHA data, as a proportion of tumours were described as 'other' and thus could truly belong in any of the other categories where there are no recorded data.

\*\*\*Not including IFS

## APPENDIX 2. BASELINE CHARACTERISTICS OF PARTICIPANTS INCLUDED IN THE INDIRECT TREATMENT COMPARISONS

**Table 49 Demographic and disease characteristics with and without weighting, VICTORIA MAIC**

|                           | Unweighted (without stabilised IPTW) |                   | Weighted (with stabilised IPTW) |                   |
|---------------------------|--------------------------------------|-------------------|---------------------------------|-------------------|
|                           | Larotrectinib<br>(n=82)              | Comparator (n=82) | Larotrectinib<br>(n=82)         | Comparator (n=82) |
| Age, years, mean (SD)     | 52.7 (17.2)                          | 58.7 (12.2)       | 56.3 (16.8)                     | 56.9 (12.1)       |
| Female, %                 | 52                                   | 54                | 52                              | 52                |
| Metastatic, %             | 93                                   | 79                | 87                              | 86                |
| ECOG PS 0-1 %             | 87                                   | 77                | 85                              | 83                |
| ECOG PS 2-3 %             | 13                                   | 23                | 15                              | 17                |
| <b>Prior LOT, n (%)</b>   |                                      |                   |                                 |                   |
| 0                         | 39 (48)                              | 39 (48)           | -                               | -                 |
| 1                         | 20 (24)                              | 20 (24)           | -                               | -                 |
| 2                         | 19 (23)                              | 19 (23)           | -                               | -                 |
| 3                         | 4 (5)                                | 4 (5)             | -                               | -                 |
| <b>Tumour type, n (%)</b> |                                      |                   |                                 |                   |
| CRC                       | 17 (21)                              | 17 (21)           | -                               | -                 |
| NSCLC                     | 15 (18)                              | 15 (18)           | -                               | -                 |
| Salivary gland            | 15 (18)                              | 15 (18)           | -                               | -                 |
| STS                       | 23 (28)                              | 23 (28)           | -                               | -                 |
| Thyroid                   | 12 (15)                              | 12 (15)           | -                               | -                 |

Sources: Brose (2025)<sup>50</sup> Tables 1 and 2.

CRC: Colorectal Cancer. ECOG: Eastern Cooperative Oncology Group. LOT: Line Of Therapy. NSCLC: Non-Small Cell Lung Cancer. IPTW: Inverse Probability Of Treatment Weighting. PS: Performance Status. SD: Standard Deviation. STS: Soft Tissue Sarcoma.

**Table 50 Demographic and disease characteristics without and without weighting, FLATIRON**

|                       | Unweighted        |                      | Weighted          |                              |
|-----------------------|-------------------|----------------------|-------------------|------------------------------|
|                       | Comparator (n=28) | Larotrectinib (n=85) | Comparator (n=28) | Larotrectinib (ESS: n=13.14) |
| Age ≥ 65 years, %     | 39.3              | 29.4                 | 39.3              | 39.3                         |
| NTRK1                 | 82.0              | 42.4                 | 82.0              | 82.0                         |
| Brain metastases, %   | 17.9              | 9.4                  | 17.9              | 17.9                         |
| ECOG PS 0-1, %        | 50.0              | 87.1                 | 50.0              | 50.0                         |
| ECOG PS 2-4, %        | 7.1               | 12.9                 | 50.0*             | 50.0                         |
| <b>Prior LOT, %</b>   |                   |                      |                   |                              |
| 0-2                   | 71.4              | 77.7                 | 71.4              | 71.4                         |
| ≥3                    | 10.7              | 22.4                 | 28.6*             | 28.6                         |
| Unknown               | 17.9              | -                    | 17.9              | -                            |
| <b>Tumour type, %</b> |                   |                      |                   |                              |
| CRC                   | 32.0              | 5.9                  | 32.0              | 32.0                         |
| STS                   | 21.0              | 22.4                 | 21.0              | 21.0                         |
| NSCLC                 | 18.0              | 12.9                 | 18.0              | 18.0                         |
| Salivary gland        | 7.0               | 21.2                 | 7.0               | 7.0                          |
| Breast                | 4.0               | 1.2                  | 4.0               | 4.0                          |
| CUP                   | 4.0               | 1.2                  | 4.0               | 4.0                          |
| Endometrial           | 4.0               | NA                   | 4.0               | -                            |
| Stomach               | 4.0               | NA                   | 4.0               | -                            |
| Biliary               | 4.0               | NA                   | 4.0               | -                            |
| Uterine               | 4.0               | NA                   | 4.0               | -                            |

Source: Bokemeyer (2023) <sup>51</sup> Table 2

CRC: Colorectal Cancer. CUP: Cancer with Unknown Primary. ECOG: Eastern Cooperative Oncology Group. ESS: Effective Sample Size. LOT: Line Of Therapy. NSCLC: Non-Small Cell Lung Cancer. NTRK: Neurotrophic Tyrosine Receptor Kinase. PS: Performance Status. STS: Soft Tissue Sarcoma.

\*Imputed in the MAIC

**Table 51 Demographic and disease characteristics without and without weighting, EPI VITRAKVI**

|                                  | Unweighted (without IPTW) |                   |
|----------------------------------|---------------------------|-------------------|
|                                  | Larotrectinib (n=51)      | Comparator (n=42) |
| Age, years, mean (SD)            | 2.01 (3.49)               | 0.73 (1.81)       |
| Female, %                        | 41.2                      | 35.7              |
| Metastatic, %                    | 19.6                      | 7.1               |
| <b>Prior systemic therapy, %</b> |                           |                   |
| 0                                | 37.3                      | 100               |
| 1-2                              | 51.0                      | 0                 |

|                                                                                          |           |           |
|------------------------------------------------------------------------------------------|-----------|-----------|
| ≥3                                                                                       | 11.8      | 0         |
| Time from locally advanced/metastatic disease diagnosis to index date, mean (SD), months | 5.1 (8.6) | 0.7 (1.4) |
| Primary tumour location (%)                                                              |           |           |
| Limbs                                                                                    | 54.9      | 69.0      |
| Non-parameningeal head and neck                                                          | 17.6      | 2.4       |
| Thoracic                                                                                 | 9.8       | 9.5       |
| Abdomen/pelvis                                                                           | 3.9       | 14.3      |
| Orbit                                                                                    | 5.9       | 2.4       |
| Kidney                                                                                   | 3.9       | 2.4       |
| Paraspinal                                                                               | 3.9       | 0         |

Source: Orbach (2024) <sup>54</sup> Table 1  
IPTW: Inverse Probability of Treatment Weighting. SD: Standard Deviation

### APPENDIX 3. EAG'S SURVIVAL ANALYSIS OF SACT AND BROSE *ET AL*

#### Overview

As part of the EAG's additional work, parametric survival models were fitted to pseudo-IPD from two sources of non-trial evidence:

- SACT (Systemic Anti-Cancer Therapy) dataset <sup>3</sup>: representing real-world outcomes for NHS patients treated with larotrectinib during its availability in the CDF.
- Brose et al. (2025) <sup>50</sup> VICTORIA dataset: representing real-world outcomes in a broader international context, with different tumour-type composition and patient characteristics.

Digitised Kaplan–Meier (KM) data representing treatment duration (as a proxy for PFS) and OS from SACT, and PFS and OS from Brose *et al.* were reconstructed using the Guyot algorithm. Six standard parametric functions were fitted to e: exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. Model selection was based on AIC/BIC goodness-of-fit statistics and visual fit of each curve, including an assessment of the clinical plausibility of alternative extrapolations.

#### SACT OS

The SACT population reflects NHS-treated patients, incorporating real-world prior therapy patterns (average 1.27 lines), real-world tumour-type distribution, and reflects NHS-relevant subsequent treatment use.

Parametric models were fitted to reconstructed KM data. AIC/BIC results are summarised in Table 52. Figure 8 compares the relative visual fits of each extrapolation to the observed data.



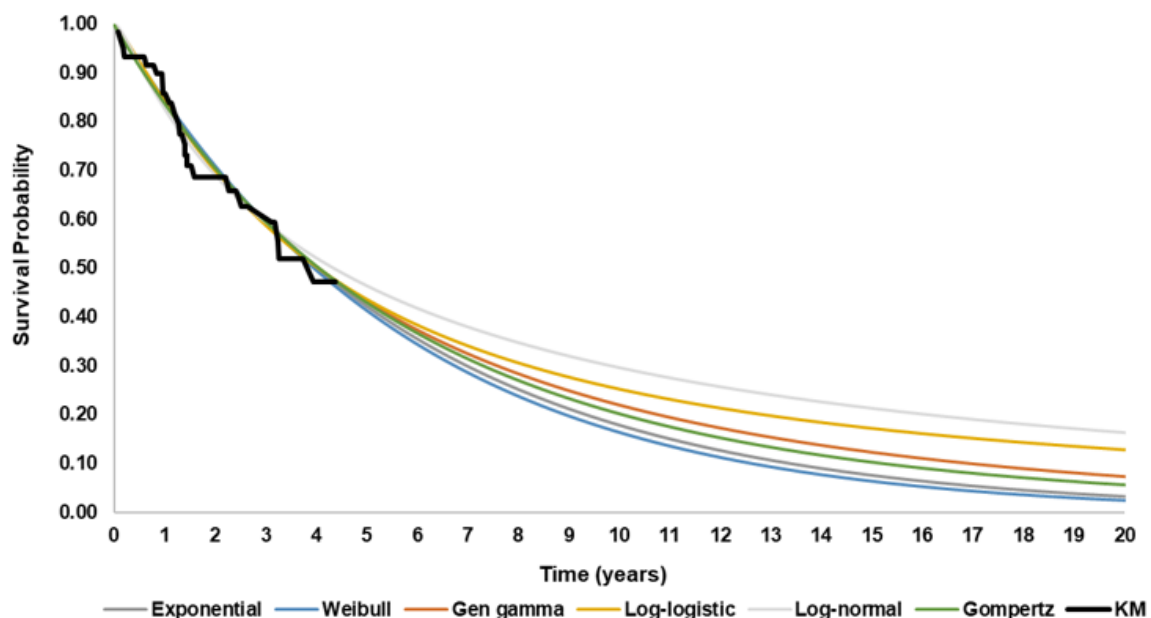
The exponential model provided the best statistical fit (lowest AIC and BIC) and was selected for use in EAG base case 3. Visual inspection indicated that all models captured the early portion of the KM curve adequately, with only limited divergence becoming more evident in the extrapolated tail. This is indicative of a relatively constant hazard rate in the observed period. Whilst the exponential distribution represents the second-most pessimistic extrapolation, the selection of parametric function is not a significant driver of cost-effectiveness in this analysis due to the relative agreement of the alternative extrapolations.

**Table 52 AIC and BIC for parametric models fitted to SACT OS**

| Model             | AIC     | AIC ranking | BIC     | BIC ranking |
|-------------------|---------|-------------|---------|-------------|
| Exponential       | 232.653 | 1           | 234.747 | 1           |
| Generalised gamma | 234.358 | 2           | 238.547 | 2           |
| Weibull           | 234.617 | 3           | 238.806 | 3           |
| Log-normal        | 234.639 | 4           | 238.827 | 4           |
| Log-logistic      | 234.899 | 5           | 239.088 | 5           |
| Gompertz          | 236.411 | 6           | 242.694 | 6           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion

**Figure 8 Parametric extrapolations of SACT OS**



### SACT TTD survival analysis

Table 53 summarises the statistical fit of each distribution to the SACT time to treatment discontinuation (TTD) dataset. Figure 9 compares the visual fits of each extrapolation to the observed data. There was good agreement between the parametric models in terms of statistical fit, and

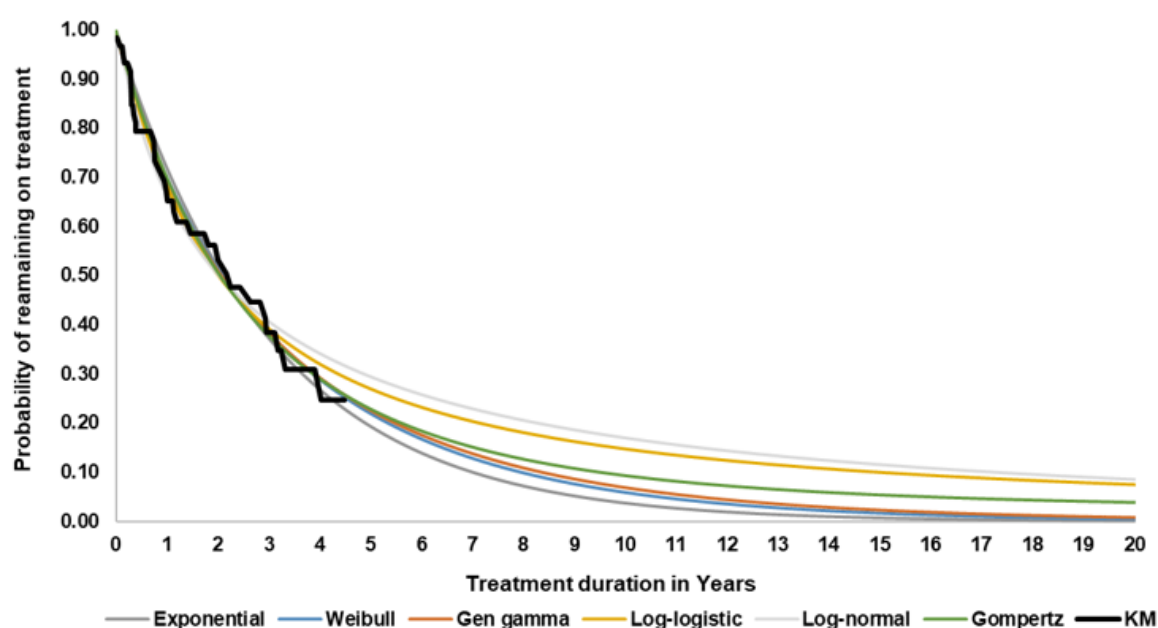
exponential again provided the best statistical fit and was selected for use in EAG base case 3. Whilst this represents the most pessimistic of the fitted curves, the larotrectinib trial data indicated that a reasonable proportion of patients continued treatment beyond progression. As TTD here is used as a proxy for PFS, it may be reasonable to adopt an extrapolation with a higher hazard rate, with the caveat that this may underestimate real-world treatment costs.

**Table 53 AIC and BIC for parametric models fitted to SACT TTD**

| Model             | AIC    | AIC ranking | BIC    | BIC ranking |
|-------------------|--------|-------------|--------|-------------|
| Exponential       | 232.65 | 1           | 234.75 | 1           |
| Log-logistic      | 234.36 | 2           | 238.55 | 2           |
| Weibull           | 234.62 | 3           | 238.81 | 3           |
| Gompertz          | 234.64 | 4           | 238.83 | 4           |
| Log-normal        | 234.90 | 5           | 239.09 | 5           |
| Generalised gamma | 236.41 | 6           | 242.69 | 6           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion

**Figure 9 Parametric extrapolations of SACT TTD**



### Brose et al. OS

Brose et al. (2025) provides an externally validated real-world evidence source for an NTRK fusion-positive solid tumour population, also used by the company in the VICTORIA MAIC.

The exponential distribution again provided the best statistical fit, and the exponential and Weibull curves overlapped almost completely. Divergent long-term extrapolations indicated moderate

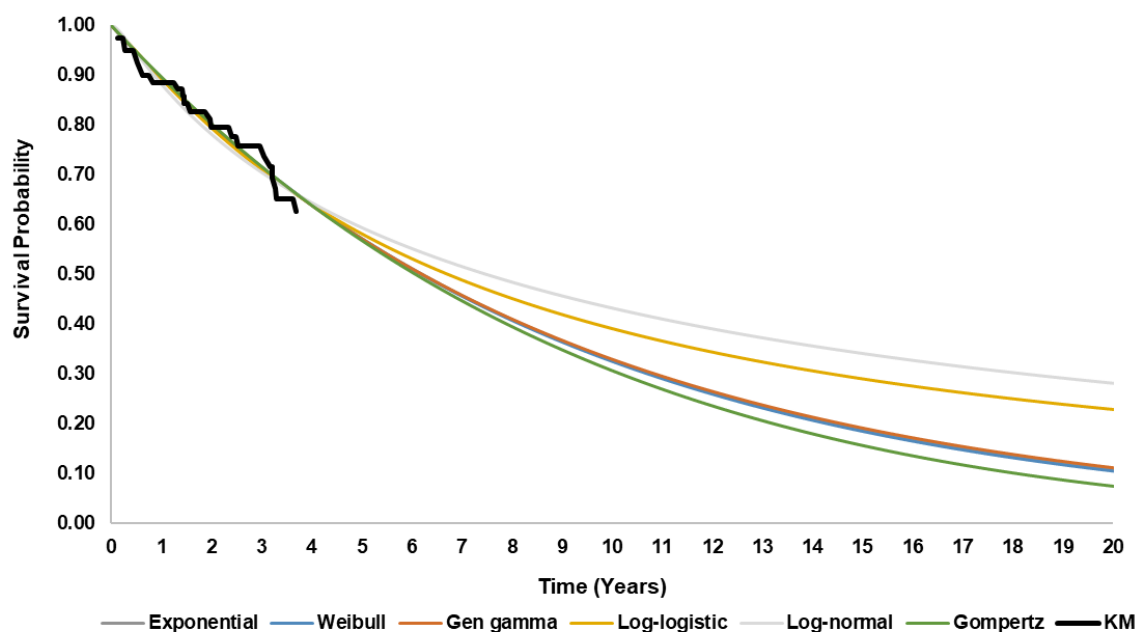
uncertainty arising from the relative immaturity of this dataset, though the four non-log-scale accelerated failure time models make highly consistent predictions of long-term survival. The exponential distribution was selected for the above reasons and for consistency with the selected functional form applied for OS in the SACT dataset. Table 54 provides a comparison of statistical fit, and Figure 10 compares the visual fits of each extrapolation to the observed data.

**Table 54 AIC and BIC for parametric models fitted to Brose et al OS**

| Model             | AIC    | AIC ranking | BIC    | BIC ranking |
|-------------------|--------|-------------|--------|-------------|
| Exponential       | 285.86 | 1           | 288.27 | 1           |
| Gompertz          | 287.84 | 2           | 292.66 | 2           |
| Weibull           | 287.86 | 3           | 292.67 | 3           |
| Log-logistic      | 288.15 | 4           | 292.96 | 4           |
| Log-normal        | 288.33 | 5           | 293.14 | 5           |
| Generalised Gamma | 289.86 | 6           | 297.08 | 6           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion

**Figure 10 Parametric extrapolations of Brose et al OS**



### Brose et al. PFS

The log-normal model provided the best statistical fit to PFS on SoC in Brose et al. Visual inspection of extrapolated curves showed notable divergence between lighter-tailed (e.g. Weibull) and heavier-tailed (e.g. log-normal, log-logistic) distributions, which has implications for long-term survival

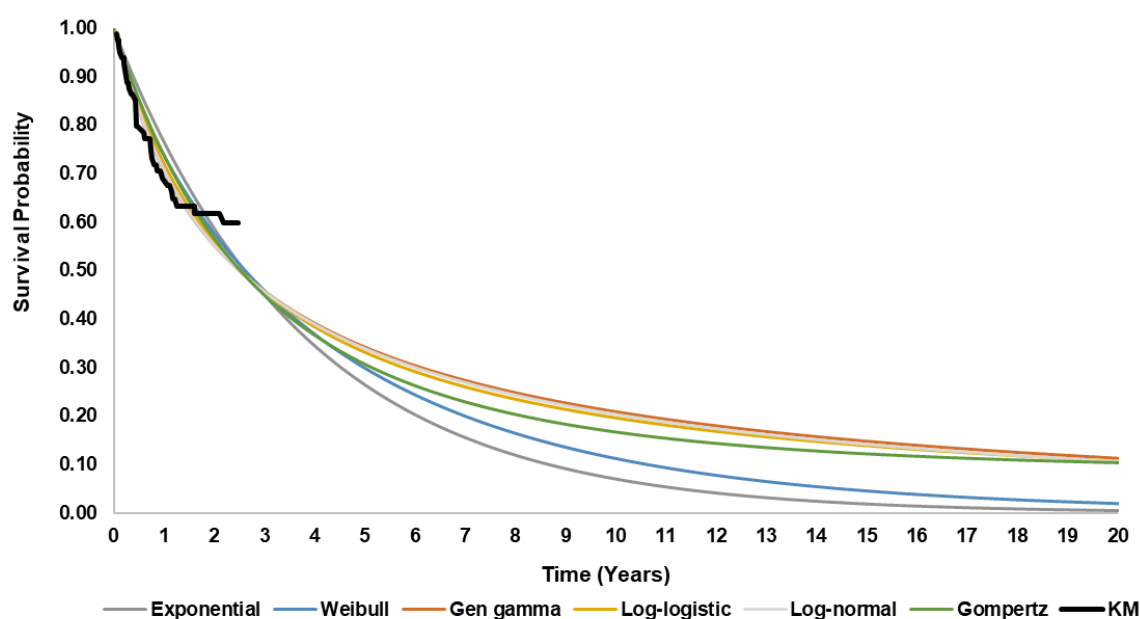
estimates. For consistency with assumptions around the functional form of PFS in the other analyses, the exponential distribution was again selected for use in the scenario on EAG base case 3. Table 55 provides a comparison of statistical fit, and Figure 11 compares the visual fits of each extrapolation to the observed data.

**Table 55 AIC and BIC for parametric models fitted to Brose et al PFS**

| Model             | AIC    | AIC ranking | BIC    | BIC ranking |
|-------------------|--------|-------------|--------|-------------|
| Log-normal        | 395.33 | 1           | 400.14 | 1           |
| Exponential       | 396.48 | 2           | 398.89 | 2           |
| Log-logistic      | 397.02 | 3           | 401.84 | 3           |
| Weibull           | 397.08 | 4           | 401.89 | 4           |
| Generalised Gamma | 397.32 | 5           | 404.54 | 6           |
| Gompertz          | 397.51 | 6           | 402.32 | 5           |

AIC= Akaike's information criterion; BIC= Bayesian information criterion

**Figure 11 Parametric extrapolations of Brose et al PFS**



## Single Technology Appraisal

### Larotrectinib for treating NTRK fusion-positive advanced solid tumours (MA review of TA630) [ID6292]

#### EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 7 January 2026** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

## Issue 1 Incorrect proportion of trial population who received subsequent therapies

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Description of proposed amendment                                                                                                                                                                                                                                                                         | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | EAG Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Section 1.3, Page 17 and Section 3.6, Page 91</p> <p>The EAG stated that <i>“Post-progression outcomes are uncertain due to lack of maturity and there is potential confounding due to high rates of subsequent therapy use in the trial.”</i></p> <p>Section 3.2.4, Page 65</p> <p>The EAG stated that <i>“Firstly, the relatively high rates of subsequent therapies further support the EAG’s view that the ePAS9 and SAS3 populations have limited applicability to NHS practice, where patients receive larotrectinib where no other satisfactory treatment option is available, and would not be eligible for subsequent NTRK inhibitor treatment.”</i></p> <p>Section 4.2.5, Page 112</p> <p>The EAG stated that <i>“it appeared that up to █████ adult patients in ePAS9 received further systemic therapy (i.e. there were █████ initiations</i></p> | <p>“High rates” should not be used to describe the proportion of patients in the larotrectinib trials who received subsequent therapies.</p> <p>“In ePAS9, a total of █████ patients (████) started a subsequent therapy, and in SAS3 a total of █████ patients (████) started a subsequent therapy.”</p> | <p>It was mentioned in the Company’s response to CQ B9 (Table 21), the █████ patients did not receive any subsequent therapy.</p> <p>In CQ B9, the patients who received various subsequent therapies (ePAS9) can be counted more than once in each row so we cannot sum them up (e.g., some patients received combination therapy). Notably, in ePAS9 a total of █████ patients (████) started a subsequent therapy, and in SAS3 a total of █████ patients (████) started a subsequent therapy. These figures are lower than those cited by the EAG.</p> | <p>Thank you for clarifying the absolute overall rates of subsequent treatment use.</p> <p>Unfortunately, the figures provided in this response are not equivalent to those described in the EAR and cannot be considered an appropriate correction. That is, the highlighted sections of the EAR refer specifically to adult patients, and to the rates of systemic therapy and radiotherapy/surgery.</p> <p>We have however added text clarifying in both the discussion of adult and paediatric outcomes explaining that the figures provided may include patients more than once, and have provided overall</p> |

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Description of proposed amendment | Justification for amendment | EAG Response                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>of subsequent systemics in this population), and a further █████ underwent radiotherapy or surgery. Other systemic therapies were used in █████ adult patients in SAS3 following progression, with radiotherapy, radioactive iodine therapy, and a combination of systemic and radiotherapy used in a further █████ patients (████).” &amp; “Furthermore, such high rates of subsequent systemic therapy use may belie differences in the underlying population, as this use does not represent NHS practice, per the data collected in SACT.”</i></p> <p>Section 4.26, Page 131<br/> <i>The EAG stated that “As has been discussed previously, the high rate of systemic therapy use in patients who progressed on larotrectinib is likely to have influenced utility, with patients who continue to provide responses after progression more likely to represent those who have achieved disease stability or a response to a new line of therapy.”</i></p> |                                   |                             | <p>proportions supplied here for context.</p> <p>Reference to ‘high rates’ of systemic therapy use is a subjective judgement made relative to the observed rates of subsequent systemic therapy use in SACT. Reference to ‘high rates’ of subsequent therapy use in the EAR therefore remains unchanged.</p> |

## Issue 2 Status of Study 20289

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                               | Description of proposed amendment                                                                               | Justification for amendment                                                                                                                                                                                                                                                                                  | EAG Response                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| <p>Section 1.3, Page 18<br/>The EAG stated that “<i>Studies 20289 and 20290 (formerly NAVIGATE and SCOUT trials) are ongoing.</i>”</p> <p>Section 3.2.1, Page 45<br/>The EAG stated that “Study 20288 is now completed, and studies 20289 and 20290 are still ongoing, with results presented at the 20<sup>th</sup> July 2024 data cut.”</p> <p>Page 49, Table 7<br/>The EAG stated duration of Study 20289 as “<i>October 2015 – ongoing</i>”.</p> | <p>Study 20289 (formerly NAVIGATE) is <b>completed</b> (Date of completion 29<sup>th</sup> September 2025).</p> | <p>Study 20289 was completed in September 2025<br/>(<a href="https://clinicaltrials.gov/study/NCT02576431">https://clinicaltrials.gov/study/NCT02576431</a>) and latest data cut-off (July 2025) which will present final results is still under analysis, as stated in the Company’s response to CQ A4.</p> | <p>Thank you. Amendments to Sections 1.3, Page 18, 3.2.1, Page 45 and Table 7, Page 49 have been made accordingly.</p> |



### Issue 3 Incorrect number of cancer types

| Description of problem                                                                                                                                                                                                                               | Description of proposed amendment                                                                                                                                                                    | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                         | EAG Response                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <p>Section 2.1.2, Page 34</p> <p>The EAG stated that <i>“Forty-two cancer types were covered in this database,<sup>1</sup> with the most prevalent being salivary gland, soft-tissue sarcoma, thyroid, uterus sarcoma and rhabdomyosarcoma.”</i></p> | <p>Forty-<b>five</b> cancer types were covered in this database,<sup>1</sup> with the most prevalent being salivary gland, soft-tissue sarcoma, thyroid, uterus sarcoma and <b>bone sarcoma</b>.</p> | <p>The paper reports 45 tumour types included in the database (page 1, results section).</p> <p>Rhabdomyosarcoma is the fifth most prevalent tumour type in adults only (figure D). If there is no distinction of age, bone sarcoma is the fifth most prevalent (figure C).</p> <p>This correction solely intends to correct minor reporting mistake but is not considered to have an impact on the submission.</p> | <p>Thank you. This has been amended accordingly on Page 34.</p> |

### Issue 4 Termination of entrectinib’s appraisal

| Description of problem                                                                                                                                                                                        | Description of proposed amendment                                                                      | Justification for amendment                                                                                                                                                            | EAG Response                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <p>Section 2.2, Page 36</p> <p>The EAG stated that <i>“Current service provision for NTRK fusion-positive cancers that are locally advanced or metastatic, where surgery would significantly increase</i></p> | <p>We propose to remove any mention of entrectinib as an option for NTRK-fusion positive patients.</p> | <p>Since publication of the EAG report, entrectinib has been terminated as a treatment option for TRK fusion-positive cancers (TA1118). As a result, larotrectinib is now the only</p> | <p>Reference to the termination of Entrectinib was added to Section 2.2, Page 36.</p> |

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Description of proposed amendment | Justification for amendment                                                                                                                                                                                                                                                                                                                                        | EAG Response                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <p><i>morbidity and where there are “no satisfactory treatment options” is monotherapy with larotrectinib or entrectinib, both ‘histology-independent’ TRK inhibitors that are currently on managed access agreements through the Cancer Drugs Fund (CDF). Where these conditions are not met, then Standard of Care (SoC) treatment (established clinical management) directed at the histology is used, through more traditional chemotherapy, radiotherapy, immunotherapy and surgical options. The exact nature of SoC varies by tumour type, tumour size or whether the tumour is locally advanced or metastatic. Entrectinib, an alternative targeted NTRK fusion inhibitor, is not available for routine commissioning and so cannot be considered a comparator in this TA review.7”</i></p> |                                   | <p>available TRK inhibitor in NHS clinical practice. This change does not materially affect the EAG’s conclusions, but it impacts the TRK-inhibitor treatment landscape.</p> <p>Reference: TA118 (<a href="#">Overview   Entrectinib for treating NTRK fusion-positive solid tumours in people 12 years and over (terminated appraisal)   Guidance   NICE</a>)</p> |                                                 |
| <p>Section 5.3.3, Page 165.</p> <p>The EAG stated that “The EAG does not consider this a source of health inequality per the NICE reference</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                   |                                                                                                                                                                                                                                                                                                                                                                    | <p>This text has been removed from the EAR.</p> |

| Description of problem                                                                                                                                                                                                                        | Description of proposed amendment | Justification for amendment | EAG Response |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------|--------------|
| case and notes that access to entrectinib (another TRK inhibitor) will continue through the CDF, meaning options for patients with NTRK fusion-positive tumours will remain available in the even that access to larotrectinib is withdrawn.” |                                   |                             |              |

#### Issue 5 Incorrect number of patients with non-primary CNS tumours having ECOG status 0-1

| Description of problem                                                                                                                                    | Description of proposed amendment                                                                           | Justification for amendment                                                                                                                                                                     | EAG Response                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Section 3.2.3, Page 51<br>The EAG stated that “Most patients had an ECOG performance status 0 or 1 (█ of non-primary CNS and █ of primary CNS patients).” | “Most patients had an ECOG performance status 0 or 1 (█ of non-primary CNS and █ of primary CNS patients).” | Number of patients should be consistent as presented in CS and in Table 9 of the EAR for patients with non-primary CNS (ECOG performance status 0, █ [█] and ECOG performance status 1, █ [█]). | Section 3.2.3, Page 51 was amended as suggested. |

#### Issue 6 Breakdown of prior line of therapy in trial population

| Description of problem | Description of proposed amendment                         | Justification for amendment                           | EAG Response                                     |
|------------------------|-----------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------|
| Section 3.2.3, Page 52 | “█ and █ of the trial evidence had one and two prior LOT, | The breakdown was provided for one and two LOT in the | Edits made to Section 3.2.3 and Table 9, Page 52 |

| Description of problem                                                                                                                                                                       | Description of proposed amendment                   | Justification for amendment                                                                  | EAG Response |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------|--------------|
| The EAG stated that “ <i>Just over ( ) of the trial evidence had either one or two prior LOT (no breakdown was provided between one and two LOT), and ( ) had three or more prior LOT.</i> ” | respectively, and ( ) had three or more prior LOT.” | Company’s response to CQ A5 (Table 2) for patients with primary and non-primary CNS tumours. |              |

#### Issue 7 Incorrect number of patients with metastatic disease in SACT population

| Description of problem                                                                                                                                  | Description of proposed amendment                                                                         | Justification for amendment                                                                                                                                   | EAG Response                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Section 3.2.3, Page 52<br>The EAG stated that “A ( ) proportion of patients in ePAS9 had metastatic disease ( ) compared with the SACT database (41%).” | “A ( ) proportion of patients in ePAS9 had metastatic disease ( ) compared with the SACT database (40%).” | Number of patients should be consistent with values provided (SACT population with metastatic disease 25/60[40%] in CS (Table 28), and in Table 9 of the EAR. | Edit made to Section 3.2.3, Page 52. |

### Issue 8 Incorrect death events in SAS3 population

| Description of problem                                                                                                                        | Description of proposed amendment                                                                  | Justification for amendment                                                                                                                                                               | EAG Response                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| <p>Section 3.2.4, Page 62.</p> <p>The EAG wrote that “<i>The median OS was not estimable, and [REDACTED] death events were recorded.</i>”</p> | <p>“The median OS was not estimable, and [REDACTED] ([REDACTED]%) death events were recorded.”</p> | <p>There has been a confusion between death events for ePAS9 ([REDACTED]) and SAS3 ([REDACTED]). The number of death events should be consistent with data provided in CS (Table 14).</p> | <p>Edits made to Section 3.2.4, Page 62.</p> |

### Issue 9 HMF MAIC critique did not consider the full publication available

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                              | Description of proposed amendment                                                                                                                         | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                     | EAG Response                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Section 3.4, Page 77<br/>Section 3.4.1.3, Page 80<br/>Section 3.4.6.3, Page 85</p> <p>The EAG stated that the HMF MAIC is only presented in a conference abstract with limited information (i.e., Bokemeyer C, Abrams K, García-Foncillas J, Italiano A, Lassen U, Linsell L, et al. 508P Survival outcomes of patients with tropomyosin receptor kinase fusion-positive cancer receiving larotrectinib versus standard of care: a matching-</p> | <p>The EAG should review the full publication of the HMF MAIC as shared in the Company’s response to the CQ (A23) and adapt its critique accordingly.</p> | <p>It is inaccurate to mention that the HMF MAIC is only presented in a conference abstract with limited information. The full publication provided to the EAG during clarification (A23) provides additional details on the HMF MAIC and has in part addressed the EAG’s concerns regarding limited information on study design, baseline patient characteristics, and overlap assessment.</p> <p>The publication provides a comprehensive overview of the</p> | <p>Section 3.4 was updated throughout. The additional information from the HMF publication does not fundamentally change the EAG’s position on the reliability and applicability of this MAIC to the decision problem.</p> |

| Description of problem                                                    | Description of proposed amendment | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | EAG Response |
|---------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| adjusted indirect comparison using real world data. In: ESMO ASIA; 2024). |                                   | <p>baseline characteristics of patients included in the HMF MAIC, along with an overlap assessment. A summary is outlined below:</p> <p>The HMF standard-of-care cohort included 24 adult patients with TRK fusion-positive solid tumours, similar to the larotrectinib trial population in that both groups were defined by the presence of NTRK gene fusions and had advanced or metastatic disease. Median age in HMF was approximately 59 years, which is broadly comparable to the larotrectinib trials, and both cohorts included a mix of tumour types, reflecting the tumour-agnostic nature of TRK fusion cancers. Additionally, both populations had prior systemic therapy exposure, supporting a degree of clinical similarity in treatment history.</p> <p>While there were differences in tumour-type distribution, HMF had more breast, pancreas, and prostate cancers, whereas larotrectinib trials included more bone/soft tissue and colorectal</p> |              |

| Description of problem | Description of proposed amendment | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | EAG Response |
|------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
|                        |                                   | <p>tumours, matching adjusted for key baseline factors such as age group, prior lines of therapy, and fusion type. After matching, the ESS was 36 in the base case, which is typical for rare, heterogeneous populations. Weight distribution was well-controlled, with most weights <math>\leq 1</math> and no concerns about outliers. Sensitivity analyses adding further factors reduced ESS, underscoring the challenge of achieving full overlap. Overall, despite some differences, the shared biology (NTRK fusion) and advanced disease status provide a meaningful basis for comparison, with matching helping to address residual imbalances.</p> <p>Reference: Bokemeyer, C., Abrams, K. R., Garcia-Foncillas, J., Italiano, A., Lassen, U., Linsell, L., Marian, M., Paracha, N., Sullivan, S. D., Brega, N., &amp; Thompson, J. (2025). Clinical benefit from molecularly guided cancer care: A matching-adjusted indirect comparison of larotrectinib versus standard of care. JCO Precision</p> |              |

| Description of problem                                                                   | Description of proposed amendment                                                                                                                                                                            | Justification for amendment                                                                                                                                             | EAG Response                               |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
|                                                                                          |                                                                                                                                                                                                              | Oncology.<br><a href="https://doi.org/10.1200/PO-25-00159">https://doi.org/10.1200/PO-25-00159</a>                                                                      |                                            |
| Section 3.4.7.2, Page 87 (Table 24)<br>Unweighted OS data are noted as NR in table 24.   | 'NR' for unweighted OS should be amended as follows:<br><ul style="list-style-type: none"> <li>- Larotrectinib: 60.1 (23.3-NE)</li> <li>- SoC: 13.0 (6.4-18.3)</li> <li>- HR: 0.18 (0.10 to 0.34)</li> </ul> | The unweighted OS data for the HMF MAIC should be reported based on the full publication as shared in A23 of the Company's response to the EAG clarification questions. | Section 3.4.7.2, Page 87 has been updated. |
| Section 3.4.8.1, Page 88<br>The EAG stated that " <i>HMF tumour types are unknown.</i> " | HMF tumour types are bone/soft tissue, breast, colon/rectum, head and neck, lung, pancreas, prostate, skin and urinary tract.                                                                                | HMF tumour types are known and should be reported based on the full publication as shared in A23 of the Company's response to the EAG clarification questions.          | Section 3.4.8.1, Page 88 has been updated. |

#### Issue 10 Selection criteria for VICTORIA

| Description of problem                                                                                                                           | Description of proposed amendment                                                                                                                                                                      | Justification for amendment                                                                                                                                                        | EAG Response                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Section 3.4.1.1, Page 79<br>The EAG report stated the selection criteria for the VICTORIA study as " <i>No prior or current TRK inhibitor</i> ". | Patients involved in larotrectinib clinical trials were excluded from the RW control cohort. Those who received TRK inhibitors in the real-world setting after index SOC therapy were allowed but were | Clarification that patients enrolled in VICTORIA might have received or were receiving TRK inhibitors. In that case, only the line(s) of therapy before this TRKi were considered. | Section 3.4.1.1, Page 79, Table 20 was updated accordingly. |



| Description of problem | Description of proposed amendment                    | Justification for amendment | EAG Response |
|------------------------|------------------------------------------------------|-----------------------------|--------------|
|                        | censored at the initiation of TRK inhibitor therapy. |                             |              |

#### Issue 11 Critique on applicability of and selection bias in the MAICs

| Description of problem                                                                                                                                                                                                             | Description of proposed amendment                                                                                                                                                                                       | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | EAG Response                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <p>Section 3.4.2.1, Pages 80, 81</p> <p>Section 3.4.8.2, Page 89</p> <p>Section 3.6, Page 92</p> <p>The EAG highlighted applicability and selection bias concerns, as several solid tumour types were excluded from the MAICs.</p> | <p>There should be due consideration given to the merits of the MAICs, given the methodological constraints encountered due to the rare nature of NTRK fusions and the tumour-agnostic indication of larotrectinib.</p> | <p>Although the MAICs focused on tumour types with sufficient real-world data to enable robust matching, this does not undermine their applicability. While larotrectinib is licensed for all NTRK fusion-positive solid tumours, the MAICs necessarily focused on tumour types with sufficient real-world data to enable robust matching. This reflects methodological constraints rather than selection bias and does not undermine their applicability.</p> <p>Larotrectinib is a tumour-agnostic therapy, and its efficacy is driven by the presence of an NTRK fusion rather than tumour histology. The selected tumour types represent the most</p> | <p>Not a factual inaccuracy, but a matter of interpretation. No changes made.</p> |

| Description of problem | Description of proposed amendment | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                          | EAG Response |
|------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
|                        |                                   | common and clinically relevant NTRK fusion-positive cancers, ensuring that the comparisons reflect real-world practice. Furthermore, pooled trial data demonstrate consistent outcomes across multiple tumour types, and scenario analyses using alternative MAICs confirm the stability of results. Taken together, these factors support the generalisability of the MAIC findings to the broader NTRK fusion-positive population. |              |

## Issue 12 Details of propensity scores generated in VICTORIA

| Description of problem                                                                                                                                                                                                              | Description of proposed amendment                                                                                                                                                     | Justification for amendment                                         | EAG Response                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section 3.4.5.1, Page 83<br><i>The EAG stated that “In VICTORIA, IPTW was generated on the basis of the propensity score, but no details were given on the logistic regression upon which the propensity scores were based, and</i> | VICTORIA publication illustrated that IPTW is calculated based on variables including age at index, sex, ECOG PS at index, race, and presence of metastases at index date (figure 1). | This clarifies variables on which the propensity scores were based. | Not a factual inaccuracy. Although the IPTW variables are provided, the process by which those variables were derived from the logistic regression are not presented. |

|                                                                 |  |  |  |
|-----------------------------------------------------------------|--|--|--|
| no details were provided of the propensity score calculations.” |  |  |  |
|-----------------------------------------------------------------|--|--|--|

### Issue 13 Propensity scores and IPTW weighting in VICTORIA

| Description of problem                                                                                                                                                                                                                                           | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Justification for amendment                                                                                                                             | EAG Response                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <p>Section 3.4.5.1, Page 83</p> <p><i>The EAG stated that “Although this is not reported explicitly, the EAG presumes that the derivation of propensity scores and IPTW weighting would have been carried out separately for each tumour/line subgroup.”</i></p> | <p>In VICTORIA, exact matching was performed on tumour type and line of therapy. As a result, larotrectinib-treated and comparator patients were identical on these variables within each matched set, and they did not confound the treatment comparison. Propensity scores and IPTW were therefore estimated in the pooled matched cohort rather than within tumour/line subgroups, avoiding instability from small sample sizes and limited overlap while preserving the exact-match structure.</p> | <p>As this was not reported explicitly, the company wanted to clarify that propensity scores and IPTW were not carried out separately per subgroup.</p> | <p>Thank you for this clarification. The manuscript has been amended accordingly.</p> |

#### Issue 14 Critique on Flatiron MAIC does not fully reflect evidence presented

| Description of problem                                                                                                                                | Description of proposed amendment                                                                                                             | Justification for amendment                                                                                                                                                                                               | EAG Response                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Section 3.4.5.2, Page 84</p> <p>The EAG stated that the Flatiron MAIC had a “<i>substantially lower ESS, indicating an unstable estimate.</i>”</p> | <p>EAG should consider the Company's sensitivity and scenario analyses performed with the Flatiron MAIC and reflect this in its critique.</p> | <p>The EAG's conclusion of a small ESS leading to unstable estimate is inaccurate, as the Company has performed additional analyses and the results are directionally consistent and supported by multiple scenarios.</p> | <p>Not a factual inaccuracy. Both the main and additional analyses suffer from similar flaws. The MAIC Flatiron additional analyses do not address the significant concerns raised by the EAG including the very low ESS.</p> <p>See also Ishak KJ, Chandler C, Liu FF, Klijn S. MSR65 Can Low Effective Sample Size in Matching-Adjusted Indirect Comparisons (MAICS) Lead to Bias? Findings From a Simulation Study. Value in Health. 2024 Dec 1;27(12):S450.</p> |

### Issue 15 Incorrect ORR reported for VICTORIA MAIC

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                      | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                       | Justification for amendment                                                              | EAG Response                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| <p>Section 3.4.7.1, Pages 85, 86</p> <p>The EAG stated that the “<i>Unweighted ORR across all five tumour types was 73% (95% CI 62.7 to 83.0) for larotrectinib. This is more favourable to larotrectinib than the ePAS9 pooled analyses (65% [95% CI 59 to 70]) and the BHM main analyses (ORR █% [95% Predl █ to █]). ORR was 52.8% (37.2 to 69.9) in the comparator cohort although this estimate is limited by significant missing data (52%).</i>”</p> | <p>“Unweighted ORR across all five tumour types was <b>73.8%</b> (95% CI 62.7 to 83.0) for larotrectinib. This is more favourable to larotrectinib than the ePAS9 pooled analyses (65% [95% CI 59 to 70]) and the BHM main analyses (ORR █% [95% Predl █ to █]). ORR was <b>53.8%</b> (37.2 to 69.9) in the comparator cohort although this estimate is limited by significant missing data (52%).”</p> | <p>The ORRs from VICTORIA MAIC should be consistent with the referenced publication.</p> | <p>Section 3.4.7.1, Pages 85, 86 were amended accordingly.</p> |

**Issue 16 Incorrect CNS weighting and paediatric CNS data inclusion assumption**

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | EAG Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <p>Section 4.2.3.1. Page 101.</p> <p>The EAG stated <i>“The model uses OS and PFS data notionally derived from the full distribution of tumour sites in the ePAS9 and SAS3 pooled datasets, but the weightings applied in the model imply that paediatric patients with primary CNS tumours were excluded – though it appears they comprised part of the population included in the analysis of survival outcomes.”</i></p> <p>Section 4.2.3.1. Page 102.</p> <p>The EAG stated <i>“The model did not account for paediatric primary CNS outcomes, resource use, or HRQoL. This is an important source of uncertainty, given the size of the primary CNS tumour population.”</i></p> <p>Section 4.2.5.1, Page 110.</p> <p>The EAG stated <i>“The company selected the Weibull distribution to model OS for adult patients (and paediatric CNS patients) on larotrectinib in the base case.”</i></p> | <p>Section 4.2.3.1. Page 101</p> <p>“The model uses OS and PFS data notionally derived from the full distribution of tumour sites in the ePAS9 and SAS3 pooled datasets, with weightings applied such that paediatric patients with primary CNS tumours contribute to the CNS weighting, which is modelled as an adult tumour location.”</p> <p>Section 4.2.3.1. Page 102</p> <p>“The model did not account for paediatric primary CNS as a separate tumour location with their own outcomes, resource use, or HRQoL. This is an important source of uncertainty, given the size of the primary CNS tumour population.”</p> <p>Section 4.2.5.1, Page 110</p> <p>“The company selected the Weibull distribution to model OS for adult patients on larotrectinib in the base case.”</p> | <p>In the base case, paediatric patients with primary CNS tumours contribute to the CNS weighting, which is modelled as an adult tumour location. However, they are not excluded, as their data is incorporated into the paediatric OS and PFS curves.</p> <p>Including a clarification that paediatric primary CNS was not included as a separate tumour location is more accurate as these patients are still included in the model as per point above.</p> <p>The adult survival data analysed only includes adult patients, consequently, the EAG statement can be misinterpreted as the Weibull was fit to paediatric CNS patients. Paediatric CNS patients are included and are incorporated into the paediatric OS and PFS curves.</p> | <p>We have amended the text in the EAR to the following for clarity.</p> <p>First instance:</p> <p>“The model uses OS and PFS data notionally derived from the full distribution of tumour sites in the ePAS9 and SAS3 pooled datasets, but paediatric patients with primary CNS tumours contribute to the primary CNS weighting, which is only explicitly modelled as an adult tumour location. However, OS and PFS data on paediatric primary CNS patients was included in the modelled paediatric OS and PFS curves.”</p> <p>Second instance:</p> <p>Text amended per the company’s suggestion.</p> <p>Third instance:</p> <p>Text amended per the company’s suggestion.</p> |

### Issue 17 Incorrect statement that the Company did not submit separate ICERs for adults and paediatrics

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                           | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | EAG Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <p>Section 4.2.3.1. Page 103.</p> <p>The EAG stated <i>“the use of a single pooled ICER to represent cost-effectiveness in these populations is not meaningful for decision making, increasing decision uncertainty in the adult population, whilst artificially decreasing the ICER. The EAG requested that analysis be presented which consider these populations separately (CQ A3, A13, B2), which the company declined to provide.”</i></p> | <p>“the use of a single pooled ICER to represent cost-effectiveness in these populations is not meaningful for decision making, increasing decision uncertainty in the adult population, whilst artificially decreasing the ICER. In response to CQ B2 the company provided ICERs for the base case and all scenarios separately for adult and paediatric populations. However, the company declined to provide additional subgroup analyses requested by the EAG <b>(CQ A3, A13)</b>”</p> | <p>The original statement implied that no separate ICERs were provided, which was factually incorrect. The revised wording acknowledges that the company did submit separate ICERs for adults and paediatrics (CQ B2), while still noting that additional subgroup analyses requested by the EAG (CQ A3, A13) were not provided. These were not provided as mentioned in CQ A3 and A13 due to the requested ITC being limited by data availability, population comparability, methodological constraints (lack of common comparator and ability to account for all treatment effect modifiers and prognostic factors), and lack of IPD for all RWE datasets. Furthermore, the additional requested BHM analyses would have been limited by the sample size, increasing the uncertainty and instability of the BHM.</p> | <p>We have amended the EAR per the company's suggestion, but have provided additional clarification as follows:</p> <p>“In response to CQ B2 the company provided ICERs for the base case and other scenarios separately for adult and paediatric populations (although paediatric primary CNS resource use and HRQoL was not represented in paediatric population ICERs). However, the company declined to provide the additional subgroup analyses requested by the EAG (CQ A3, A13).”</p> |

### Issue 18 Incorrect justification for comparator selection



| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Justification for amendment                                                                                                      | EAG Response                                          |
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| <p>Section 4.2.4., Page 104, Table 27.</p> <p>The EAG stated the following:</p> <p>Colorectal cancer (incl. appendix proxy) - Company justification (from submission):</p> <p><i>“ESMO 2023 guidelines recommend TRK testing after ≥2 lines; thus larotrectinib modelled vs third-line comparator.”</i></p> <p>STS (adult, non-GIST; incl. bone sarcoma proxy) - Company justification (from submission):</p> <p><i>“Recommended by clinicians as representative of second-line STS; used as proxy for bone sarcoma due to limited data.”</i></p> <p>Pancreatic cancer - Company justification (from submission):</p> <p><i>“Validated by advisory board as appropriate comparator for second-line pancreatic cancer.”</i></p> | <p>Colorectal cancer (incl. appendix proxy) - Company justification (from submission):</p> <p>“ESMO 2023 guidelines recommend TRK testing after ≥2 lines, thus larotrectinib modelled vs third-line comparator; validated by clinicians.”</p> <p>STS (adult, non-GIST; incl. bone sarcoma proxy) - Company justification (from submission):</p> <p>“Recommended by the ESMO 2021 guidelines and clinicians as representative of second-line STS; used as proxy for bone sarcoma due to limited data.”</p> <p>Pancreatic cancer - Company justification (from submission):</p> <p>“In line with the ESMO 2023 guidelines and validated by advisory board as appropriate comparator for second-line pancreatic cancer.”</p> | <p>The selection of these comparators is recommended by guidelines and were validated by UK clinicians in an advisory board.</p> | <p>Amendments made per the company's suggestions.</p> |

## Issue 19 Incorrect survival curve milestones

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Justification for amendment | EAG Response |              |             |              |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
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| <p>Section 4.2.5.1, Page 114, Table 28.</p> <p>Survival curve milestones were incorrectly reported.</p> <p>Section 4.2.5.1, Page 114.</p> <p>The EAG stated that “A major concern is the divergence between OS and PFS in the trial data, which generates post-progression survival (PPS) outcomes on larotrectinib that are not credible. The company’s preferred models predicts █████ survival at 20 years, yet only █████ of these patients are progression free. This implies that paediatric patients on larotrectinib spend an average of █████ years in PFS but survive for a further █████ years following disease</p> | <p>Section 4.2.5.1, Page 114, Table 28</p> <table><tr><th>Distribution</th><th>OS – 10 yrs</th><th>PFS – 10 yrs</th><th>OS – 20 yrs</th><th>PFS – 20 yrs</th><th>OS – 50 yrs</th><th>PFS – 50 yrs</th></tr><tr><td>Larotrectinib arm</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Exponential (most pessimistic)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr><tr><td>Weibull (base-case)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr><tr><td>Gompertz (most optimistic)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr><tr><td>SoC arm</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Exponential (most pessimistic)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr><tr><td>Weibull (base-case)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr><tr><td>Gompertz (most optimistic)</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td><td>█████</td></tr></table> <p>Section 4.2.5.1, Page 114</p> <p>“A major concern is the divergence between OS and PFS in the trial data, which generates post-progression survival (PPS) outcomes on larotrectinib that are not credible. The company’s preferred models predicts █████ survival at 20 years, yet only █████ of these patients are progression free. This implies that paediatric patients on larotrectinib spend an average of █████ years in PFS (<b>median PFS: █████ years</b>) but survive for a further █████ years following disease progression (<b>median OS: █████ years</b>). In contrast, patients in the SoC arm, patients spent an average of</p> | Distribution                | OS – 10 yrs  | PFS – 10 yrs | OS – 20 yrs | PFS – 20 yrs | OS – 50 yrs | PFS – 50 yrs | Larotrectinib arm |  |  |  |  |  |  | Exponential (most pessimistic) | █████ | █████ | █████ | █████ | █████ | █████ | Weibull (base-case) | █████ | █████ | █████ | █████ | █████ | █████ | Gompertz (most optimistic) | █████ | █████ | █████ | █████ | █████ | █████ | SoC arm |  |  |  |  |  |  | Exponential (most pessimistic) | █████ | █████ | █████ | █████ | █████ | █████ | Weibull (base-case) | █████ | █████ | █████ | █████ | █████ | █████ | Gompertz (most optimistic) | █████ | █████ | █████ | █████ | █████ | █████ | <p>Survival curve milestones should be consistent with the CEM. Area under the curve values were calculated using rectangles with model cycle length intervals (1 week) but were unable to reproduce EAG values such as the 20.75 years (vs. 23.10 years as per company calculations).</p> <p>The mean PFS and OS are positively skewed so adding the median PFS and OS presents a more accurate description of the data.</p> <p>As the issues with post progression survival in SOC relate to the EPI</p> | <p>Survival curve milestones in Table 28 have been corrected.</p> <p>Mean years spent in state have also been corrected.</p> <p>The extended SoC survival estimates produced through application of the MAIC HRs still ultimately originate from the larotrectinib trial. The poor agreement between the MAIC-adjusted model and literature comparison is a function of both</p> |
| Distribution                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | OS – 10 yrs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PFS – 10 yrs                | OS – 20 yrs  | PFS – 20 yrs | OS – 50 yrs | PFS – 50 yrs |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Larotrectinib arm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                             |              |              |             |              |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Exponential (most pessimistic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Weibull (base-case)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Gompertz (most optimistic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| SoC arm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                             |              |              |             |              |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Exponential (most pessimistic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Weibull (base-case)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |
| Gompertz (most optimistic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | █████                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | █████                       | █████        | █████        | █████       | █████        |             |              |                   |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |         |  |  |  |  |  |  |                                |       |       |       |       |       |       |                     |       |       |       |       |       |       |                            |       |       |       |       |       |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                  |

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Justification for amendment                                                                           | EAG Response                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>progression. In contrast, patients in the SoC arm, patients spent an average of █ years in the PFS health state but survived for an average of only █ months following progression. There is no clear biological or clinical mechanism for a persistent treatment effect of this magnitude following progression. These predictions are also inconsistent with the company's naïve literature comparison analysis, which suggested 2.20 years in PFS and 10.33 months survival post-progression. The issue arises in part because of the substantially larger HR for OS than for PFS arising from the MAIC with EPI VITRAKVI, which as discussed in Section 3.4, the EAG considers inappropriate, and results</i></p> | <p>█ years in the PFS health state (<b>median PFS: █ years</b>) but survived for an average of only █ months following progression (<b>median OS: █ years</b>). There is no clear biological or clinical mechanism for a persistent treatment effect of this magnitude following progression. These predictions are also inconsistent with the company's naïve literature comparison analysis, which suggested <b>2.27</b> years in PFS and <b>10.34</b> months survival post-progression. The issue arises in part because of the substantially larger HR for OS than for PFS arising from the MAIC with EPI VITRAKVI, which as discussed in Section 3.4, the EAG considers inappropriate, and results in almost overlapping OS and PFS curves for SoC. This in turn yields an implausibly large modelled treatment effect upon PPS, implying a 56-fold prolongation of PPS with larotrectinib relative to SoC, far beyond what could be inferred from the HRs produced by comparison with EPI VITRAKVI, which themselves have serious limitations. Despite the large inverse treatment effect applied to SoC, life-year gain was substantially higher on SoC using the MAIC (████) compared to the naïve literature-based comparison (<b>3.13 years</b>). This provides further evidence that the survival data from using <b>EPI VITRAKVI</b> is flawed and may be subject to confounding due to the use of subsequent therapies.”</p> | <p>VITRAKVI MAIC, the final sentence should refer to the EPI VITRAKVI MAIC rather than the trial.</p> | <p>the trial and the MAIC, that is, even the very large treatment effect estimated by the MAIC cannot generate realistic OS estimates for SoC. The paragraph already alludes to the serious limitations of the EPI VITRAKVI MAIC. No adjustment has been made to this text.</p> |

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Description of proposed amendment | Justification for amendment | EAG Response |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------|--------------|
| <p><i>in almost overlapping OS and PFS curves for SoC. This in turn yields an implausibly large modelled treatment effect upon PPS, implying a 56-fold prolongation of PPS with larotrectinib relative to SoC, far beyond what could be inferred from the HRs produced by comparison with EPI VITRAKVI, which themselves have serious limitations. Despite the large inverse treatment effect applied to SoC, life-year gain was substantially higher on SoC using the MAIC (██████) compared to the naïve literature-based comparison (3.05 years). This provides further evidence that the survival data from the larotrectinib trials is flawed and may be subject to confounding due to the use of subsequent therapies."</i></p> |                                   |                             |              |

## Issue 20 Incorrect PD utilities range

| Description of problem                                                                                                                                                                                                                         | Description of proposed amendment                                                                                                                                                      | Justification for amendment                                                                                                                                                                                                                                                                                                                                                                                                                | EAG Response                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| <p>Section 4.2.6, Page 124.</p> <p>The EAG stated that the “<i>Published utilities for PFS health states ranged between 0.43-0.83 for patients on treatment, while PD utilities range between 0.30–0.64 across relevant tumour types.</i>”</p> | <p>“Published utilities for PFS health states ranged between 0.43-0.83 for patients on treatment, while PD utilities range between <b>0.30–0.73</b> across relevant tumour types.”</p> | <p>Michels <i>et al.</i> (2022) reported a PD utility of 0.73, and therefore the upper limit of the PD utility range should reflect this value.</p> <p>Reference: Michels RE, Arteaga CH, Peters ML, Kapiteijn E, Van Herpen CM, Krol M. Economic evaluation of a tumour-agnostic therapy: Dutch economic value of Larotrectinib in TRK fusion-positive cancers. <i>Applied Health Economics and Health Policy</i>. 2022;20(5):717-29.</p> | <p>The EAR has been amended as suggested, thank you for highlighting this error.</p> |

## Issue 21 Inaccurate justification of exploratory analyses using Company’s base case

| Description of problem                                                                                                   | Description of proposed amendment                                                                 | Justification for amendment                                                                         | EAG Response                                                                |
|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| <p>Section 5.2.2, Page 147, Table 36.</p> <p>The EAG stated that the “<i>Separate curves fitted to immature (and</i></p> | <p>Separate curves fitted to immature (and potentially confounded) paediatric OS data implies</p> | <p>Describing the critique of the MAIC by using “proxied” instead of “wrong” population conveys</p> | <p>Point noted – we have amended ‘wrong’ to ‘inappropriate’ in the EAR.</p> |

| Description of problem                                                                                                                                                                                                                           | Description of proposed amendment                                                                                                                                                         | Justification for amendment                                                                                                                                     | EAG Response                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>potentially confounded) paediatric OS data implies implausible post-progression survival (PPS). EPI-VITRAKVI MAIC flawed, subject to a high degree of uncertainty and in <b>wrong</b> population, resulting in implausible SoC outcomes."</i> | implausible post-progression survival (PPS). EPI-VITRAKVI MAIC flawed, subject to a high degree of uncertainty and in a <b>proxied</b> population, resulting in implausible SoC outcomes. | the critique of the MAIC to be related to the proxy. Using "wrong" as a descriptor on its own can be misunderstood as a different issue in data or methodology. | The EAR consistently makes the point that assuming IFS is equivalent in natural history and treatment response to all paediatric tumour types is not appropriate, that is, using IFS as a proxy population is inappropriate. |

## Issue 22 Inaccurate assessment of the impact of EAG corrected severity modifier

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                     | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                                                 | Justification for amendment                                                                                                                                                                                                                                                                                                                                    | EAG Response                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section 5.2.1, Page 145.<br><br>The EAG stated that the " <i>The EAG's corrected base case below applies the QALY weight multiplier to incremental QALYs on larotrectinib only, with the total QALYs presented based on the unadjusted values generated directly by the model engines. This had only a <b>minor</b> impact on the ICER calculations, but represents a significant presentational error, as total QALYs</i> | "The EAG's corrected base case below applies the QALY weight multiplier to incremental QALYs on larotrectinib only, with the total QALYs presented based on the unadjusted values generated directly by the model engines. This had <b>no</b> impact on the ICER calculations <b>as the incremental QALYs remain the same</b> , but represents a significant presentational error, as total QALYs | The application of severity modifier to total QALYs which are then used to generate incremental QALYs, or directly to incremental QALYs, mathematically generate the same result i.e. $a \times x - b \times x$ is equivalent to $x \times (a - b)$ . There is a minor change in ICER from the other EAG corrections, however this should not be confused with | Thank you for highlighting this, we have amended the EAR as suggested in the first case.<br><br>In the second case, the text has been amended as follows: "While there is no impact of this correction on the ICER itself, the error is nevertheless material from a methodological and presentational perspective, |

| Description of problem                                                                                                                                                                                                                                                                                                                                                                                                               | Description of proposed amendment                                                                                                                                                                                                                                                                                                                                       | Justification for amendment                            | EAG Response                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <p>on both larotrectinib and SoC are misrepresented.”</p> <p>Section 5.3.1, Page 160.</p> <p>The EAG stated that “<i>While the numerical impact of this correction on the ICER is relatively small, the error is nevertheless material from a methodological and presentational perspective, as the total QALYs reported in the company’s base case do not reflect the reference-case interpretation of severity weighting.</i>”</p> | <p>on both larotrectinib and SoC are misrepresented.”</p> <p>“While the numerical impact of this correction on the ICER <b>unaffected</b>, the error is nevertheless material from a methodological and presentational perspective, as the total QALYs reported in the company’s base case do not reflect the reference-case interpretation of severity weighting.”</p> | <p>the severity modifier presentation corrections.</p> | <p>as the total QALYs reported in the company’s base case do not reflect the reference-case interpretation of severity weighting.”</p> |

### Issue 23 Inaccurate confidentiality markings

| Location of incorrect marking                                             | Description of incorrect marking                                                                                       | Amended marking                                                                                                                                                                                                                                                                                                                             |  |  | EAG Response |                                  |                                |                                          |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--------------|----------------------------------|--------------------------------|------------------------------------------|
| Section 3.2.2, Page 50 (Table 8)<br><br>Section 3.2.4, Page 55 (Table 11) | Total number of patients in CS (n=364), ePAS9 (n=304) and SAS3 (n=60) should not be confidential as data is published. | <div>The current evidence includes 60 patients with primary CNS tumours, compared with 9 in the original submission.</div> <div>Table 1 Pooled analyses of larotrectinib trial evidence: summary of characteristics</div> <table><tr><td></td><td>Original TA630 submission (2019)</td><td>TA630 review submission (2025)</td></tr></table> |  |  |              | Original TA630 submission (2019) | TA630 review submission (2025) | This has been amended in Tables 8 and 11 |
|                                                                           | Original TA630 submission (2019)                                                                                       | TA630 review submission (2025)                                                                                                                                                                                                                                                                                                              |  |  |              |                                  |                                |                                          |

| Location of incorrect marking                                  | Description of incorrect marking                                                                                          | Amended marking                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | EAG Response                 |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-------------------------|-----------------------|------------------------------------------------------|----------|-----------------------------------|-----------------------------------------------|-------------------------|-----------------------|--|
|                                                                |                                                                                                                           | <table><tr><td>Sample size</td><td>102</td><td>364</td></tr><tr><td>Patients with CNS tumours</td><td>9</td><td>60</td></tr></table> <p>Table 2 Overall response in ePAS9 and SAS3 analysis sets</p> <table><tr><td></td><td><b>ePAS9</b><br/>(n=304)</td><td><b>SAS3</b><br/>(n=60)</td></tr></table>                                                                                                                                                                                                            | Sample size                  | 102                     | 364                   | Patients with CNS tumours                            | 9        | 60                                |                                               | <b>ePAS9</b><br>(n=304) | <b>SAS3</b><br>(n=60) |  |
| Sample size                                                    | 102                                                                                                                       | 364                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                              |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
| Patients with CNS tumours                                      | 9                                                                                                                         | 60                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                              |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
|                                                                | <b>ePAS9</b><br>(n=304)                                                                                                   | <b>SAS3</b><br>(n=60)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                              |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
| Section 3.2.2, Page 51                                         | Median age of patients with non-CNS tumours should not be confidential, as it is published.                               | The median age of patients was 44.5 years (range 0.0 to 90.0) for non-CNS solid tumours and [REDACTED] for primary CNS tumours.                                                                                                                                                                                                                                                                                                                                                                                   | This has been amended on p51 |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
| Section 3.2.4.1, Page 55, Table 11<br>Section 3.2.4.5, Page 67 | Number of patients with complete response (n=198) is not confidential. These are presented in CS as it is published data. | <p>Table 11 shows that in the ePAS9 analysis set the ORR was 65% (95% CI 59 to 70), with confirmed response in 198 out of 304 patients.</p> <p>Table 3 Overall response in ePAS9 and SAS3 analysis sets</p> <table><tr><td></td><td><b>ePAS9</b><br/>(n=304)</td><td><b>SAS3</b><br/>(n=60)</td></tr><tr><td>Number (%) of patients with OR (confirmed CR/pCR/PR)</td><td>198 (65)</td><td><div><div></div><div></div></div></td></tr></table> <p>In ePAS9, 198 patients (65%) had achieved a response (IRC).</p> |                              | <b>ePAS9</b><br>(n=304) | <b>SAS3</b><br>(n=60) | Number (%) of patients with OR (confirmed CR/pCR/PR) | 198 (65) | <div><div></div><div></div></div> | This has been amended in Table 11 and page 67 |                         |                       |  |
|                                                                | <b>ePAS9</b><br>(n=304)                                                                                                   | <b>SAS3</b><br>(n=60)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                              |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
| Number (%) of patients with OR (confirmed CR/pCR/PR)           | 198 (65)                                                                                                                  | <div><div></div><div></div></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                              |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |
| Section 3.2.4.1, Page 57                                       | The predicted response rate of an as-yet unevaluated tumour type                                                          | An estimate for the distribution of the predicted response rate of an as-yet unevaluated tumour type is presented in Figure 1 and shows a very widespread across tumour types; this predicts that                                                                                                                                                                                                                                                                                                                 | This has been amended on p57 |                         |                       |                                                      |          |                                   |                                               |                         |                       |  |



| Location of incorrect marking     | Description of incorrect marking                                                                                                                                                                                       | Amended marking                                                                                                                                                                                                                                                                                                                                                                                                                                                         | EAG Response                 |                |                         |                   |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|----------------|-------------------------|-------------------|------|--|--|--|----------------|-------------------------|-------------------|----------------|-------------------------|-------------------|---------|-----|-----|-------------|----|---|---|-----------------------------------|
|                                   | should be marked as confidential.                                                                                                                                                                                      | █% of all as-yet unevaluated tumour types with an NTRK gene fusion would show response rates of 50% or higher.                                                                                                                                                                                                                                                                                                                                                          |                              |                |                         |                   |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |
| Section 3.2.4, Page 61 (Table 12) | Number of patients in ePAS9 and SAS3, including response rate for ePAS9 should not be confidential as the data is published.                                                                                           | <p>Table 4 ORR by baseline characteristics (ePAS9 and SAS3, data cut 20th July 2024)</p> <table><tr><th></th><th colspan="3">ePAS9</th><th colspan="3">SAS3</th></tr><tr><th></th><th>Total patients</th><th>Patients with CR/pCR/PR</th><th>ORR %<br/>[95% CI]</th><th>Total patients</th><th>Patients with CR/pCR/PR</th><th>ORR %<br/>[95% CI]</th></tr><tr><td>Overall</td><td>304</td><td>198</td><td>65 [59, 70]</td><td>60</td><td>█</td><td>█</td></tr></table> |                              | ePAS9          |                         |                   | SAS3 |  |  |  | Total patients | Patients with CR/pCR/PR | ORR %<br>[95% CI] | Total patients | Patients with CR/pCR/PR | ORR %<br>[95% CI] | Overall | 304 | 198 | 65 [59, 70] | 60 | █ | █ | This has been amended in table 12 |
|                                   | ePAS9                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                              | SAS3           |                         |                   |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |
|                                   | Total patients                                                                                                                                                                                                         | Patients with CR/pCR/PR                                                                                                                                                                                                                                                                                                                                                                                                                                                 | ORR %<br>[95% CI]            | Total patients | Patients with CR/pCR/PR | ORR %<br>[95% CI] |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |
| Overall                           | 304                                                                                                                                                                                                                    | 198                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 65 [59, 70]                  | 60             | █                       | █                 |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |
| Section 3.2.4.4, Page 67          | Time to first responses in ePAS9 (0.89 to 22.90) and SAS3 (0.92 to 49.87), and number of patients who had their first response after 9 months of therapy (4% in ePAS9 and 10% in SAS3), should be marked confidential. | ...time to first responses was wide in ePAS9 (█ to █) and SAS3 (█ to █), and a █ of patients had their first response after 9 months of therapy (█% in ePAS9 and █% in SAS3), ...                                                                                                                                                                                                                                                                                       | This has been amended on p67 |                |                         |                   |      |  |  |  |                |                         |                   |                |                         |                   |         |     |     |             |    |   |   |                                   |

| Location of incorrect marking                            | Description of incorrect marking                                                | Amended marking                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | EAG Response               |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
|----------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------|------------------|----------------|--------------|----------------|-----------|-----------|-----------------------------|--|-----------------------|------------|----------------------------|---------|
| Section 3.2.4.6, Page 67                                 | Fatal TEAEs should be marked confidential.                                      | A total of █ (█%) fatal TEAE occurred, although none were considered related to larotrectinib.                                                                                                                                                                                                                                                                                                                                                                                                                                      | Amended on p67             |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Section 4.2.5.7, Page 123.                               | Subsequent therapy in ePAS9 data should be marked as confidential.              | This showed that the use of potentially curative options such as surgery █ or radiotherapy █ was used in only a very small number of paediatric patients in ePAS9                                                                                                                                                                                                                                                                                                                                                                   | Amended.                   |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Section 5.1.1, Page 142                                  | The PAS price discount of larotrectinib should be marked as confidential.       | The cost-effectiveness results presented in the CS are based on a confidential PAS discount (█%) off the list price of larotrectinib                                                                                                                                                                                                                                                                                                                                                                                                | Amended.                   |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Appendix 1, Pages 174-177 (Table 48) – LAROTRACKING data | LAROTRACKING data are not confidential as the data is published, as per the CS. | <div>LAROTRACKING data confidentiality marking to be removed</div> <table><tr><td><b>LAROTRACKING [N=26]</b></td></tr><tr><td>Females: 69.2%</td></tr><tr><td>Median age: 56.6</td></tr><tr><td>ECOG 0: 33.3%*</td></tr><tr><td>ECOG 1: 50%*</td></tr><tr><td>ECOG 2: 16.7%*</td></tr><tr><td>ECOG 3: 0</td></tr><tr><td>ECOG 4: 0</td></tr><tr><td>Primary brain tumour: 11.5%</td></tr><tr><td> </td></tr><tr><td>Primary CNS tumour: 0</td></tr><tr><td>Sarcoma: 0</td></tr><tr><td>Lung adenocarcinoma: 15.4%</td></tr></table> | <b>LAROTRACKING [N=26]</b> | Females: 69.2% | Median age: 56.6 | ECOG 0: 33.3%* | ECOG 1: 50%* | ECOG 2: 16.7%* | ECOG 3: 0 | ECOG 4: 0 | Primary brain tumour: 11.5% |  | Primary CNS tumour: 0 | Sarcoma: 0 | Lung adenocarcinoma: 15.4% | Amended |
| <b>LAROTRACKING [N=26]</b>                               |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Females: 69.2%                                           |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Median age: 56.6                                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| ECOG 0: 33.3%*                                           |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| ECOG 1: 50%*                                             |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| ECOG 2: 16.7%*                                           |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| ECOG 3: 0                                                |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| ECOG 4: 0                                                |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Primary brain tumour: 11.5%                              |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
|                                                          |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Primary CNS tumour: 0                                    |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Sarcoma: 0                                               |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |
| Lung adenocarcinoma: 15.4%                               |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            |                |                  |                |              |                |           |           |                             |  |                       |            |                            |         |

| Location of incorrect marking | Description of incorrect marking | Amended marking                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | EAG Response |
|-------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
|                               |                                  | <div></div> <div>Thyroid: 7.7% (anaplastic)</div> <div>Papillary thyroid carcinoma: 30.8%</div> <div>Glioma: 0</div> <div>Colorectal: 0</div> <div>Forearm spindle cell sarcoma: 0</div> <div>Head: 0</div> <div>Oesophagus: 0</div> <div>Salivary gland carcinoma: 0</div> <div>Salivary gland adenocarcinoma: 3.8%</div> <div>Breast: 7.7%</div> <div>Melanoma: 0</div> <div>Pancreas: 0</div> <div>GIST: 0</div> <div>Cholangiocarcinoma 0</div> <div>Bone: 0</div> <div>Gastric: 0</div> <div>Cervix: 0</div> <div>CMN: 0</div> <div>Prostate: 0</div> <div>Appendix: 0</div> <div>Duodenal: 0</div> <div>External auditory canal: 0</div> <div>Hepatic: 0</div> <div>Ankle: 3.8%</div> <div>Parotid: 11.5%</div> <div>Caecum: 3.8%</div> |              |

| Location of incorrect marking | Description of incorrect marking | Amended marking                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | EAG Response |
|-------------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
|                               |                                  | <div>Cancer of unknown primary: 3.8%</div> <div>Metastatic: 42.3%</div> <div>Locally advanced with systemic therapy or with surgical resection resulting in morbidity: 57.7%</div> <div>0 prior therapies: 23.1%</div> <div>1-3 prior therapies: 76.9%</div> <div>NTRK1: 46.2%</div> <div>NTRK2: 7.7%</div> <div>NTRK3: 46.2%</div> <div>NTRK negative: 0</div> <div>Tumour stage 0: 4.2%</div> <div>Tumour stage I: 4.2%</div> <div>Tumour stage II: 8.3%</div> <div>Tumour stage III: 41.7%</div> <div>Tumour stage IV: 25%</div> <div>Tumour stage NA: 7.7%</div> <div>Tumour stage cannot be assessed: 16.7%</div> |              |

# Larotrectinib for NTRK fusion-positive advanced solid tumours – data review

## About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling



National Disease Registration Service  
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# 1. Executive summary

## Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of larotrectinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of larotrectinib in the CDF population, during the managed access period. This report presents the results of the use of larotrectinib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 75% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

## Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 21 April 2020 and 31 December 2024, 66 CDF applications for larotrectinib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 60 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)<sup>1</sup>.



## Results

60/61 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 26.9 months [95% CI: 14.4, 45.4] (818 days). Treatment duration at 6, 12, 18, 24, 36, and 48 months was calculated and showed that patients still receiving treatment at 6 months was 79% [95% CI: 70%, 90%], 67% [95% CI: 56%, 81%] at 12 months, 59% [95% CI: 47%, 74%] at 18 months, 53% [95% CI: 41%, 70%] at 24 months, 39% [95% CI: 26%, 57%] at 36 months, and 26% [95% CI: 15%, 48%] at 48 months.

At data cut off, 53% (N=32) of patients were identified as no longer being on treatment. Of these 32 patients:

- 47% (N=15) of patients stopped treatment due to disease progression
- 13% (N=4) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 9% (N=3) of patients died not on treatment
- 9% (N=3) of patients died on treatment
- 6% (N=2) of patients stopped treatment due to acute toxicity
- 3% (N=1) of patients chose to end their treatment
- 3% (N=1) of patients were treated palliatively and did benefit from the treatment they received
- 9% (N=3) of patients completed treatment as planned

The median OS was 45.2 months (1,376 days), confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced. OS at 6, 12, 18, 24, 36, and 48 months was calculated and showed that the OS at 6 months was 93% [95% CI: 87%, 100%], 86% [95% CI: 77%, 95%] at 12 months, 69% [95% CI: 57%, 83%] at 18 months, 69% [95% CI: 57%, 95%] at 24 months, 60% [95% CI: 47%, 77%] at 36 months, and 49% [95% CI: 34%, 69%] at 48 months.

A treatment duration and OS sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

## Conclusion

This report analysed SACT real-world data for patients treated with larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours in the CDF. It evaluated treatment duration, OS and treatment outcomes for all patients treated with larotrectinib for this indication.

## Background to this report

### Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

The CDF is a source of funding for cancer drugs in England<sup>2</sup>. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period<sup>3</sup>.

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

## NICE Appraisal Committee review of larotrectinib for treating NTRK fusion-positive advanced solid tumours [TA630]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of larotrectinib (Bayer plc) in treating NTRK fusion-positive advanced solid tumours [TA630] and published guidance for this indication in May 2020<sup>4</sup>.

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours through the CDF for a period of 57 months, from April 2020 to December 2024. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from ongoing clinical trials (NAVIGATE<sup>5</sup>, SCOUT<sup>6</sup> and LOXO-TRK-14001<sup>7</sup>) evaluating larotrectinib in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the NAVIGATE<sup>5</sup>, SCOUT<sup>6</sup> and LOXO-TRK-14001<sup>7</sup> studies will be the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the clinical trials.

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- 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 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'

Treatment duration was not an area of clinical uncertainty but has been included in this report.

## Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (Bayer plc) formed a working group to agree the Data Collection Agreement (DCA). The DCA sets out the real-world data to be collected and analysed to support the NICE re-appraisal of larotrectinib. It also detailed the eligibility criteria for patient access to larotrectinib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for larotrectinib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

## 2. Methods

### CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) 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). NHS England, through the National Disease Registration Service (NDRS), 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 NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

## Larotrectinib clinical treatment criteria

- 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 (i.e. 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 measurable 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

### 12 weeks after initiation of larotrectinib the following eligibility criteria apply.

- 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

## CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.
2. If two trusts apply for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.
3. If two applications are submitted for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

## Initial CDF cohorts

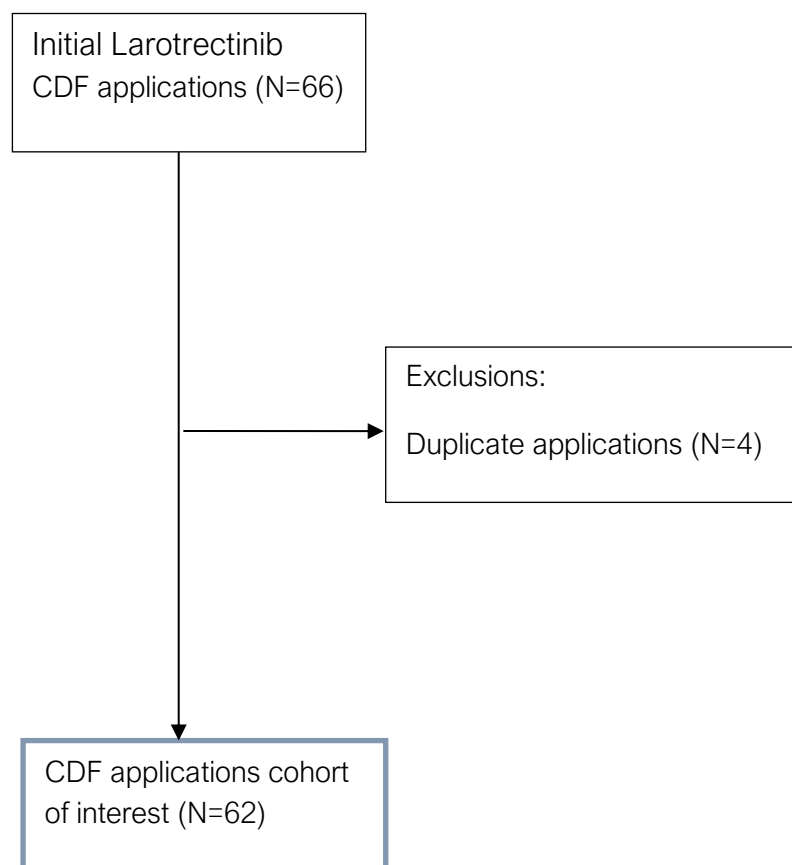
The analysis cohort is limited to the date larotrectinib entered the CDF for this indication, onwards.

Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 21 April 2020 to 31 December 2024. A snapshot of SACT data was taken on 5 April 2025 and made available for analysis on 24 April 2025 and includes SACT activity up to 31 December 2024. Tracing the patients' vital status was carried out on 23 April 2025 using the Personal Demographics Service (PDS)<sup>1</sup>.

There were 66 applications for CDF funding for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours between 21 April 2020 and 31 December 2024 in the NHS England Blueteq database. Following de-duplication this relates to 62 unique patients.

**Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours between 21 April 2020 and 31 December 2024**



## Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for larotrectinib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

## Addressing clinical uncertainties

### Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items<sup>8</sup> used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)<sup>8</sup> are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

#### Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

#### Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

#### Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.



All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death, and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Larotrectinib is administered orally. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next. Larotrectinib is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patient's date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
  - SACT v2.0 data item #41
  - SACT v3.0 data item #58 - #60
- there is no further SACT records for the patient following a three-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

## Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

$$\text{OS (days)} = \text{Date of death (or follow up)} - \text{treatment start date}$$

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

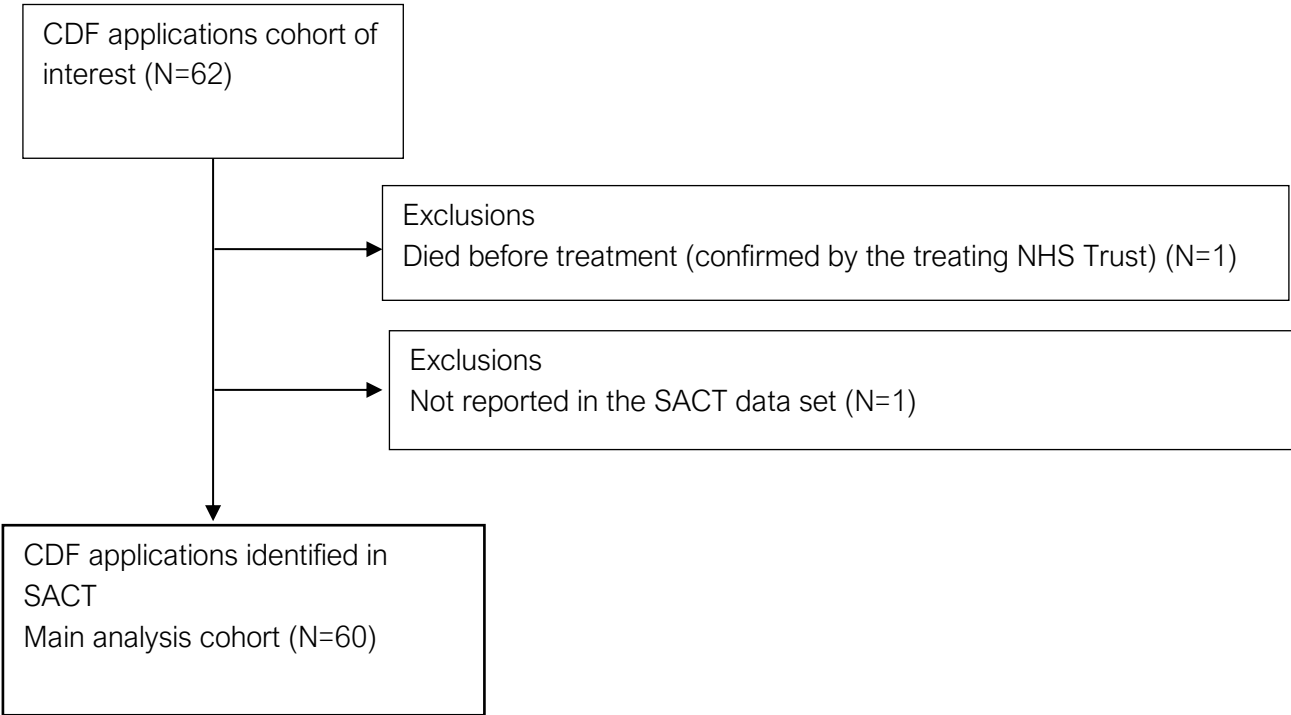
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

### 3. Results

#### Cohort of interest

Of the 62 applications for CDF funding for Larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours, one patient died before treatment and one patient was missing from SACT<sup>a</sup> (see Figure 2).

**Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours between 21 April 2020 and 31 December 2024**



<sup>a</sup> The patient who died before treatment was confirmed by the relevant trust by the NHSE data liaison team.

A maximum of 61 larotrectinib records are expected in SACT for patients who were alive, eligible, and confirmed to have commenced treatment (Figure 2). 99% (60/61) of these applicants for CDF funding have a treatment record in SACT.

## Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 47% complete.

**Table 1: Completeness of key SACT data items for the larotrectinib cohort (N=60)**

| Variable                               | Completeness (%) |
|----------------------------------------|------------------|
| Primary diagnosis                      | 100%             |
| Date of birth (used to calculate age)  | 100%             |
| Gender                                 | 100%             |
| Start date of regimen                  | 100%             |
| Start date of cycle                    | 100%             |
| Administration date                    | 100%             |
| Performance status at start of regimen | 47%              |

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with larotrectinib in at least three months<sup>9</sup>. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 32 patients. Of these 32 patients, 24 (75%) had an outcome summary recorded in the SACT dataset.

**Table 2: Completeness of outcome summary for patients that have ended treatment (N=32)**

| Variable                                     | Completeness (%) |
|----------------------------------------------|------------------|
| Outcome summary of why treatment was stopped | 75%              |

## Completeness of Blumetq key variables

Table 3 and Table 4 present the completeness of key data items required from Blumetq.

**Table 3: Initiation of treatment with larotrectinib and funded for the first twelve weeks (N=60)**

| Variable                                | Completeness (%) |
|-----------------------------------------|------------------|
| Site and histology of tumour origin     | 98%              |
| Type of disease                         | 98%              |
| Type of surgical resection <sup>b</sup> | 98%              |
| Lines of systemic therapy               | 98%              |
| NTRK gene                               | 98%              |
| Gene fusion partner                     | 97%              |
| Brain metastases                        | 98%              |

**Table 4: Information as to the RECIST response assessment made at 10 weeks after initiation of larotrectinib (N=43)**

| Variable                                    | Completeness (%) |
|---------------------------------------------|------------------|
| Larotrectinib response                      | 100%             |
| Weeks between start and response assessment | 98%              |
| Larotrectinib cerebral response             | 100%             |
| Weeks between start and cerebral response   | 91%              |
| Larotrectinib continuation                  | 100%             |

<sup>b</sup> Not applicable is a valid value if locally advanced disease for which systemic therapy has been indicated, or metastatic disease has been selected.

## Patient characteristics

The median age of the 60 patients receiving larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours was 37.5 years; and was consistent for both genders.

**Table 5: Patient characteristics (N=60)**

| Patient characteristics <sup>c</sup> |          |    |     |
|--------------------------------------|----------|----|-----|
|                                      |          | N  | %   |
| Gender                               | Male     | 34 | 57% |
|                                      | Female   | 26 | 43% |
| Age band                             | 0 to 4   | 8  | 13% |
|                                      | 5 to 9   | 9  | 15% |
|                                      | 10 to 14 | 4  | 7%  |
|                                      | 15 to 19 | 1  | 2%  |
|                                      | 20 to 24 | 1  | 2%  |
|                                      | 25 to 29 | 2  | 3%  |
|                                      | 30 to 39 | 6  | 10% |
|                                      | 40 to 49 | 8  | 13% |
|                                      | 50 to 59 | 7  | 12% |
|                                      | 60 to 69 | 8  | 13% |
|                                      | 70 to 79 | 5  | 8%  |
|                                      | 80+      | 1  | 2%  |

<sup>c</sup> Figures may not sum to 100% due to rounding.

| Patient characteristics                |         |    |     |
|----------------------------------------|---------|----|-----|
|                                        |         | N  | %   |
| Performance status at start of regimen | 0       | 11 | 18% |
|                                        | 1       | 14 | 23% |
|                                        | 2       | 3  | 5%  |
|                                        | 3       | 0  | 0%  |
|                                        | 4       | 0  | 0%  |
|                                        | Missing | 32 | 53% |

## Blueteq data items

Table 6 and Table 7 present the distribution of Blueteq data items.

**Table 6: Initiation of treatment with larotrectinib and funded for the first twelve weeks (N=60)**

| Blueteq data items <sup>d</sup>     |                             | N  | %   |
|-------------------------------------|-----------------------------|----|-----|
| Site and histology of tumour origin | Primary brain tumour        | 15 | 25% |
|                                     | Sarcoma                     | 12 | 20% |
|                                     | Infantile fibrosarcoma      | 4  | 7%  |
|                                     | Lung adenocarcinoma         | 4  | 7%  |
|                                     | Non-squamous NSCLC          | 4  | 7%  |
|                                     | Primary CNS tumour          | 3  | 5%  |
|                                     | Thyroid                     | 3  | 5%  |
|                                     | Glioma                      | 3  | 5%  |
|                                     | Papillary thyroid carcinoma | 2  | 3%  |
|                                     | Lung                        | 2  | 3%  |

<sup>d</sup> Figures may not add to 100% due to rounding.

| Blueteq data items                  |                                                                                                                                                                                                                                     | N  | %   |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|
| Site and histology of tumour origin | Colorectal adenocarcinoma                                                                                                                                                                                                           | 2  | 3%  |
|                                     | Forearm spindle cell sarcoma                                                                                                                                                                                                        | 1  | 2%  |
|                                     | Head adenocarcinoma                                                                                                                                                                                                                 | 1  | 2%  |
|                                     | Oesophagus adenocarcinoma                                                                                                                                                                                                           | 1  | 2%  |
|                                     | Salivary gland carcinoma                                                                                                                                                                                                            | 1  | 2%  |
|                                     | Salivary gland adenocarcinoma                                                                                                                                                                                                       | 1  | 2%  |
|                                     | Not captured                                                                                                                                                                                                                        | 1  | 2%  |
| Type of disease                     | Metastatic disease                                                                                                                                                                                                                  | 24 | 40% |
|                                     | Locally advanced with systemic therapy                                                                                                                                                                                              | 18 | 30% |
|                                     | Locally advanced with surgical resection resulting in morbidity                                                                                                                                                                     | 17 | 28% |
|                                     | Not captured                                                                                                                                                                                                                        | 1  | 2%  |
| Type of surgical resection          | Recurrent disease with no further treatment option                                                                                                                                                                                  | 1  | 2%  |
|                                     | Limb reconstruction                                                                                                                                                                                                                 | 1  | 2%  |
|                                     | Extensive resection of forearm and left elbow                                                                                                                                                                                       | 1  | 2%  |
|                                     | Would have required chest surgery. Previously had massive chest surgery in the neonatal period with prolonged admission to NICU requiring intubation and ventilation, with associated neurological sequelae (subdural haemorrhage). | 1  | 2%  |
|                                     | Excision of whole lump                                                                                                                                                                                                              | 1  | 2%  |
|                                     | Extensive brain surgery                                                                                                                                                                                                             | 1  | 2%  |
|                                     | Resection would be required in an eloquent part of brain, risk of morbidity                                                                                                                                                         | 1  | 2%  |
|                                     | Mid brain tumour                                                                                                                                                                                                                    | 1  | 2%  |



| Blueteq data items <sup>e</sup> |                                                                                                                                                            | N  | %   |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|
| Type of surgical resection      | Excision and risk of morbidity is because blood vessels are very close to it.                                                                              | 1  | 2%  |
|                                 | Transection of spinal cord                                                                                                                                 | 1  | 2%  |
|                                 | This is locally advanced disease that has not responded to 1st line therapy; it is in very precarious position and the child is at risk of losing eyesight | 1  | 2%  |
|                                 | Gross total resection or debulk                                                                                                                            | 1  | 2%  |
|                                 | Thalamic resection                                                                                                                                         | 1  | 2%  |
|                                 | Neurosurgical resection not possible due to the diffuse nature of the tumour in the brain stem. Allergy to first line chemotherapy                         | 1  | 2%  |
|                                 | Large brain tumour, not resectable                                                                                                                         | 1  | 2%  |
|                                 | Unmanageable cardiothoracic surgery                                                                                                                        | 1  | 2%  |
|                                 | Craniotomy and significant resection of brain                                                                                                              | 1  | 2%  |
|                                 | Involvement of radial nerve                                                                                                                                | 1  | 2%  |
|                                 | Inoperable. Widespread in all fluid spaces                                                                                                                 | 1  | 2%  |
|                                 | Not applicable                                                                                                                                             | 40 | 69% |
|                                 | Not captured                                                                                                                                               | 1  | 2%  |
| Lines of systemic therapy       | 1 line of systemic therapy                                                                                                                                 | 47 | 78% |

<sup>e</sup> Figures may not add to 100% due to rounding.

| Blumetq data items <sup>f</sup> |                                                                                                                                                                             | N  | %   |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|
| Lines of systemic therapy       | 2 lines of systemic therapy                                                                                                                                                 | 5  | 8%  |
|                                 | 3 or more lines of systemic therapy                                                                                                                                         | 6  | 10% |
|                                 | Larotrectinib is being used as first line therapy for locally advanced or metastatic disease as the patient has no satisfactory systemic therapy options as described above | 1  | 2%  |
|                                 | Not captured                                                                                                                                                                | 1  | 2%  |
| NTRK gene                       | NTRK1                                                                                                                                                                       | 22 | 37% |
|                                 | NTRK2                                                                                                                                                                       | 18 | 30% |
|                                 | NTRK3                                                                                                                                                                       | 19 | 32% |
|                                 | Not captured                                                                                                                                                                | 1  | 2%  |
| Gene fusion                     | TPM3                                                                                                                                                                        | 5  | 8%  |
|                                 | SQSTM1                                                                                                                                                                      | 4  | 7%  |
|                                 | ETV6                                                                                                                                                                        | 4  | 7%  |
|                                 | ETV6-NTRK3                                                                                                                                                                  | 4  | 7%  |
|                                 | TPM3-NTRK1                                                                                                                                                                  | 3  | 5%  |
|                                 | SPECC1L-NTRK2                                                                                                                                                               | 2  | 3%  |
|                                 | EML4                                                                                                                                                                        | 2  | 3%  |
|                                 | TPR                                                                                                                                                                         | 2  | 3%  |
|                                 | KANK1-NTRK2                                                                                                                                                                 | 2  | 3%  |
|                                 | LMNA                                                                                                                                                                        | 2  | 3%  |
|                                 | ETV6 exon 4 and NTRAK 3 exon 14                                                                                                                                             | 1  | 2%  |
|                                 | STRN3                                                                                                                                                                       | 1  | 2%  |

<sup>f</sup> Figures may not add to 100% due to rounding.

| Blueteq data items <sup>9</sup> |                                                 | N | %  |
|---------------------------------|-------------------------------------------------|---|----|
| Gene fusion                     | SPECC1L-ADORA2A                                 | 1 | 2% |
|                                 | G344W                                           | 1 | 2% |
|                                 | DFFB exon 1(Novel fusion)                       | 1 | 2% |
|                                 | IRF2BP2-NTRK1                                   | 1 | 2% |
|                                 | SGTB                                            | 1 | 2% |
|                                 | EEF1G                                           | 1 | 2% |
|                                 | ETV6 (NM_NM_001987.4) exon 5                    | 1 | 2% |
|                                 | KANK1-NTRK2 fusion                              | 1 | 2% |
|                                 | TNS3                                            | 1 | 2% |
|                                 | KCTD16-NTRK2                                    | 1 | 2% |
|                                 | NOS1AP                                          | 1 | 2% |
|                                 | KCTD8                                           | 1 | 2% |
|                                 | SCAPER-NTRK3                                    | 1 | 2% |
|                                 | LHFPL3                                          | 1 | 2% |
|                                 | SPECC1L                                         | 1 | 2% |
|                                 | BCR[NM_004327.4] (Ex1::NTRK2[NM_06180.4})(Ex12) | 1 | 2% |
|                                 | BCR-NTRK2                                       | 1 | 2% |
|                                 | TPR-NTRK1                                       | 1 | 2% |
|                                 | SQSTM1-NTRK3                                    | 1 | 2% |
|                                 | (LMNA(exon11)-NTRK1(exon10)                     | 1 | 2% |
|                                 | NACC2                                           | 1 | 2% |

<sup>9</sup> Figures may not add to 100% due to rounding.

| Blueteq data items <sup>h</sup> |                                                                                                                                                                                                         | N  | %   |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|
| Gene fusion                     | The RT PCR technique (see AmoyDx kit description) does not allow exact typing of the partner of NTRK3 gene but gives an exhaustive list of the potential ones; this tumour was positive under channel 7 | 1  | 2%  |
|                                 | FGFR                                                                                                                                                                                                    | 1  | 2%  |
|                                 | LMNA-NTRK1                                                                                                                                                                                              | 1  | 2%  |
|                                 | MEF2D-NTRK1                                                                                                                                                                                             | 1  | 2%  |
|                                 | Not known                                                                                                                                                                                               | 1  | 2%  |
|                                 | Not captured                                                                                                                                                                                            | 2  | 4%  |
| Brain metastases                | The patient does not have brain metastases                                                                                                                                                              | 51 | 85% |
|                                 | Brain metastases with previous cerebral surgery                                                                                                                                                         | 6  | 10% |
|                                 | Brain metastases and no cerebral surgery                                                                                                                                                                | 2  | 3%  |
|                                 | Not captured                                                                                                                                                                                            | 1  | 2%  |

<sup>h</sup> Figures may not add to 100% due to rounding.

Table 7: Information as to the RECIST response assessment made at 10 weeks after initiation of larotrectinib (N=43)

| Blueteq data items                          |                                      | N  | %   |
|---------------------------------------------|--------------------------------------|----|-----|
| Larotrectinib response                      | Partial response                     | 28 | 65% |
|                                             | Stable disease                       | 12 | 28% |
|                                             | Complete response                    | 3  | 7%  |
| Weeks between start and response assessment | 6                                    | 1  | 2%  |
|                                             | 7                                    | 2  | 5%  |
|                                             | 8                                    | 3  | 7%  |
|                                             | 8 (CT) and 15 (MRI)                  | 1  | 2%  |
|                                             | 9                                    | 4  | 9%  |
|                                             | 9.5                                  | 1  | 2%  |
|                                             | 10                                   | 18 | 42% |
|                                             | 11                                   | 5  | 12% |
|                                             | 12                                   | 4  | 9%  |
|                                             | 13                                   | 1  | 2%  |
|                                             | 16                                   | 1  | 2%  |
|                                             | 17                                   | 1  | 2%  |
|                                             | Not captured                         | 1  | 2%  |
| Larotrectinib cerebral response             | No metastatic intracerebral response | 29 | 67% |
|                                             | Primary brain tumour                 | 9  | 21% |
|                                             | Partial response in CNS              | 3  | 7%  |
|                                             | Stable disease in CNS                | 2  | 5%  |
| Weeks between start and cerebral response   | 6                                    | 1  | 2%  |
|                                             | 7                                    | 2  | 5%  |
|                                             | 9                                    | 2  | 5%  |
|                                             | 9.5                                  | 1  | 2%  |

| Blueteq data items                        |                         | N  | %    |
|-------------------------------------------|-------------------------|----|------|
| Weeks between start and cerebral response | 10                      | 15 | 35%  |
|                                           | 11                      | 2  | 5%   |
|                                           | 12                      | 4  | 9%   |
|                                           | 16                      | 1  | 2%   |
|                                           | 26                      | 1  | 2%   |
|                                           | Not applicable          | 10 | 23%  |
|                                           | Not captured            | 4  | 9%   |
| Larotrectinib continuation                | Will continue treatment | 43 | 100% |

## NTRK testing captured in NDRS molecular dataset

40,472 unique patients had a record in the NDRS molecular dataset with either a positive, borderline or negative NTRK test result between 31 July 2018 and 31 December 2024. Of these 40,472 patients, 39,363 unique patients (97%) had a cancer registered in the cancer registration dataset at the time this report was produced.

**Table 8: NTRK test results (N=39,363)<sup>i,j</sup>**

| Cancer group              | Borderline | Negative | Positive | Total  |
|---------------------------|------------|----------|----------|--------|
| Lung                      | 10         | 18,178   | 110      | 18,298 |
| Lower GI                  | 5          | 4,146    | 26       | 4,177  |
| HPB                       | 1          | 2,110    | 9        | 2,120  |
| Other                     | 5          | 1,973    | 33       | 2,011  |
| Oesophagogastric          | 1          | 1,997    | 10       | 2,008  |
| Gynaecological            | 1          | 1,787    | 14       | 1,802  |
| Brain and CNS             | 7          | 1,528    | 28       | 1,563  |
| Prostate                  | 2          | 1,319    | 2        | 1,323  |
| Soft tissue and bone      | 2          | 1,204    | 28       | 1,234  |
| Skin                      | 2          | 1,094    | 16       | 1,112  |
| Head and neck             | 2          | 849      | 40       | 891    |
| Endocrine                 | 1          | 760      | 24       | 785    |
| Breast                    | 1          | 737      | 14       | 752    |
| Haematology               |            | 663      | 5        | 668    |
| Urology excl. prostate    | 1          | 597      | 3        | 601    |
| Thoracic and mesothelioma |            | 351      | 1        | 352    |

Of the 404 patients with a positive or borderline result, 251 (62%) had a gene fusion captured in the NDRS molecular dataset. It is important to note that a substantial proportion of the testing (>60%) in this cohort was performed by methods which do **not** capture specific details of the gene fusions and partner genes involved, including immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR). In cases where positive results from these methodologies have been confirmed by Next-generation sequencing (NGS) in the Genomic Laboratory Hubs (GLHs), specific fusion details have been captured and are included in the dataset.

<sup>i</sup> If a patient had more than one diagnosis in the Cancer Registration dataset, the diagnosis date closest to the lab test date was selected. In some cases, the test date was not submitted, or a patient might have more than one tumour registered on the same date, in both cases, patients will be counted multiple times.

<sup>j</sup> Blueteq data was not included in this section.

Table 9: Characterisation of gene fusion (N=404)

| Cancer group              | NTRK1      | NTRK2     | NTRK3      | Unknown    | Total      |
|---------------------------|------------|-----------|------------|------------|------------|
| Lung                      | 18         | 3         | 18         | 81         | 120        |
| Head and neck             | 4          | 2         | 22         | 14         | 42         |
| Other                     | 13         | 3         | 17         | 5          | 38         |
| Brain and CNS             | 15         | 12        | 6          | 2          | 35         |
| Lower GI                  | 21         |           | 3          | 7          | 31         |
| Soft tissue and bone      | 13         |           | 8          | 9          | 30         |
| Endocrine                 | 10         |           | 12         | 3          | 25         |
| Skin                      | 11         | 1         | 3          | 3          | 18         |
| Breast                    | 1          | 2         | 8          | 4          | 15         |
| Gynaecological            | 7          |           | 2          | 6          | 15         |
| Oesophagogastric          | 1          |           | 1          | 9          | 11         |
| HPB                       | 4          | 1         | 2          | 3          | 10         |
| Haematology               |            |           | 4          | 1          | 5          |
| Urology excl. prostate    | 1          |           | 2          | 1          | 4          |
| Prostate                  |            | 1         |            | 3          | 4          |
| Thoracic and mesothelioma |            |           |            | 1          | 1          |
| <b>Total</b>              | <b>119</b> | <b>25</b> | <b>108</b> | <b>152</b> | <b>404</b> |

Of the 60 patients with a CDF application and a record in SACT, 25 have a record in the molecular dataset.

Table 10: Characterisation of gene fusion (N=25)

| Cancer group         | NTRK1    | NTRK2    | NTRK3    | Unknown  | Total     |
|----------------------|----------|----------|----------|----------|-----------|
| Brain and CNS        | 2        | 4        | 1        | 1        | 8         |
| Lung                 | 1        |          | 2        | 2        | 5         |
| Soft tissue and bone | 2        |          | 1        | 2        | 5         |
| Endocrine            | 1        |          | 2        |          | 3         |
| Other                |          |          | 1        | 1        | 2         |
| Gynaecological       |          |          |          | 1        | 1         |
| Lower GI             | 1        |          |          |          | 1         |
| <b>Total</b>         | <b>7</b> | <b>4</b> | <b>7</b> | <b>7</b> | <b>25</b> |



## Time to subsequent treatments in SACT

8/60 (13%) unique patients treated with larotrectinib between 21 April 2020 and 31 December 2024 have subsequent therapies in the SACT dataset, received after the patient's last larotrectinib cycle.

The median time from a patient's last larotrectinib cycle in SACT to their next treatment was 77 days<sup>k</sup>.

The median time from a patient's first larotrectinib cycle in SACT to their next treatment was 416.5 days.

Table 11 reports regimens prescribed after larotrectinib, as recorded in the SACT dataset

**Table 11: Distribution of first treatments prescribed after a patient's last larotrectinib cycle (N(Patients)=8)<sup>l</sup>**

| Regimen                  | Number of subsequent treatments | %   |
|--------------------------|---------------------------------|-----|
| Trial                    | 2                               | 25% |
| Cabozantinib             | 1                               | 12% |
| Carboplatin + Pemetrexed | 1                               | 12% |
| Entrectinib              | 1                               | 12% |
| Lenvatinib               | 1                               | 12% |
| Repotrectinib            | 1                               | 12% |
| Temozolomide             | 1                               | 12% |

Of the 8 patients who received a subsequent treatment, two went on to receive second subsequent treatment following Larotrectinib:

- one patient received treatment with cabozantinib
- one patient received treatment with lomustine

<sup>k</sup> If a patient has >1 subsequent regimen recorded in SACT, time to next treatment only includes the regimen immediately after Larotrectinib. For the eight patients included in table 11, two patients went on to receive a second subsequent treatment at the time this report was produced.

<sup>l</sup> These data have not been validated/confirmed with trusts or by the NHSE data liaison team

# Treatment duration

Of the 60 patients with CDF applications, 32 (53%) were identified as having completed treatment by 31 December 2024 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with larotrectinib in at least three months (see Table 15).

The median follow-up time in SACT was 13.3 months (405 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Trusts submit their SACT return to the submission portal three months after the month's treatment activity has ended; this provides a maximum follow-up of 55.8 months for the CDF cohort.

By the end of the follow-up period, 31 December 2024, 32 patients had ended treatment, and 28 patients were still receiving treatment.

Table 13: Breakdown by patients' treatment status <sup>m,n,o</sup>

| Patient status                  | Frequency (N) | Percentage (%) |
|---------------------------------|---------------|----------------|
| Treatment ongoing               | 28            | 47%            |
| Treatment stopped               | 10            | 17%            |
| Patient died – not on treatment | 19            | 32%            |
| Patient died – on treatment     | 3             | 5%             |
| Total                           | 60            | 100%           |

Table 14 shows the 6, 12, 18, 24, 36 and 48-month treatment duration for patients receiving larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours.

<sup>m</sup> Figures may not sum to 100% due to rounding.

<sup>n</sup> Table 15 presents the outcome summary data reported by trusts. This includes patients from Table 13 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

<sup>o</sup> 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: <https://digital.nhs.uk/ndrs/data/data-sets/sact/sact-cdf-methodologies>

Table 14: Treatment duration at 6, 12, 18, 24, 36, and 48-month intervals

| Time period | Treatment duration (%) |                                 |                                 |
|-------------|------------------------|---------------------------------|---------------------------------|
|             | (%)                    | Lower Confidence Interval (LCI) | Upper Confidence Interval (UCI) |
| 6 months    | 79%                    | 70%                             | 90%                             |
| 12 months   | 67%                    | 56%                             | 81%                             |
| 18 months   | 59%                    | 47%                             | 74%                             |
| 24 months   | 53%                    | 41%                             | 70%                             |
| 36 months   | 39%                    | 26%                             | 57%                             |
| 48 months   | 26%                    | 15%                             | 48%                             |

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration for all patients was 26.9 months [95% CI: 14.4, 45.4] (818 days).

Figure 3: Kaplan-Meier treatment duration (N=60)

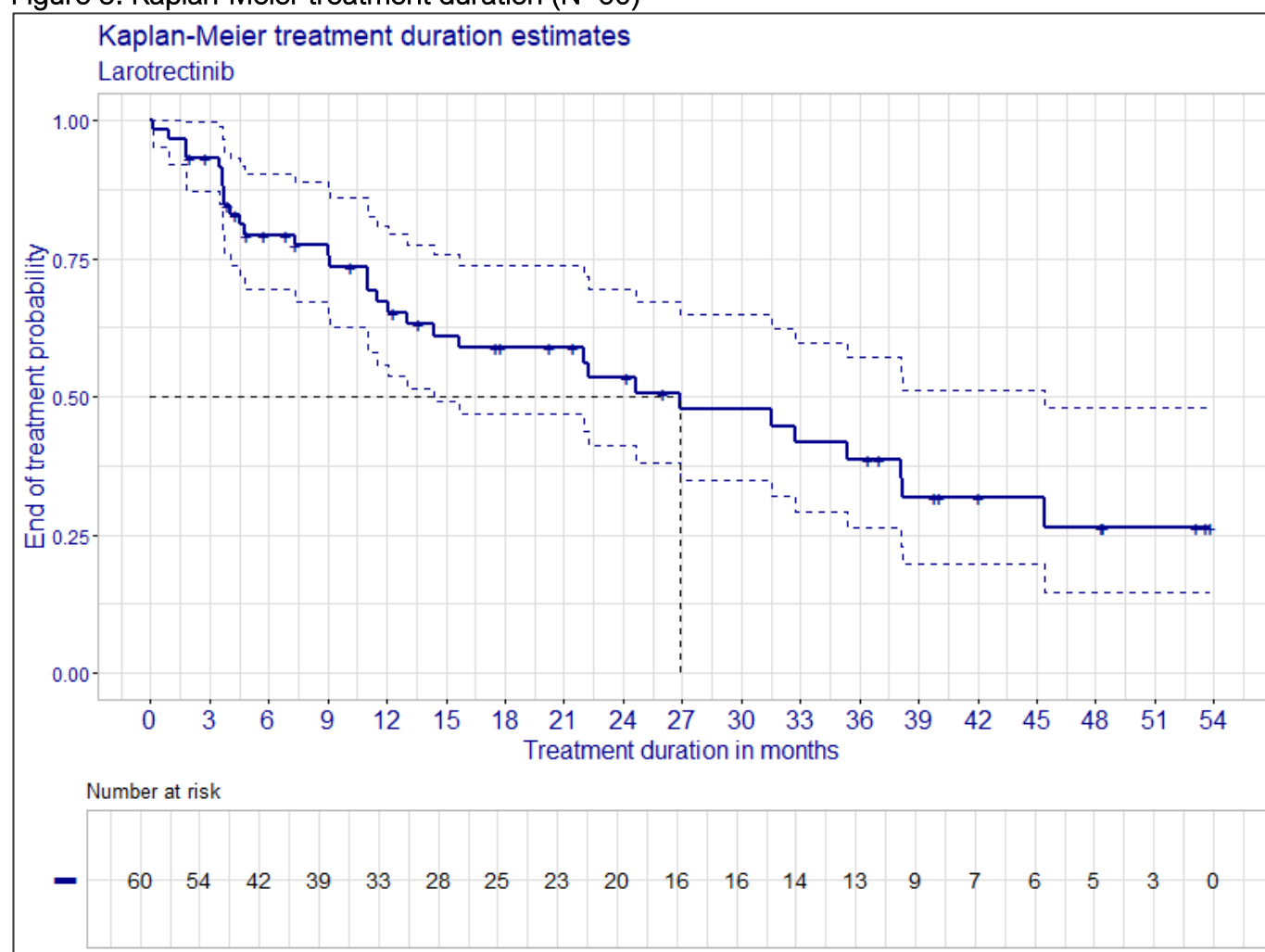


Table 15 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 53% (N=32) of patients had ended treatment at 31 December 2024.

**Table 15: Treatment outcomes for patients that have ended treatment (N=32)<sup>p,q</sup>**

| Outcome                                           | Frequency (N) | Percentage (%) |
|---------------------------------------------------|---------------|----------------|
| Progressive disease during chemotherapy           | 15            | 47%            |
| No treatment in 3 months                          | 4             | 13%            |
| Patient died not on treatment                     | 3             | 9%             |
| Patient died on treatment                         | 3             | 9%             |
| Treatment completed as prescribed                 | 3             | 9%             |
| Acute chemotherapy toxicity                       | 2             | 6%             |
| Patient choice (stopped or interrupted treatment) | 1             | 3%             |
| Palliative treatment and the patient did benefit  | 1             | 3%             |
| <b>Total</b>                                      | <b>32</b>     | <b>100%</b>    |

<sup>p</sup> Figures may not sum to 100% due to rounding.

<sup>q</sup> Table 15 presents the outcome summary data reported by trusts. This includes patients from Table 13 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Table 16: Treatment outcomes and treatment status for patients that have ended treatment (N=32)

| Outcome <sup>r</sup>                              | Patient died <sup>s</sup><br>not on<br>treatment | Treatment<br>stopped | Patient died<br>on treatment |
|---------------------------------------------------|--------------------------------------------------|----------------------|------------------------------|
| Progressive disease during chemotherapy           | 13                                               | 2                    |                              |
| No treatment in 3 months                          |                                                  | 4                    |                              |
| Patient died not on treatment                     | 3                                                |                      |                              |
| Patient died on treatment                         |                                                  |                      | 3                            |
| Treatment completed as prescribed                 | 2                                                | 1                    |                              |
| Acute chemotherapy toxicity                       |                                                  | 2                    |                              |
| Patient choice (stopped or interrupted treatment) | 1                                                |                      |                              |
| Palliative treatment and the patient did benefit  |                                                  | 1                    |                              |
| <b>Total</b>                                      | <b>19</b>                                        | <b>10</b>            | <b>3</b>                     |

<sup>r</sup> Relates to outcomes submitted by the trust in Table 15.<sup>s</sup> Relates to treatment status in Table 13 for those that have ended treatment.

## Overall survival (OS)

Of the 60 patients with a treatment record in SACT, the minimum follow-up was 3.7 months (113 days) from the last CDF application. Patients were traced for their vital status on 23 April 2025. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 19.4 months (591 days). The median follow-up is the patients’ median observed time from the start of their treatment to death or censored date.

The maximum follow-up period for survival for the CDF cohort was 59.5 months, all patients were traced on 23 April 2025.

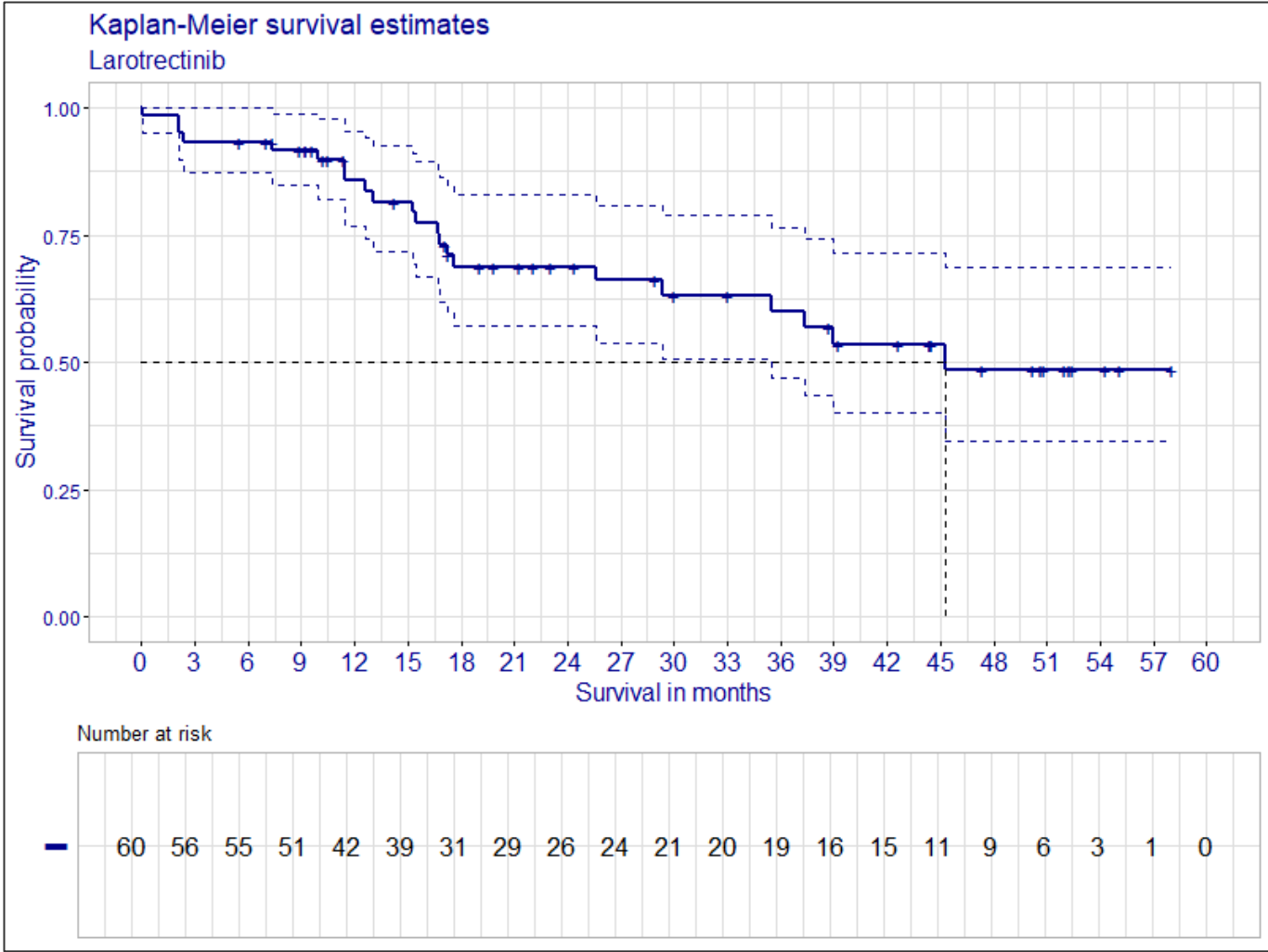
By the end of the follow-up period, 23 April 2025, 22 patients had died, and 38 patients were still alive.

Table 18: OS at 6, 12, 18, 24, 36 and 48-month intervals

| Time period | OS (%) |                                 |                                 |
|-------------|--------|---------------------------------|---------------------------------|
|             | (%)    | Lower Confidence Interval (LCI) | Upper Confidence Interval (UCI) |
| 6 months    | 93%    | 87%                             | 100%                            |
| 12 months   | 86%    | 77%                             | 95%                             |
| 18 months   | 69%    | 57%                             | 83%                             |
| 24 months   | 69%    | 57%                             | 83%                             |
| 36 months   | 60%    | 47%                             | 77%                             |
| 48 months   | 49%    | 34%                             | 69%                             |

Figure 4 provides the Kaplan-Meier curve for OS, censored at 23 April 2025. The median OS was 45.2 months<sup>t</sup> (1,376 days).

Figure 4: Kaplan-Meier survival plot (N=60)



<sup>t</sup> Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

## 4.Sensitivity analyses

### 6-months follow up

### Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, applications were limited to 1 July 2024 and SACT activity was followed up to 31 December 2024.

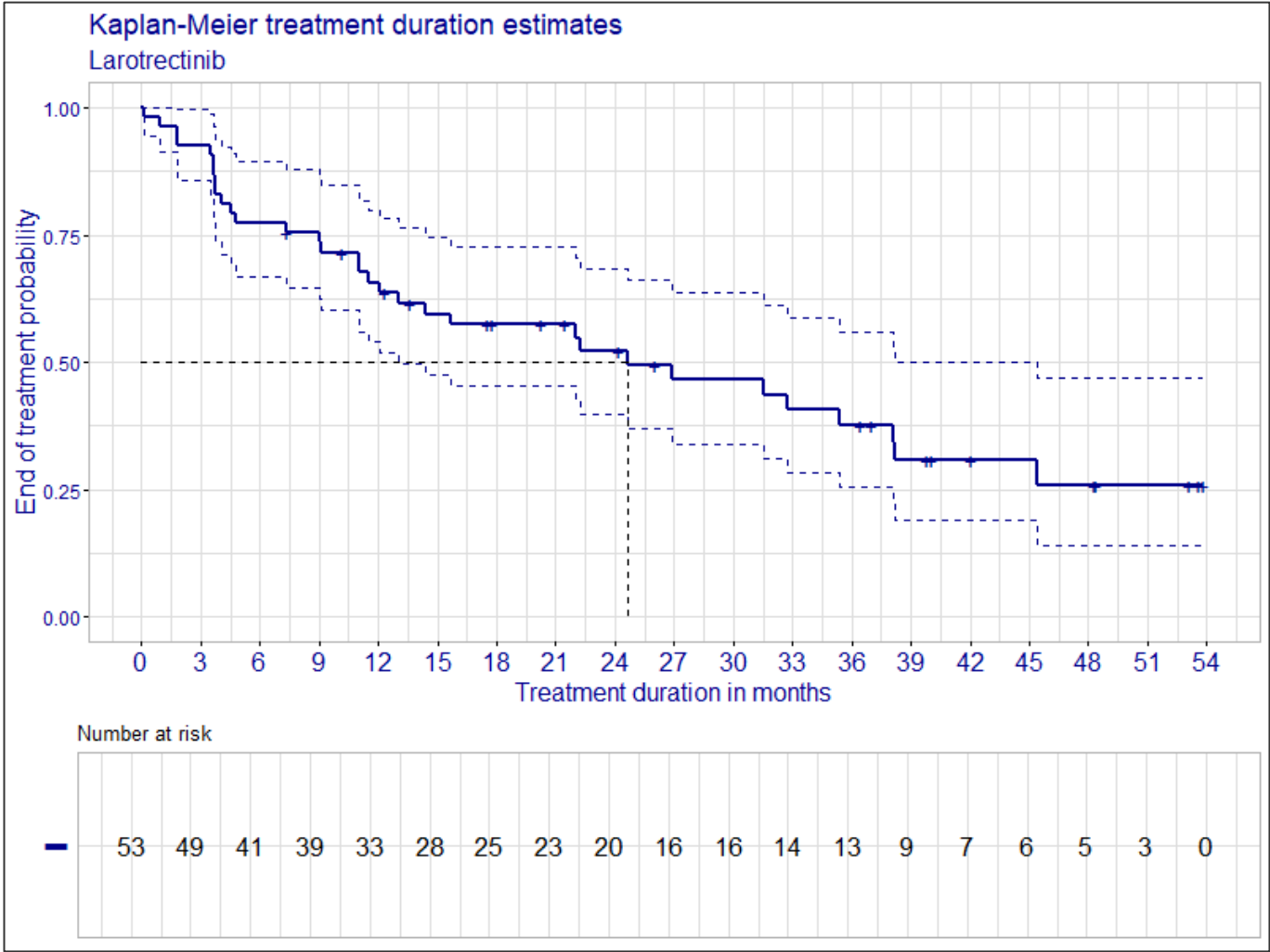
Following the exclusions above, 53 patients (88%) were identified for inclusion. The median follow-up time in SACT was 17.5 months (534 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

The Kaplan-Meier curve for treatment duration is shown in Figure 5. The median treatment duration for patients in this cohort was 24.6 months [95% CI: 13, 45.4] (749 days) (N=53).

By the end of the follow-up period, 31 December 2023, 32 patients had ended treatment, and 21 patients were still receiving treatment.



Figure 5: Kaplan-Meier treatment duration plot (N=53)



## Overall survival (OS)

Sensitivity analysis was also carried out for OS on a cohort with at least six months follow-up. To identify the cohort, applications were limited to 22 October 2024 and patients were traced for their vital status on 23 April 2025.

Following the exclusions above, 59 patients (99%) were identified for inclusion. The median follow-up time was 19.8 months (603 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The Kaplan-Meier curve for OS is shown in Figure 6. The median OS for patients in this cohort was 45.2 months<sup>u</sup> (1,376 days).

By the end of the follow-up period, 23 April 2025, 22 patients had died, and 37 patients were still alive.

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<sup>u</sup> Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Figure 6: Kaplan-Meier survival plot (N=59)

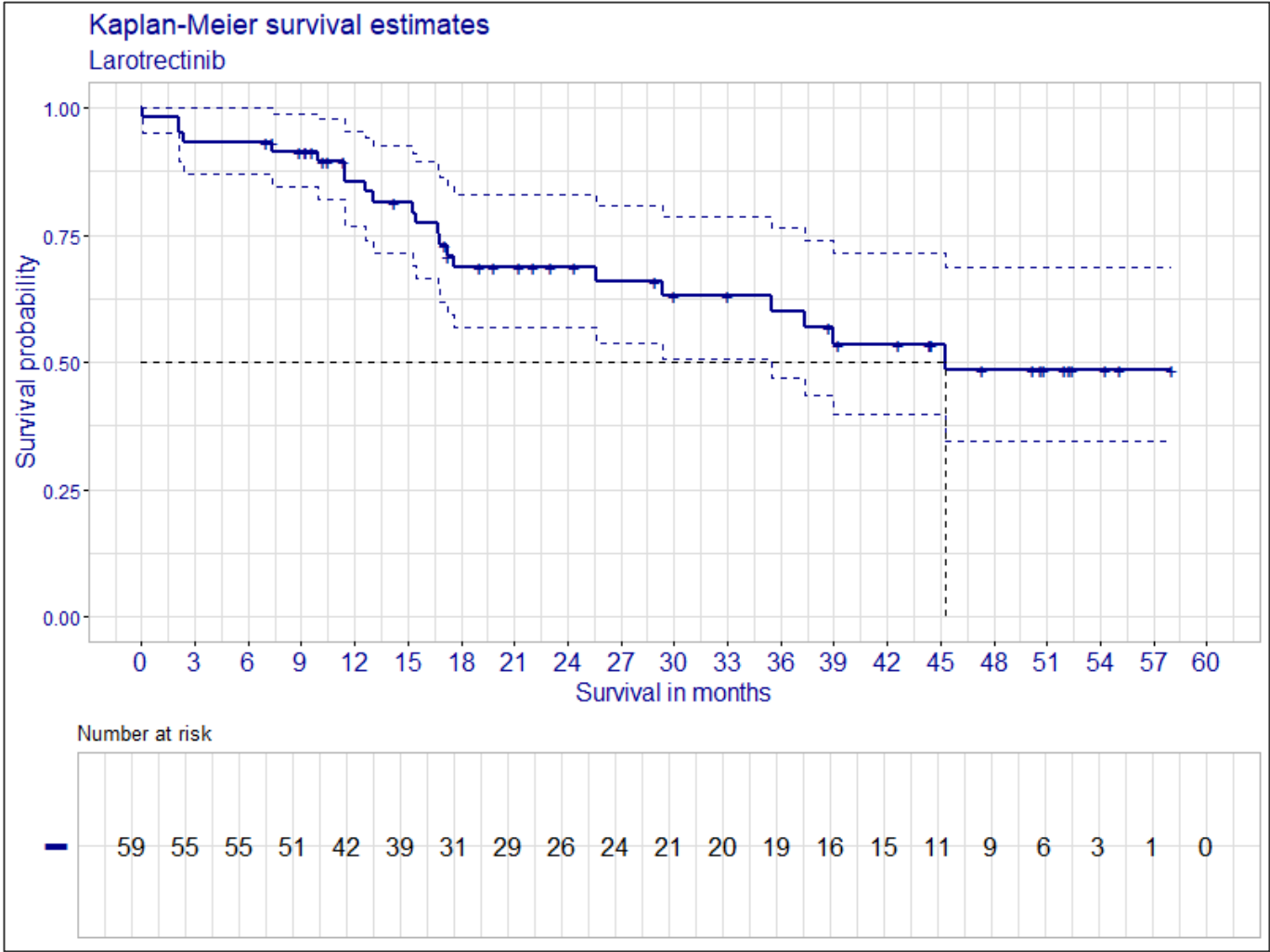


Table 19: Median treatment duration and OS, full cohort and sensitivity analysis

| Metric                    | Main CDF cohort<br>Standard analysis:<br>Full cohort | Sensitivity analysis:<br>6 months follow-up<br>cohort: treatment duration | Sensitivity analysis:<br>6 months follow-up<br>cohort: OS |
|---------------------------|------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------|
| N                         | 60                                                   | 53                                                                        | 59                                                        |
| Median treatment duration | 26.9 months [95% CI: 14.4, 45.4] (818 days)          | 24.6 months [95% CI: 13, 45.4] (749 days)                                 |                                                           |
| OS <sup>v</sup>           | 45.2 months (1,376 days)                             |                                                                           | 45.2 months (1,376 days)                                  |

<sup>v</sup> Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

## 5. Conclusions

61 patients received larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours [TA630] through the CDF in the reporting period (21 April 2020 to 31 December 2024). 60 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. One additional patient with a Blueteq application died before treatment and this was confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset show that 57% (N=34) of patients who received larotrectinib for the treatment of NTRK fusion-positive advanced solid tumours were male and 43% (N=26) of patients were female. 28% (N=17) of the cohort was aged between 0 and 9 years, while a further 38% (N=23) were aged between 40 and 69. 46% (N=28) of patients had a performance status between 0 and 2 at the start of their regimen, and performance status was missing for 53% of patients (N=32).

At data cut off, 53% (N=32) of patients were identified as no longer being on treatment. Of these 32 patients:

- 47% (N=15) of patients stopped treatment due to disease progression
- 13% (N=4) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 9% (N=3) of patients died not on treatment
- 9% (N=3) of patients died on treatment
- 6% (N=2) of patients stopped treatment due to acute toxicity
- 3% (N=1) of patients chose to end their treatment
- 3% (N=1) of patients were treated palliatively and did benefit from the treatment they received
- 9% (N=3) of patients completed treatment as planned

Median treatment duration was 26.9 months [95% CI: 14.4, 45.4] (818 days). Treatment duration at 6, 12, 18, 24, 36, and 48 months was calculated and showed that patients still receiving treatment at 6 months was 79% [95% CI: 70%, 90%], 67% [95% CI: 56%, 81%] at 12 months, 59% [95% CI: 47%, 74%] at 18 months, 53% [95% CI: 41%, 70%] at 24 months, 39% [95% CI: 26%, 57%] at 36 months, and 26% [95% CI: 15%, 48%] at 48 months.

The median OS was 45.2 months (1,376 days), confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced. OS at 6, 12, 18, 24, 36, and 48 months was calculated and showed that the OS at 6 months was 93% [95% CI: 87%, 100%], 86% [95% CI: 77%, 95%] at 12 months, 69% [95% CI: 57%, 83%] at 18 months,

69% [95% CI: 57%, 95%] at 24 months, 60% [95% CI: 47%, 77%] at 36 months, and 49% [95% CI: 34%, 69%] at 48 months.

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for OS was the same as the full cohort. Treatment duration for the full cohort was only slightly different with a treatment duration of 26.9 months [95% CI: 14.4, 45.4] compared to the sensitivity analysis which was 24.6 months [95% CI: 13, 45.4], this difference is not statistically significant.

## 6. References

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