

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Larotrectinib for treating NTRK fusion-positive  
solid tumours**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using larotrectinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using larotrectinib in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 7 February 2020

Second appraisal committee meeting: 4 March 2020

Details of membership of the appraisal committee are given in section 5.

## 1 Recommendations

- 1.1 Larotrectinib is not recommended, within its marketing authorisation, for treating advanced neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children who have no satisfactory treatment options.
- 1.2 This recommendation is not intended to affect treatment with larotrectinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or their parents or carers.

### Why the committee made these recommendations

There is no standard treatment for NTRK fusion-positive solid tumours, so current treatment is based on where in the body the cancer starts. Larotrectinib is a histology-independent treatment. This means that it targets a genetic alteration, NTRK gene fusion, that is found in many different tumour types irrespective of where the cancer starts.

Evidence from trials suggests that tumours with NTRK gene fusions shrink in response to larotrectinib. But it is difficult to know how well larotrectinib works because it has not been compared in the trials with other treatments. There is little or no evidence about whether larotrectinib works well for every type of NTRK fusion-positive tumour.

The cost-effectiveness estimates for larotrectinib are very uncertain because of limitations in the data, such as the substantial uncertainty about how long people would live after their disease gets worse. Further data collection would help to address the uncertainties in the clinical evidence. However, larotrectinib does not

have the potential to be a cost-effective use of NHS resources at its current price so it is not recommended for routine commissioning, or through the Cancer Drugs Fund.

## 2 Information about larotrectinib

### *Marketing authorisation indication*

2.1 Larotrectinib (Vitrakvi, Bayer) has a conditional marketing authorisation for 'the treatment of adult and paediatric patients with solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion:

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and
- who have no satisfactory treatment options'.

### *Dosage in the marketing authorisation*

2.2 Adults: The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. Children: Dosing in children is based on body surface area. The recommended dose is 100 mg/m<sup>2</sup> larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

### *Price*

2.3 The cost of larotrectinib is £5,000 per 100-ml vial of 20 mg/ml oral solution (excluding VAT; BNF online, accessed January 2020; £15,000 per 30-day supply). Larotrectinib will be available as hard capsules (25 mg and 100 mg) to be taken orally twice daily (company submission). The company has a commercial arrangement which would have applied if the technology had been recommended.

## 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Bayer and a review of this submission by the evidence review group (ERG), and the technical

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report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee discussed the following issues (issues 1 to 19), which were outstanding after the technical engagement stage.

### ***NTRK gene fusions***

#### **Larotrectinib targets a genetic mutation rather than a tumour type and there are challenges in appraising it**

3.1 Traditional oncology approaches treat tumours based on their type. More recently, targeted therapies based on the tumour's genetic information have been used for some indications. Larotrectinib is indicated for any solid tumours with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. Because many tumour types respond to it, the company considers larotrectinib to be 'tumour-agnostic' or 'histology-independent'. NTRK gene fusions may be able to drive tumour growth, so targeting treatment to the cause of the disease could mean higher rates of response to therapy and potentially better outcomes. The committee accepted that it was expected to appraise larotrectinib within its conditional marketing authorisation using NICE's single technology appraisal process. But it recognised the challenges of appraising a histology-independent treatment within this process.

#### **Solid tumours with NTRK gene fusions are rare and better characterisation is needed**

3.2 NTRK gene fusions occur rarely (less than 1%) in common tumours such as lung, colorectal and breast cancers. Some rare tumour types have more than 90% NTRK fusion prevalence (for example, mammary analogue secretory carcinoma and infantile fibrosarcoma). There are many tumour types with known NTRK gene fusions and all solid tumour types are included in larotrectinib's marketing authorisation. NTRK fusions can involve portions of the NTRK1, NTRK2 and NTRK3 genes with another unrelated gene partner (over 80 different partner genes

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identified). The European public assessment report (EPAR) for larotrectinib noted that ETV6-NTRK3 is the most frequent fusion found in high NTRK-prevalent tumours. It also noted there is evidence to support ETV6-NTRK3 fusions driving the growth of these tumour types regardless of other characteristics. For all other NTRK fusions, the driving role of cancer growth has not been properly studied. It is not known if there are tissue-specific mechanisms for bypassing response to drugs for NTRK fusions or effects from other drivers of tumour growth. The committee concluded that better characterisation of NTRK gene fusions was needed to fully support the histology-independent approach.

### **Further data on whether NTRK gene fusions affect prognosis are needed**

3.3 It is not known whether patients with NTRK gene fusions have a different prognosis to those who do not have them. Evidence of an association between NTRK gene fusions and different disease presentation is weak and based on data from very few patients. The company assumed there was no prognostic effect of NTRK gene fusions in its base-case analysis. The ERG considered that it was unclear whether NTRK fusions affect prognosis or whether they are associated with other factors that affect prognosis such as age and Eastern Cooperative Oncology Group (ECOG) status. Prognosis could also vary by tumour type and NTRK gene fusion type. The committee concluded that further data would be needed to establish whether NTRK gene fusions affect prognosis.

### ***Treatment pathway and comparator***

#### **People with NTRK fusion-positive solid tumours would value new treatment options**

3.4 There is no defined clinical pathway for people with solid tumours expressing the NTRK gene fusion. Treatment currently follows care guidelines for specific tumour types, with surgery, targeted therapy, immunotherapy and chemotherapy for the more common cancers. Treatment for rarer cancers is generally limited to surgery, radiotherapy

and chemotherapy. The patient experts explained that people who have a solid tumour with a gene alteration would want treatment with a targeted therapy because longer survival and a better side effect profile are likely. The aim of treatment for some inoperable tumours is to shrink the solid tumour so that surgery might be a treatment option. The committee concluded that people with NTRK fusion-positive solid tumours would value new treatment options.

**Larotrectinib's position in the treatment pathway is a major uncertainty and further data are needed**

3.5 Larotrectinib is indicated for 'the treatment of adult and paediatric patients with tumours that display a NTRK gene fusion and who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and no satisfactory treatment options'. The ERG considered that the positioning of larotrectinib would depend on which treatments clinicians consider unsatisfactory. This would vary because it involves assessing response rates and adverse events and discussing options with patients. The patient experts considered that any targeted therapy should be used as early in the treatment pathway as possible to maximise patient access. The clinical expert stated that for some sarcomas there are very few treatment options. In larotrectinib's summary of product characteristics it states that it should only be used if there are no treatment options with established clinical benefit, or when such treatment options have been exhausted. This is because the regulatory authority considered that larotrectinib's benefit had been established in single-arm trials in a relatively small sample of patients. But it also considered that its effect may differ depending on tumour type and other possible gene alterations, so it should not displace any effective therapies. The company therefore positioned larotrectinib as a last-line treatment, after all other treatments have been exhausted, by choosing the comparators best supportive care for common cancers and chemotherapy for rarer cancers. The committee considered this positioning appropriate and in line with the marketing authorisation.

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However, the committee recognised that if larotrectinib's efficacy was further established, it was possible that clinicians would want to use it earlier in the pathway. This would displace other potentially effective therapies and is outside larotrectinib's current marketing authorisation. Further evidence about this is being collected as part of larotrectinib's conditional marketing authorisation. The committee concluded that larotrectinib's positioning was a major uncertainty and collecting further data would determine how larotrectinib would be used in clinical practice.

## ***Diagnosis***

### **The diagnostic pathway for NTRK fusions has implications for identifying patients and on diagnosis costs**

3.6 All solid tumour types could potentially have an NTRK gene fusion although they are rare in common tumour types (see section 3.2). Therefore, many people would need screening to identify who would benefit from larotrectinib. Currently, NTRK testing is not routinely done in the NHS for all solid tumours. However, it is available for mammary analogue secretory carcinoma and secretory breast carcinoma with immunohistochemistry techniques (a method that uses antibodies to detect the gene fusion protein). Whole genome sequencing (a method of determining the whole DNA sequence of a cancer, used for discovering mutations) can also identify NTRK gene fusions. It is available for children's cancers and sarcomas, although confirmation of the results is needed with DNA-based next generation sequencing (a faster method of sequencing targeted regions of the cancer's DNA). The committee concluded that the diagnostic pathway for NTRK gene fusions was important, with implications for identifying patients and on costs of diagnosis.

**The diagnostic pathway is uncertain until NHS England establishes a national service for genomic testing of all advanced solid tumours**

3.7 The Cancer Drugs Fund clinical lead explained that NHS England is currently establishing a national service for cancer genomic testing. This service will replace all current genomic testing done locally. It involves setting up 7 genomic laboratory hubs across England to do next generation sequencing and interpret all results before returning them to the requesting clinician. The committee understood that until the genomic laboratory hubs are fully established, genomic testing for NTRK gene fusions by next generation sequencing will be done after all NHS commissioned treatment options have been used. When the hubs are fully established, next generation sequencing-based testing to identify gene alterations, including NTRK gene fusions, will be done at the point of diagnosis of locally advanced or metastatic solid tumours. The Cancer Drugs Fund clinical lead estimated that 100,000 solid tumours will be tested per year once the service is fully established. He noted that other targeted therapies will likely become available soon for different diseases and genomic testing will also be needed before these treatments are used. The committee acknowledged the ongoing developments in genomic testing practice to identify NTRK fusion-positive solid tumours. The committee considered that the rapid change to the diagnostic testing pathway being led by NHS England was a unique situation. It concluded that the diagnostic testing pathway was uncertain until NHS England's plans are fully established in clinical practice.

**Diagnostic techniques will improve as the genomic laboratory hubs validate their techniques and NTRK gene fusions are better characterised**

3.8 The diagnostic specificity of any test needs to be very high to exclude patients who do not have an NTRK gene fusion and so would not benefit from larotrectinib. This particularly affects common tumour types with low NTRK prevalence (for example, lung, colorectal and breast tumours) in which the number of false-positive results could outnumber true-positive

results if the test is not specific enough. The committee was aware that currently, DNA-based next generation sequencing and whole genome sequencing were not sensitive enough to screen for NTRK gene fusions. Clinical experts considered that DNA and RNA-based next generation sequencing with a confirmatory immunohistochemistry test would be appropriate and minimise the number of false-positive results. Some factors may reduce the specificity of these tests such as tissue degradation and human error. The committee noted that the last-line positioning of larotrectinib reduced the risk of displacing active treatments for patients with false-positive results for NTRK gene fusions, whose tumours would not respond to larotrectinib. However, there were concerns about the ethics of treatment for any patients with false-positive results because of adverse events. The committee concluded that diagnostic techniques will improve as the genomic laboratory hubs validate their techniques and NTRK gene fusions are better characterised (see section 3.2).

### ***Clinical evidence***

**The key clinical evidence comes from a pooled analysis of 3 single-arm clinical trials and is appropriate for decision making**

- 3.9 The company presented a pooled analysis of 102 patients from 3 trials:
- NAVIGATE is an ongoing trial for patients of 12 years and over with locally advanced or metastatic tumours with an NTRK gene fusion who have had prior therapy or who would be unlikely to derive clinical benefit from standard care. NAVIGATE contributed 62 patients to the pooled analysis.
  - SCOUT is an ongoing trial for children with locally advanced or metastatic solid tumours or primary central nervous system (CNS) tumours. SCOUT contributed 32 patients to the pooled analysis.
  - LOXO-TRK-14001 was a dose-finding study in patients with solid tumours with NTRK gene fusions, which contributed 8 patients to the

pooled analysis. The group analysed for efficacy was further split by patients with primary CNS tumours (n=9) and all other patients (n=93).

The ERG considered that the recruited patients represented a proportion of those who might be eligible for larotrectinib in the NHS because they were likely to have solid tumours with NTRK gene fusions. The committee noted the small patient numbers from each of the trials making up the pooled analysis. Also, it noted that the trials were single arm and did not include a control group. Given the rarity of the gene fusion, the committee concluded that the evidence was appropriate for decision making.

**The key clinical evidence is not generalisable to NHS clinical practice and further data are needed**

3.10 The company considered the results to be generalisable to NHS clinical practice and did not do any adjustments for baseline characteristics. The ERG noted that patients in each study were recruited by convenience sampling and there was no systematic attempt to represent the distribution of tumour types in NHS clinical practice. Therefore, a substantial proportion of the population in the clinical evidence base had high NTRK-prevalent tumour types because these patients were easier to recruit. This over-representation of high NTRK prevalence tumour types could have affected response rate estimates (see section 3.13), included fewer false positives (see section 3.8) and included a higher proportion of children with potential to be cured (see section 3.19). Rare tumour types were over-represented, which meant that more people have active chemotherapy options compared with best supportive care (see section 3.4). In addition to under-represented tumour types, there were tumour types that were not represented at all in the clinical evidence. So the committee would need to accept that unrepresented solid tumours (for which there is no data) would respond to larotrectinib. The ERG also considered that not enough information was provided to explore patient characteristics in the trial and whether these were generalisable to the population who would have treatment in NHS clinical practice. The

committee considered that the diversity of tumour types would make adjusting for patient characteristics by tumour type very difficult, but this was not explored. The ERG considered that it was unclear whether patients had exhausted their treatment options; the trial inclusion criteria may be different to the marketing authorisation because the definition of satisfactory is open to interpretation (see section 3.5). This could have led to considerable bias. The committee concluded that the key clinical evidence was not generalisable to NHS clinical practice because of the distribution of tumour types, including potentially unrepresented tumour types, and the unknown effect of patient characteristics. Further data collection is needed to explore the types of tumour and distribution of patients, which were major uncertainties.

**The size of larotrectinib's benefit on long-term survival cannot be reliably estimated because the data are immature**

3.11 The primary outcome measure of the 2 larger trials was overall response rate. The committee considered that the evidence showed a clinically relevant overall response rate of 72% across multiple tumour types. But it considered that this may not be generalisable to the broader range of tumour types expected in NHS clinical practice (see section 3.10). Also, it was aware of considerable uncertainty around the extent to which the response translated into clinically meaningful survival benefits. The progression-free survival outcome measure was immature, with only 37% of patients having progressed disease (excluding primary CNS tumours). Also, overall survival was very immature with only 14% mortality in the trials. The immaturity of the data meant that the extrapolation of survival estimates was very uncertain (see section 3.20). The committee concluded that the immaturity of the survival data meant that the size of larotrectinib's benefit on long-term survival could not be reliably estimated.

## ***Heterogeneity in response***

### **The trials are not designed to assess heterogeneity in response**

3.12 The committee was aware of several biological reasons why heterogeneity, or a difference, in response to larotrectinib might be seen. For example, response might be different by histology, by NTRK gene fusion or fusion partner, by the presence of codrivers of the disease and by age (for example for children's indications). None of the statistical protocols of the trials included in the pooled analysis were designed to test heterogeneity in response by any factor. NAVIGATE was a 'basket' trial (that is, a trial that included patients who had different types of cancer but the same gene mutation) which involved many small groups of patients stratified by tumour type. If a response was seen in one of these groups, a response to larotrectinib for that tumour type was assumed and it was further expanded to increase the sample size. However, the company later pooled all the analyses from 3 different studies of all patients in whom efficacy could be evaluated (see section 3.9). The EPAR states that selection bias on pooling the data is possible and there may be some tumour types that do not respond (type 1 error). The ERG explained that the company assumed an equal response to larotrectinib independent of tumour type and response was not formally assessed by tumour type. The committee concluded that the trials were not designed to assess heterogeneity in response.

### **Assuming equal response to larotrectinib across tumour types and fusion types is inappropriate**

3.13 The committee noted the challenges of assessing response because the individual subgroups were too small for meaningful analysis. For example, some tumour types with few patients in the trials, such as pancreatic tumours (n=1) and congenital mesoblastic nephroma (n=1), had 0% response or 100% response respectively. This may be because of chance findings or because of biological differences in the tumour type. For example, as noted in the EPAR, tissue-specific mechanisms for bypassing

response to drugs have been seen when targeting other gene mutations (such as colorectal cancer not responding to BRAF mutation inhibitors). Tumour tissue can also affect type of NTRK gene fusion, gene fusion partners and presence of other mutations. The response by NTRK gene fusion showed heterogeneity, with low response in NTRK2 and higher response in NTRK3 (82%). There was also heterogeneity in response by gene fusion partner. The most common fusion partner, ETV6-NTRK3, had an overall response of 84%, higher than all other fusion partners combined. The clinical experts could not comment on whether heterogeneity in the response to larotrectinib would be expected across different tumour types. The company's model assumed equal response for all tumour types and fusion types, based on the overall response from the trial population (see section 3.9) and did not explore any other assumption. The committee concluded that given the observed differences in response and the poor characterisation of NTRK gene fusions and fusion partners, assuming equal response was inappropriate. Adjustment should be made for potential differences by subgroup.

### **Bayesian hierarchical modelling is a useful way to consider the heterogeneity in response to larotrectinib**

3.14 The ERG presented the Bayesian hierarchical model (BHM) framework as an approach to characterise heterogeneity. The BHM framework was developed specifically for basket trials and is useful when there is limited information. This method allows for analysis of a pooled overall response rate, adjusting for the observed heterogeneity of extreme results. Extreme results can be obtained when patient numbers in the trial are very limited, meaning that even small changes in the absolute number of responders can considerably affect the rate of response (see section 3.13). The ERG noted that because the tumour types with more response events also had high response rates, the low response rates seen in tumour types with fewer response events reduced the overall response in the pooled analysis from 72% to 57% (including primary CNS tumours, see section 3.15). The committee acknowledged that the results of the

ERG's BHM approach were substantially different to the company's approach, which assumed that the response was the same across the different tumour types. The committee considered the reduced overall response output of the BHM, with wide credibility intervals, to be more appropriate for decision making because it incorporated some adjustment for heterogeneity. The ERG noted that the BHM approach could also be used for survival outcomes because response was not explicitly modelled in the company's base case. However, the company did not provide the data needed to do this analysis and the survival results were likely to be too immature for meaningful interpretation of the results. The committee concluded that the BHM was a useful tool for exploring heterogeneity in response to larotrectinib and should be considered as part its decision-making.

### **Patients with primary CNS tumours should be included in the response analysis**

3.15 There were 9 out of 102 patients with primary CNS tumours. Although the results for this group were analysed separately from the main efficacy analysis, they were included in the economic analysis. The company explained that larotrectinib response in patients with primary CNS tumours was assessed by investigators using the response assessment in neuro-oncology (RANO) criteria rather than the independent review committee assessed response evaluation criteria in solid tumours (RECIST) v1.1 criteria. Surgery and radiotherapy for CNS tumours can lead to varying amounts of scarring and inflammation, which may affect radiological assessment. Also, in the EPAR it states that larotrectinib is a substrate of P-glycoprotein, a key constituent of the blood-brain barrier. This may mean that the dose of larotrectinib reaching the brain is reduced. The ERG considered that primary CNS tumours may have a lower response to larotrectinib or that the high proportion of NTRK2 gene fusions within primary CNS tumours may explain the low response. The ERG noted that including the primary CNS data in the BHM reduced the estimated overall response rate. But it did not state a preference for including or excluding

primary CNS data from the BHM. The committee concluded that there was uncertainty about whether primary CNS tumours respond to larotrectinib. However, it considered that primary CNS data should be included in the BHM until more is known about larotrectinib's efficacy in the brain and NTRK2 gene fusions are better characterised, so the results are more generalisable to the population in the marketing authorisation.

### ***Indirect treatment comparisons***

#### **The naive comparison with a pooled comparator arm is likely to be biased**

3.16 To establish relative clinical effectiveness compared with current clinical practice, larotrectinib was compared with multiple comparators by tumour site-specific pathway. The company's base-case analysis created a pooled comparator arm by looking at data from last-line treatment arms in published NICE appraisals and in the literature to represent best supportive care. Survival estimates were weighted by the distribution of the efficacy population to allow a naive indirect comparison with an estimate of survival expectancy for this population. The ERG considered this method could introduce bias in many ways, including generalisability of the trial population (see section 3.10) and uncertainty over the potential prognostic importance of NTRK (see section 3.3). This method also limited the ability to adjust for any heterogeneity (see section 3.13). This was because it assumed that survival was independent of tumour type and other factors, therefore assuming a common natural history for all tumour types in the analysis. The ERG explained that the size and direction of bias was impossible to establish. The committee appreciated the difficulty in estimating a comparator population for rare tumours across multiple tumour types. But it concluded that the company's method had unadjusted bias that did not account for significant heterogeneity (see section 3.13) and could not adjust for important prognostic factors and baseline characteristics.

**The 2 confirmatory analyses also have biases, but will be considered in decision making**

3.17 The company presented 2 further indirect treatment comparisons, as confirmatory analyses, to approximate the comparator arm. A response-based analysis assumed patients whose tumours did not respond to larotrectinib were equivalent to those who had best supportive care. The group was split into those whose tumours responded and those whose tumours did not respond to larotrectinib. Those whose did not respond were assumed to represent the comparator arm. The advantages of the response-based analysis were that eligibility criteria of the trial were considered, and the ERG's adaptation of this model allowed for exploration of heterogeneity (see section 3.13). However, this method assumed surrogacy between response and survival outcomes, which may differ significantly by tumour type and have known biases. A previous line of treatment analysis compared the time to progression on the previous line of treatment with the time in progression-free survival on larotrectinib for each patient. This ratio was used as a hazard ratio to approximate a comparator arm for progression-free survival and it was assumed that overall survival behaved the same. The advantage of the previous line of treatment analysis was that each patient acted as their own control, which was particularly beneficial for a histology-independent population. However, the ERG had concerns with how this analysis was implemented. It considered that a patient's previous unsuccessful line of therapy may not represent best supportive care and it noted that the method was uninformative for overall survival, which was a major uncertainty of the base-case analysis. The committee noted that both confirmatory analyses also had substantial biases and that all the indirect treatment comparisons had structural uncertainty. Therefore, it concluded that it would consider the outputs of all indirect treatment comparisons in its decision making.

## ***The company's economic models***

### **The most appropriate model structure for decision making is uncertain**

3.18 The company's economic models were based on the indirect treatment comparisons (see sections 3.16 and 3.17). The company's base-case structure was a 3-state partitioned survival model (progression-free, progressed and death). Survival estimates were extrapolated from the larotrectinib efficacy population and comparator arm survival estimates calculated using the method in section 3.16. Other model parameters such as utility, time on treatment and adverse events were also included to create part-models (termed 'engines' in the company submission) for each tumour type comparator. The company also provided economic models based on the confirmatory analyses in section 3.17. The ERG adapted the response-based model to a dual-partitioned survival model with the larotrectinib arm response defined by output from the BHM (see section 3.14). This allowed for some exploration of uncertainty from heterogeneity in response. The ERG also considered that this would account for issues with post-progression treatments (see section 3.22) because these would be the same in both treatment arms. The ERG considered the previous line of treatment analysis was not implemented appropriately and was uninformative for overall survival, so did not consider this model structure further. The committee recognised the difficulty in modelling treatments for single-arm data, and that the unique challenges of histology-independent treatments further complicated the modelling issues. The committee understood that there were limitations and uncertainties with each of the modelling approaches. It considered that when more data were available the different model structures can be explored more fully. The committee concluded that the most appropriate model structure for decision making was uncertain.

### **A different model structure is needed to explore the effect of a cure**

3.19 Most children in the evaluable population from SCOUT had no other curative options besides amputation or disfiguring surgery. The company

considered that some of these patients would be cured without larotrectinib, with lifelong morbidity from amputation or disfigurement. Therefore, it considered that a cure model could be appropriate, but cure could not be determined because of short follow up, limited sample size and high censoring of data. The committee noted considerable uncertainty around the potential for a cure and that the curative role of surgery had not been explored in either treatment arm. The committee also noted that the comparator part-model for these patients (grouped as paediatric sarcomas) did not model lifelong survival over the full time horizon. Therefore, the current model structure captured the benefit of any cure in the Kaplan–Meier survival analysis in the larotrectinib arm but did not model the possibility of cure in the comparator arm. The committee concluded that this issue would strongly bias the cost-effectiveness results in favour of larotrectinib and supported why the model structures proposed were not appropriate for a heterogeneous population. It considered that a different model structure should be used to explore the effect of a cure. Also, further information was needed on how larotrectinib would be used in clinical practice.

### ***Survival extrapolations***

#### **Survival extrapolation is highly uncertain and a key driver of the model**

3.20 Data on overall survival and progression-free survival were incomplete and the clinical trials are ongoing. To extrapolate progression-free survival and overall survival for larotrectinib, the company fitted standard distributions to the data (the exact distributions chosen are confidential and cannot be reported here). For the pooled comparator arm, the curve accepted by the committee in previous NICE guidance was used when available and assumptions used when no NICE guidance was available. The ERG noted the considerable uncertainty in extrapolating data that are immature (see section 3.11). The overall survival extrapolation showed substantial separation from the progression-free survival, which contributed to an implausible post-progression survival estimate (see

section 3.22). During the technical engagement stage, the company provided overall survival data from an updated data-cut. The ERG considered that there were no clear differences in survival characteristics but a few events at the extreme end of the curve dramatically affected the survival extrapolation and modelled survival gain. The committee considered that this could be a result of uncertain extrapolation and may not suggest a true decline in survival. This was compounded by uncertainty about the possibility of including patients whose disease was cured in the larotrectinib Kaplan–Meier curves (see section 3.19). The committee concluded that the extreme sensitivity of the model output to the survival extrapolations meant that extrapolation did not provide results that the committee could trust.

### ***Model outputs***

#### **Response to larotrectinib is a key driver of the response-based model but not the cost-effectiveness estimate**

3.21 The ERG noted that there were 2 key drivers of the cost-effectiveness estimate within the economic model. The primary costs in the model were the costs of larotrectinib, which were bound to the time on treatment or progression-free survival curve in the larotrectinib arm. The primary benefits in the model were from modelled overall survival benefit from the larotrectinib arm. The ERG used its response-based partitioned survival model to calculate the highest tumour-specific response estimate from the BHM (87% for infantile fibrosarcoma) and the lowest response estimate from the BHM (43% for colorectal cancer; see section 3.14). The difference in results showed much larger modelled incremental costs and incremental benefits for the 87% response than for the 43% response, but minimal effect on the cost-effectiveness estimate. The ERG explained that this was because higher response equated to longer time in the progression-free state which incurred increased costs, but this was offset by increased overall survival and therefore benefit of a very similar size. The committee considered that this explained the minimal effect of

changes in response on the cost-effectiveness estimate. But it noted that if these assumptions were changed, change in response caused by heterogeneity would continue to be an important determinant of cost effectiveness in the response-based analysis.

**The modelled post-progression survival outputs are implausible**

3.22 The ERG noted that the life years gained after progression were greater than both the progression-free life years gained and overall survival in the comparator arm, which it considered implausible. The ERG considered this could be a result of the highly uncertain extrapolation or because of the high proportion of patients who had post-progression treatments, such as further larotrectinib or an experimental treatment (LOXO-195) for people whose disease was resistant to TRK-inhibitors. The ERG considered that the experimental treatment (LOXO-195) used in the larotrectinib arm would not be used in clinical practice. This was because the tumour would need to have primary TRK-inhibitor resistance before people could have these treatments. The committee considered it appropriate to adjust for the benefits of these treatments. However, it noted the difficulty using adjustment techniques for an unknown treatment effect in immature survival data. The clinical expert stated that a high depth of response (prolonged benefit from shrinking the tumour) to larotrectinib might explain why post-progression survival could be higher than progression-free survival. This is because having a smaller tumour could mean longer survival even after developing resistance to larotrectinib. The committee considered this concept to be speculative because the current evidence base was very immature. It also noted that TRK-inhibitor resistance mechanisms were not well characterised and would not explain the size of the discrepancy. The ERG provided 2 scenarios based on crude adjustment of post-progression survival to match post-progression survival in the comparator arm (no comparative effect of larotrectinib after progression) or overall survival of the comparator arm. The committee considered these scenarios to be more plausible than the company's base case and appropriate for showing the

upper limit of plausible cost-effectiveness estimates for this issue. However, it considered that survival estimates, both progression-free and post-progression, were likely to be affected by immature extrapolation (see section 3.20) and including survival data from patients whose disease was cured (see section 3.19). The committee concluded that the post-progression survival estimates were implausible and that the ERG scenarios did not fully capture the issues with modelling survival.

### ***Utility values in the economic models***

#### **Assuming equal post-progression utility values in the larotrectinib arm and weighted comparator arm is appropriate**

3.23 The company provided utility values derived from health-related quality of life data collected in the SCOUT and NAVIGATE trials, mapped to EQ-5D-3L utility values for the pre-progression and progressed states. For the comparator arm utility values, a similar approach to estimating survival was used (see section 3.16). Utility values from published NICE guidance were pooled and weighted by the distribution of the efficacy population. The ERG considered that there was considerable uncertainty in the utility value estimate of the post-progression utility state for larotrectinib because it was based on few assessments of few patients, most of whom were children. The committee noted that some of the patients would have the potential to be cured (see section 3.19). It considered that the evidence for the post-progression utility values for larotrectinib was weak and there was no plausible reason why post-progression utility would be so much higher for larotrectinib than for the comparator arm for the entire population. The ERG provided a scenario with equal post-progression utility values for larotrectinib and the pooled comparator. The committee agreed that this scenario was more appropriate.

**Sensitivity analysis to see the effect of equal pre-progression utility values for larotrectinib and the pooled comparator is needed**

3.24 The company's utility values suggested a difference in pre-progression utility between larotrectinib and the pooled comparator. The Cancer Drugs Fund clinical lead considered this to be implausible because the modelled comparator in NHS clinical practice was likely to be best supportive care. Therefore, any difference in utility values between arms would represent positive effects from reduced tumour size in the pre-progression state for larotrectinib and the difference in adverse effects between treatments not captured by the adverse event modelling. The committee considered that the high number of patients having chemotherapy rather than best supportive care (see section 3.10) would bias this difference in favour of larotrectinib. The committee concluded that it was appropriate to do sensitivity analysis on the pre-progression utility values to see the effect of assuming equal values for larotrectinib and the pooled comparator.

***Resource use and costs***

**It is appropriate to include diagnostic testing costs in the economic model**

3.25 The committee understood that the NICE methods guide was not designed to address a system-wide change in diagnostic techniques and the cost of testing would depend on NHS England's testing strategy. The company considered that the planned changes in genomic testing (see section 3.7) would mean that none of the costs of testing would be borne by larotrectinib in the economic model. This was because the system would be independent of testing for NTRK gene fusions and would not be used solely for identifying NTRK gene fusions for a particular drug. The ERG's interpretation of the methods guide was that associated costs of the diagnostic test should be incorporated into the clinical and cost-effectiveness assessments. The committee agreed that this interpretation, which considered the assessment of cost of larotrectinib in current NHS clinical practice, most closely matched the methods guide. The ERG analysed a pragmatic hierarchical screening pathway for each tumour

type based on adapting current provisions for some tumour types. For tumour types that are not currently tested for any genetic mutations, the ERG assumed that immunohistochemistry would be followed by confirmatory next generation sequencing if there was a positive result. This technique provided an average cost of screening for a single patient with an NTRK gene fusion, which was included in the cost-effectiveness estimates. The committee considered this analysis was reasonable because it reflected current clinical practice but recognised that NHS England is rapidly moving towards a national service for cancer genomic testing. Therefore, the proposal from NHS England to implement next generation sequencing-based testing at diagnosis of locally advanced or metastatic disease was likely to reflect the near future once the changes to the diagnostic pathway have been established. NHS England proposed a cost per patient with an identified NTRK fusion-positive tumour to be included in the model. The committee noted that this cost was substantially less than in the ERG's scenario. The committee concluded that it was appropriate to include diagnostic testing costs in the model.

### **Adjustments are needed to the children's dose in the model and to include drug wastage costs**

- 3.26 The company used the average adult and children's doses used for the efficacy population to calculate the dose of larotrectinib applied in the model. The ERG considered this to be inappropriate because some children had a lower dose in SCOUT because it was a phase 1 dose-finding study. The ERG provided a scenario in which the full children's dose was adjusted using the percentage of adults adhering to treatment. The committee agreed that the ERG's adjustments were appropriate to better generalise the dose in SCOUT to NHS clinical practice but it noted that this did not account for potential differences in clinical effect. Additionally, the company supplied scenarios considering drug wastage after stopping treatment for 2- and 4-week treatment supplies. The committee noted that these scenarios had little effect on the cost-effectiveness estimates but considered it appropriate to include the 4-

week treatment drug wastage scenario in the model. The committee also noted that these assumptions relied on using hard capsules which are not yet available, so an additional scenario using the oral solution should have been provided.

**The model should include the costs of oral chemotherapy administration**

3.27 The company considered that administration costs and resource use should be applied in the model by the distribution of patients in the efficacy analysis. The committee considered this inappropriate because the over-representation of rare tumours that were modelled as having chemotherapy (see section 3.10) may have resulted in bias in favour of larotrectinib. However, it considered that the true distribution could not be calculated. The Cancer Drugs Fund clinical lead commented that the administration costs for oral chemotherapy were not included for larotrectinib. At the technical engagement stage, the company provided a scenario with these administration costs. The committee concluded that this scenario was appropriate for including in the economic model.

**The model should include the costs of post-progression treatments**

3.28 The company modelled the costs of larotrectinib treatment until progression, but some patients continued to have larotrectinib after progression (see section 3.22). The company provided a scenario using the time to treatment discontinuation seen in the trial to model larotrectinib costs. The committee considered this to be more appropriate because the modelled costs of larotrectinib should match the modelled benefits. However, it noted there would be further uncertainty with extrapolation of this dataset and other methods of including these costs may be more appropriate. The committee concluded that the costs of post-progression larotrectinib should be included but that this issue had not been fully explored.

## ***End of life***

### **Larotrectinib has plausible potential to meet the end-of-life criteria but there is uncertainty**

3.29 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [guide to the methods of technology appraisal](#). The company proposed that larotrectinib met the criteria for life-extending treatments for people with a short life expectancy (normally less than 24 months). The committee understood that the end-of-life criteria were not designed for histology-independent treatments and it was not presented with the data needed to assess the criteria for people with NTRK gene fusions specifically. Instead, it was presented with life expectancy data for people with the relevant tumour type irrespective of NTRK gene fusion status and life extension data estimated from the model. It acknowledged the challenges with the data available, for example:

- the distribution of tumour types in the trials and unrepresented tumour types not included in the clinical evidence (see section 3.10)
- uncertainty around larotrectinib's position in the treatment pathway (see section 3.5)
- the limited survival data available (see section 3.11)
- the prognostic importance of NTRK gene fusions (see section 3.3) and the uncertainty around the extrapolation of the survival data (see section 3.20).

The committee considered that most tumour types represented in the trials had overall survival estimates that would meet the short life expectancy criterion. But it considered that the overall survival estimates for people with thyroid cancers were likely to exceed the short life expectancy criterion and this could also be true for some of the rarer tumour types. It considered that the extension to life criterion of greater than 3 months would likely be met for most patients whose tumours

responded to larotrectinib, although the size of the benefit and the distribution of these tumour types was highly uncertain. The committee concluded that larotrectinib had plausible potential to meet NICE's criteria to be considered a life-extending treatment at the end of life. But it acknowledged that there was uncertainty in determining both the life expectancy and the exact extension to life given the immaturity of the data and potential for heterogeneity across all the different tumour types. Further data collection could resolve this uncertainty and the distribution of tumour types likely to meet the life expectancy criterion.

### ***Cost-effectiveness estimates***

#### **Larotrectinib is not plausibly cost effective and is associated with considerable uncertainty**

3.30 The company's base-case model gave a deterministic incremental cost-effectiveness ratio (ICER) of £35,309 per quality-adjusted life year (QALY) gained for larotrectinib compared with current clinical management. This included a simple discount patient access scheme for larotrectinib. The committee considered that the base case should also include the following assumptions to reflect committee preferences:

- utility values equal between post-progression treatment arms (see section 3.23)
- including the oral chemotherapy administration cost for larotrectinib (see section 3.27)
- including drug wastage costs based on 4-weekly prescription (see section 3.26)
- adjusting the children's dose to account for inclusion of the dose-finding study (see section 3.26)
- including the costs of larotrectinib after progression (see section 3.28).

After the committee meeting, the ERG provided analysis including these assumptions that showed an increase in the ICER to £46,822 per QALY

gained. This did not include incorporate diagnostic costs (see section 3.25), which would further increase the ICER.

In addition, this calculation did not include many of the scenarios that the committee considered major uncertainties of the appraisal:

- adjusting for the implausible post-progression survival (see section 3.22), which the committee considered would greatly increase the ICER, based on the 2 scenarios provided by the ERG (ICERs of £84,469 and £101,897 per QALY gained for each of the scenarios in section 3.22)
- adjusting for potential heterogeneity in response (see section 3.13), which the committee considered strongly affected the model outputs, based on the response-based model (see section 3.21)
- exploring assumptions around a potential cure affecting survival estimates (see section 3.19), which the committee considered would greatly increase the ICER, because it would increase the comparator survival estimates
- further exploration of cost-effectiveness estimates from all 3 model structures (see section 3.18), which the committee considered would have an unknown effect on the ICER but would help reduce uncertainty.

The committee considered that the ICER range was above what it would normally consider a plausibly cost-effective use of NHS resources if larotrectinib was considered to meet the end-of-life criteria. It concluded that larotrectinib was not cost effective at the current price and there was considerable unexplored uncertainty. Therefore, it could not recommend larotrectinib for routine commissioning.

## ***Cancer Drugs Fund***

### **Larotrectinib does not meet the criteria for inclusion in the Cancer Drugs Fund but collecting further data could address uncertainties in the evidence**

3.31 Having concluded that larotrectinib could not be recommended for routine use, the committee then considered if it could be recommended for treating NTRK fusion-positive solid tumours within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). The committee was aware that the company expressed a preference for larotrectinib being considered for funding through the Cancer Drugs Fund in its submission because of the uncertainty in the appraisal and while data mature. The committee recognised that larotrectinib is innovative and its use in clinical practice would help accelerate NHS England's developments in genomic testing. The committee considered whether the clinical uncertainty associated with larotrectinib's use could be addressed through collecting more data. It was aware that more data from the larotrectinib clinical trials are expected. Also, the company have some data collection ongoing as part of the regulatory commitments required by the conditions of the marketing authorisation. The committee noted that:

- The ongoing larotrectinib clinical trials will provide more mature survival data for people already enrolled in the trials. They may recruit additional patients with solid tumours at sites not already included in the clinical trials, which will provide further data to explore the heterogeneity in response to treatment.
- Real-world evidence collected within the Cancer Drugs Fund through Blueteq, SACT and the molecular dataset should provide further information on the generalisability of the clinical trials to NHS clinical practice, prevalence of NTRK gene fusions, the distribution of tumour types in England, the screening and treatment pathway.

- A non-interventional study (ON-TRK) will collect safety and efficacy data on larotrectinib and may provide further information on heterogeneity in response.

The committee considered that some of the clinical uncertainties could be addressed through data collection in the Cancer Drugs Fund. However, larotrectinib did not have plausible potential to be cost effective at its current price. Therefore, the committee concluded that larotrectinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund. It also noted that some key uncertainties in the evidence base were unlikely to be resolved with the proposed data collection, including evidence for a comparator treatment and further characterisation of NTRK gene fusions.

## ***Innovation***

### **Larotrectinib is innovative and there are benefits not captured in the analysis**

3.32 The company considered larotrectinib to be innovative because it targets a gene fusion instead of a tumour type. The patient and clinical experts agreed. The committee considered larotrectinib to be innovative because it represents a major change in the treatment of NTRK fusion-positive solid tumours. The committee understood that an important innovation was already underway as part of the NHS long-term plan to develop more sophisticated strategies to improve genomic testing in clinical practice. These advances will likely help the uptake of treatments targeted to a gene alteration. The Cancer Drugs Fund clinical lead explained that histology-independent treatments entering the market are accelerating the advances in genomic testing in the NHS. It is estimated that 100,000 solid tumours will be tested per year once the genomic medicine service is fully established, thought to be in the next 2 years. The committee acknowledged that the improvements in genomic testing would bring wider benefits to the NHS and that these benefits have not been captured in the QALY calculation. The committee concluded that larotrectinib would

be beneficial for patients, but that it had not been presented with any additional benefits that could be specifically attributed to larotrectinib that were not captured in the measurement of the QALY.

## ***Equality considerations***

### **There are no equality issues relevant to the recommendations**

3.33 The company did not consider there to be any equality issues. However, it considered that the uncertainty inherent in this appraisal may pose an equity issue. There is no precedent for appraising technologies when their clinical trials have a basket trial design and a high number of comparators across multiple tumour types. The company considered that patients should have equity of access while health technology assessment methods adapt to these challenges. The committee considered that the NICE single technology appraisal process was appropriate for appraising larotrectinib. It concluded that the uncertainties associated with the trial design (see section 3.14) and multiple comparators (see section 3.17) had been appropriately accounted for in its decision making. The Cancer Drugs Fund clinical lead also noted that there may be issues related to accessing larotrectinib because the genomic testing needed to identify NTRK fusion-positive solid tumours is still being established as a national service (see section 3.7). The committee understood that any variation in access to genomic testing will be resolved in the next 1 to 2 years.

## **4 Proposed date for review of guidance**

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh  
Chair, appraisal committee  
January 2020

## **5 Appraisal committee members and NICE project team**

### ***Appraisal committee members***

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Adam Brooke**

Technical lead

#### **Christian Griffiths**

Technical adviser

#### **Kate Moore**

Project manager

ISBN: **[to be added at publication]**