NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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 evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2026

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using larotrectinib in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 29 April 2026
- Second evaluation committee meeting: TBC
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Larotrectinib should not be used as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in people of all ages if:

- the cancer is locally advanced or metastatic, or surgery could cause severe health problems and
- there are no satisfactory treatment options.

1.2 This recommendation is not intended to affect treatment with larotrectinib that is currently funded by managed access (before final guidance publication). If this applies, NHS England and the company have an arrangement to make sure people who started treatment during the managed access period will continue to have larotrectinib until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Larotrectinib is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine that larotrectinib offers benefits in this population.

Why the committee made these recommendations

This evaluation reviews the evidence for larotrectinib for treating NTRK fusion-positive solid tumours (NICE technology appraisal guidance 630). It also reviews new evidence collected during the managed access period, which includes evidence from clinical trials and from people having treatment in the NHS in England.

There is no standard treatment for NTRK fusion-positive solid tumours, so treatment is based on where in the body the cancer starts. Larotrectinib targets a genetic

alteration (NTRK gene fusion) that is found in many different tumour types (that is, tumours with different cellular characteristics, and tumours that start in different parts of the body).

Clinical trial evidence suggests that tumours with NTRK gene fusions shrink in response to larotrectinib. But it is difficult to know how well larotrectinib works, because:

- it was not compared with other treatments in the trials
- the people in the trials did not fully reflect the people who would have larotrectinib in the NHS
- there is evidence that larotrectinib works well for some types of NTRK fusion-positive tumour and less well for some other types, and for some tumour types there is little or no evidence.

Evidence from NHS practice also suggests that tumours with NTRK gene fusions shrink in response to larotrectinib. But this is uncertain because, due to the rarity of NTRK fusions, the evidence included only a small number of people and tumour types compared with what would be seen in the NHS.

There are concerns with the economic model. This is because it assumes that different tumour types in people of different ages would respond to larotrectinib in the same way, and there are uncertainties about:

- which clinical evidence to use in the model
- by how much larotrectinib increases how long people live
- how larotrectinib affects quality of life
- what treatment people have after larotrectinib and how much it costs
- how the cost-effectiveness results would differ if calculated for individual tumour types.

Because of the uncertainties in the clinical and economic evidence, it is not possible to determine the most likely cost-effectiveness estimates for larotrectinib. So, it should not be used.

2 Information about larotrectinib

Marketing authorisation indication

2.1 Larotrectinib (Vitrakvi, Bayer) ‘as monotherapy is indicated 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 The dosage schedule is available in the summary of product characteristics for larotrectinib.

Price

2.3 The cost of larotrectinib (excluding VAT; BNF online, accessed March 2026) is:

- £14,000 per 56-pack of 100-mg capsules
- £3,500 per 56-pack of 25-mg capsules
- £5,000 per 100-ml vial of 20-mg per ml oral solution.

2.4 The company has a commercial arrangement, which would have applied if larotrectinib had been recommended.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Bayer will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Bayer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

NTRK fusion-positive solid tumours

3.1 Neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours are rare cancers driven by NTRK gene fusions that can occur in people of all ages. There are many tumour types (that is, tumours with different cellular characteristics, and tumours that start in different parts of the body) with known NTRK gene fusions, and all solid tumour types are included in larotrectinib's marketing authorisation indication (see section 2.1). NTRK gene fusions occur rarely (less than 3%) in common tumours such as lung, colorectal and breast cancers. Some rare tumour types have more than 90% NTRK fusion prevalence, such as mammary analogue secretory carcinoma and infantile fibrosarcoma. There are no NTRK fusion-specific symptoms, so symptoms of NTRK fusion-positive solid tumours depend on tumour site.

Patient, carer and clinical expert submissions described the impact of NTRK fusion-positive tumours on the quality of life of people living with the condition, and their families and carers, including substantial effects on physical, mental and social wellbeing. The submissions highlighted that people with the condition experience pain, mobility issues, loss of independence and effects on their relationships. People and their families and carers also face anxiety and psychological distress from regular hospital visits. These visits can also create financial strain and disrupt work. People often face additional uncertainty about what future treatments will be available as the disease progresses. The patient and carer experts at the committee meeting said that people’s experience of

NTRK fusion-positive tumours varies because there can be different side effects and outcomes after treatment. They highlighted the positive experience of treatment with larotrectinib, which has improved quality of life, enabled people to live more independently and reduced the burden on families and carers. The committee recognised that NTRK fusion-positive tumours can have a significant impact on the quality of life of people and their families and carers. It concluded that there is an unmet need for an effective treatment option for NTRK fusion-positive solid tumours.

Clinical management

Treatment options

3.2 There is no defined clinical pathway for people with solid tumours with NTRK gene fusions. Treatment follows care guidelines for specific tumour types. Surgery is offered for tumours that are operable. For inoperable tumours, treatment for more common cancers may include targeted therapy, immunotherapy and chemotherapy. For rarer cancers, treatments are generally limited to radiotherapy and chemotherapy. Clinical expert submissions highlighted that for some inoperable tumours, the aim of treatment is to shrink the solid tumour so that surgery might become a treatment option. If this is not possible, treatment aims to stabilise the tumour to prolong survival and preserve quality of life. Patient, carer and clinical experts said that conventional treatments are not always well tolerated, can sometimes have debilitating and life-threatening side effects and are often ineffective at controlling NTRK fusion-positive solid tumours, particularly rare tumours. They further said that attending treatment centres for regular blood tests and scans is highly burdensome for people and their families.

Larotrectinib is recommended for use within the Cancer Drugs Fund (CDF, see NICE's technology appraisal guidance on larotrectinib for treating NTRK fusion-positive solid tumours [from here, TA630]). The

clinical experts at the committee meeting explained that people who have a solid tumour with a NTRK gene alteration would want to continue having access to a targeted therapy, like larotrectinib, that helps shrink their tumour. The patient, carer and clinical experts said that larotrectinib is well tolerated, with manageable side effects and less intensive monitoring than conventional therapy. They highlighted that quality of life for people and their families and carers is incomparably better. The committee concluded that people with NTRK fusion-positive solid tumours would value continued access to a NTRK fusion specific treatment option such as larotrectinib.

Positioning in the treatment pathway

3.3 Larotrectinib is indicated for 'the treatment of adult and paediatric patients with solid 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'.

In TA630, larotrectinib was positioned as a last-line treatment after all other treatments had been tried. In this evaluation, the company positioned larotrectinib after at least 1 treatment. This was based on Systemic Anti-Cancer Therapy (SACT) data that showed that, in real-world NHS England use, 78% of people who had larotrectinib had already had 1 line of systemic therapy. The EAG highlighted that in some tumour types, where NTRK fusion is already known, larotrectinib has been used earlier in the treatment pathway. The committee questioned if the treatment pathway had changed since TA630 was published and whether larotrectinib would be used earlier than previously thought. The clinical experts explained that it would be clinically appropriate to use larotrectinib earlier in the treatment pathway, but the current NHS CDF criteria prevent earlier access. One expert said that they would prefer to use larotrectinib as the first-line

treatment for some NTRK fusion-positive solid tumours that do not respond well to standard chemotherapy. The company stated that 'no satisfactory treatment option' in the marketing authorisation allows for clinician judgement rather than adhering to a fixed treatment line. The NHS England CDF clinical lead (from here, CDF lead) noted that the CDF Blueteq criteria for larotrectinib allow for it to be used as first-line treatment if there is not another effective treatment for a particular tumour type. The committee acknowledged that healthcare professionals may be able to use larotrectinib as first-line treatment for some tumours if standard care is not considered a satisfactory treatment option. The committee concluded that larotrectinib could only be recommended for use within its marketing authorisation for treating NTRK fusion-positive solid tumours.

Clinical effectiveness

Clinical trial evidence

3.4 The company presented an updated pooled analysis of 364 patients from 3 single-arm trials:

- Study 20288 (n=13) was a phase 1 dose-escalating trial in adults with locally advanced or metastatic solid tumours.
- NAVIGATE (n=210) was a phase 2 trial of people aged 12 years and older, with recurrent, advanced solid tumours with a documented NTRK fusion.
- SCOUT (n=141) is a phase 1 and 2 trial of people aged 21 years and under with advanced solid or primary central nervous system (CNS) tumours.

In TA630, the committee felt that the clinical trial data was immature. For this evaluation, the company provided data from the 3 trials split by:

- primary CNS tumours (pooled extended primary analysis set 9; ePAS9, [n=304]) and

- non-primary CNS tumours (pooled supplementary analysis set 3; SAS3, [n=60]).

ePAS9 and SAS3 data was further split by child (0 to 17 years) and adult (18 years and over) populations. This provided more mature data with a larger sample size and broader range of tumour types (n=28). The primary outcome of the pooled analysis was objective response rate. Secondary outcomes included overall survival, progression-free survival and health-related quality of life. The objective response rate from the pooled ePAS9 data was 65% (95% confidence interval [CI] 59% to 70%). The company considers the objective response rate for the pooled SAS3 data and median overall survival results from the pooled ePAS9 and pooled SAS3 data to be confidential so they cannot be reported here.

SACT data

3.5 In TA630, the committee noted that the SACT dataset could be used to collect evidence on clinical outcomes with larotrectinib in NHS clinical practice. For this evaluation, the company presented the real-world SACT data for larotrectinib, collected between April 2020 and December 2024. The dataset included 60 people with NTRK fusion-positive advanced solid tumours, across 14 different tumour sites. The median duration of follow up was 19.4 months. The objective response rate was 72% (95% CI not reported). The median overall survival was 45.2 months (no 95% CI because of an insufficient number of events). The committee concluded that the SACT data provided further evidence on clinical outcomes and real-world evidence that was relevant to UK clinical practice.

Generalisability of clinical-effectiveness evidence

3.6 The committee considered the relevance to NHS clinical practice of the clinical-effectiveness evidence for larotrectinib from the clinical trials and the SACT dataset. It recalled that the generalisability of the trial evidence to NHS practice was a key uncertainty in TA630. It was aware that the

company's model was based on outcomes from the clinical trial (see section 3.11). The EAG stated that there were significant differences between the populations in the larotrectinib trials and the SACT dataset. These included differences in tumour type and tumour-site distribution, tumour stage (locally advanced or metastatic), previous lines of therapy, and subsequent treatments. The trial evidence included a broader range of tumour sites than the SACT dataset (28 sites compared with 14 sites) and a larger proportion of people in the trials had larotrectinib earlier in the treatment pathway than in the SACT dataset. Additionally, the proportion of people having subsequent treatments in the trials was higher than in the SACT dataset. So, the EAG was concerned about the limited applicability of the trial population to NHS practice, given the differences in the population compared with the SACT data.

The committee questioned whether the evidence from the trials was applicable to NHS clinical practice and could be useful for decision making. The clinical experts explained that the shift from site-based to molecularly defined cancers means that evidence for treatments targeting rare genomic alterations, such as NTRK fusions, will often span multiple tumour types with small patient numbers. So, the clinical experts said they would consider clinical trial evidence for larotrectinib to be broadly generalisable to NHS clinical practice. The company said that the SACT data broadly supported the external validity of the trial results to the NHS. It noted that outcomes and several baseline characteristics appeared consistent between the 2 datasets. So, this supported using the trial data to inform the clinical effectiveness of larotrectinib. The company highlighted limitations of the SACT data including:

- the highly restrictive CDF entry criteria
- the relatively small patient numbers
- the missing data such as performance status

- potential disruptions to genomic testing and the treatment pathway during the COVID-19 pandemic.

So, it thought that the SACT population may not fully represent the likely NHS population. This was supported by the clinical experts in the committee meeting. The clinical experts also explained that the lack of UK representation in the trials (only 1 UK site included) was likely a result of issues with genomic testing in the UK at the time of enrolment in the trials. The committee noted that although genomic testing was an issue in TA630, it is now considered standard practice in the NHS. The EAG said that although the SACT sample size was small and many tumour types were sparsely represented, limiting statistical power and detection of differences, the data was highly relevant to the target NHS population and provided more mature outcomes in the NHS setting. The committee acknowledged that both data sets had important limitations resulting from a highly heterogenous population and the low incidence of some rare tumour types. It thought that there were important differences between the trial population and the SACT population. But it agreed that the SACT data represented the best available evidence on how larotrectinib would be used in the NHS. The committee concluded that on balance, the clinical trial evidence lacked generalisability to NHS clinical practice and that the SACT data was more reflective of real-world use of larotrectinib in the NHS.

Pooling response rates across tumour types

3.7 The company presented single pooled tumour response outcomes across all tumour types from the clinical trial evidence. It thought that the pooled estimates were clinically meaningful because they capture the expected variability in outcomes across a heterogenous population, driven by differences such as disease course or previous treatments. The company noted that larotrectinib's mechanism of action was consistent across histologies, so observed outcome differences were primarily explained by

prognostic factors rather than differential drug activity. The company ran additional analyses using a Bayesian hierarchical modelling (BHM) framework to estimate the overall response rate; it accounted for and explored the potential heterogeneity in effects across tumour types in the trial data. The EAG said that the company's BHM showed clear and mostly unexplained heterogeneity in objective response rate by tumour types. So, pooling estimates ignored potential heterogeneity in efficacy across tumour types and may have been misleading.

The committee questioned whether it was appropriate to assume a common treatment response across tumour types for larotrectinib. The clinical experts said that the mechanism of action of larotrectinib is consistent across NTRK fusion-positive tumours, which supports the plausibility of activity across tumour types. But they also said that heterogeneity in magnitude of response across tumour types is expected given the differences in underlying tumour pathology and prognosis. The EAG said that evidence from literature on basket trials also suggested that the treatment effect can vary across tumour types even when targeting the same molecular alteration. The pooling of outcomes may therefore have obscured meaningful differences in efficacy. So, the EAG considered the BHM trial estimates to be more robust than the naive trial estimates.

The committee acknowledged that there was considerable unexplained heterogeneity in response rates by different tumour types. So it thought that pooling response rates across different tumour types introduced a high level of uncertainty in the clinical-effectiveness evidence. The committee concluded that it would like to see further exploration of

heterogeneity, including disaggregated outcomes, to help reduce uncertainty in the clinical-effectiveness estimates.

Overall survival benefit

3.8 The company presented updated overall survival estimates for larotrectinib using the July 2024 data cut of the pooled clinical trial dataset (see section 3.4). Despite the additional data collected since TA630, the EAG highlighted that the overall survival data remained immature because the median overall survival was not estimable. So, how long people live after their tumour has progressed was uncertain and may have been overestimated. The EAG also highlighted that subsequent treatment use in the trials was much higher than in the SACT population. This could have confounded post-progression survival estimates. It could also indicate that overall survival estimates may have been less favourable to larotrectinib in the NHS and limited the applicability of the overall survival estimates from the trial evidence to NHS practice. To support this, it noted that the median overall survival was reached at 45.2 months in the SACT data, which was less favourable to larotrectinib and very different to the trial estimates. The EAG also stated that the lack of comparator arm in the clinical trials and the SACT data was a fundamental limitation of the evidence. It prevented direct estimation of the overall survival benefit with larotrectinib compared with standard care.

The committee acknowledged that immature survival data and subsequent treatment use may have influenced the trial post-progression survival estimates. It questioned the plausibility of the long post-progression survival estimates. The company acknowledged the uncertainty in the overall survival benefits, but thought the estimates were clinically plausible. It said that subsequent treatments were unlikely to have a substantial impact on the overall survival estimates because only a third of people had subsequent radiotherapy or chemotherapy, and relatively few people had subsequent NTRK inhibitors (which are not

available in NHS practice). A scenario removing people who had subsequent NTRK inhibitors reportedly had minimal effect on overall survival. The company also explained that a large proportion of the survival benefit after disease progression was in children. This may have been because some of the tumours are less aggressive in some children whose condition remained stable for long periods. But the committee remained concerned with the biological plausibility of large survival benefits in people whose disease had progressed, beyond the impact of subsequent treatments. The EAG noted that the company did not provide any trial survival estimates by age or tumour type. The clinical experts explained that survival may vary substantially by patient and disease characteristics, including locally advanced or metastatic cancers. For example, initial larotrectinib treatment could enable surgical options to become feasible for locally advanced cancers, resulting in longer survival after disease progression than metastatic cancers that are treated with systemic therapies.

The committee acknowledged the plausibility of survival benefit with subsequent treatments after the disease has progressed as a benefit of initial larotrectinib. But it remained concerned with the magnitude of this benefit, particularly when compared with the overall survival in the SACT data. So the committee concluded that the true magnitude of survival benefit with larotrectinib remained uncertain, but was likely overestimated in the clinical trial evidence.

Indirect treatment comparisons

3.9 Because the clinical-effectiveness evidence used for larotrectinib in the company's submission was based on 3 single-arm trials, the company did unanchored matching adjusted indirect comparisons (MAICs) to estimate the comparative effectiveness of larotrectinib and standard care. Four MAIC analyses were presented in the company submission comparing larotrectinib with standard care, but only 2 of these were used in the

company's base-case economic model. These 2 MAICs used clinical evidence for larotrectinib from relevant clinical trials (see section 3.4) and standard care evidence as follows:

- VICTORIA, an international retrospective study that extracted historical data for adults with locally advanced or metastatic tyrosine receptor kinase fusion-positive cancer between 2013 and 2023, including various comparator treatments. It included 1 UK site and 5 tumour types.
- EPI VITRAKVI, a retrospective observational study of people with locally advanced or metastatic infantile sarcoma who were aged 21 years or younger and had a chemotherapy-based regimen between 2000 and 2022 in Germany and France.

Key prognostic covariates were matched to adjust the populations in the data sources for larotrectinib to the standard care data. For overall survival, comparing larotrectinib with standard care in adults using the VICTORIA dataset resulted in a hazard ratio of 0.44 (95% CI 0.23 to 0.83). The hazard ratio for progression-free survival was 0.29 (95% CI 0.18 to 0.46). For overall survival comparing larotrectinib with standard care in people 21 years or younger using the EPI VITRAKVI dataset resulted in a hazard ratio of 0.21 (95% CI 0.02 to 2.84). The hazard ratio for progression-free survival was 0.80 (95% CI 0.41 to 1.58).

Validity of matching adjusted indirect treatment comparisons

3.10 The committee considered the validity and generalisability of the MAIC analyses used to inform the comparative effectiveness of larotrectinib and standard care. The EAG highlighted that the MAICs had several limitations, including:

- limited tumour type coverage
- over representation of tumour types with higher response rates

- exclusion of some low-response tumour groups such as primary CNS tumours.

The EAG also highlighted methodological issues with the MAICs, including:

- challenges with fully adjusting for all key prognostic factors
- violation of the proportional hazards assumption
- small sample size
- reliance on heterogenous historical standard care datasets.

The committee noted that the standard care data derived from non-trial real-world studies had substantial differences from each other. This was important because the people in these studies were different from those in the SACT dataset, which most closely represents the population who would have larotrectinib in the NHS. So the evidence may not have reflected NHS clinical practice. The committee was also concerned with the high level of early censoring in the MAIC using the VICTORIA dataset. It questioned whether this affected the robustness of the comparative effectiveness estimates for larotrectinib and standard care. The company said that people were censored because during the VICTORIA study they subsequently had an NTRK inhibitor. But the committee thought that the censoring may be informative. This was because people who became eligible for a subsequent NTRK inhibitor may have already progressed on standard care treatment and so may have had a poorer prognosis, even before switching. So the high level of early censoring likely limited the usefulness of the MAIC analysis. The company acknowledged the limitations and potential unmeasured confounding. But it said that the MAIC approach represented the most feasible method to estimate the comparative effectiveness of larotrectinib in this rare population. It further said that key prognostics factors were adjusted for, and broadly consistent

hazard ratios were observed across all MAIC analyses.

The committee remained concerned about the suitability of the standard care comparator. It noted that people in the VICTORIA standard care arm had a confirmed NTRK-positive tumour but were either not eligible for, or chose not to enter, an NTRK inhibitor trial. This meant that they may have differed to people who did go on to have NTRK-targeted treatments in ways (for example clinical or prognostic differences) that were not fully measured or adjusted for in the MAIC. So important unobserved factors could have remained even after matching. The clinical expert noted that this created uncertainty about whether this group was appropriate for estimating comparative effectiveness. The EAG thought that although the MAIC using the VICTORIA dataset may represent the most robust approach in terms of matching, the overall evidence of comparative effectiveness of larotrectinib from the MAICs remained uncertain. This was because it thought that there were methodological limitations and challenges in extrapolating results from a small number of tumour types to the broader population of people with NTRK fusion-positive solid tumours. The EAG also highlighted concern with the MAIC using the EPI VITRAKVI study. This was because EPI VITRAKVI only included people with infantile fibrosarcoma, a tumour site shown to have a good response to larotrectinib in the trial. So, the EAG considered that the MAIC using EPI VITRAKVI should not be used to extrapolate response for all tumour types in people 21 years and under. The committee concluded that the comparative effectiveness of larotrectinib and standard care from the MAIC analyses was not appropriate for decision making.

Economic model

Company's modelling approaches

3.11 The company used a partitioned survival model structure with 3 health states: pre-progression, post-progression and death. The cycle length was 1 week and the time horizon was 80 years. The larotrectinib arm was modelled as tumour site independent, using pooled survival estimates and health state utility values across all tumour types from the larotrectinib clinical trials. The standard care arm was stratified by 12 different tumour sites to reflect differences in resource use and health state utility values across these tumour sites. To inform health state occupancy in the larotrectinib arm, the company fitted separate Weibull progression-free survival and overall survival curves for adults and children, using the pooled trial data. In the standard care arm, progression-free survival and overall survival curves were derived by applying MAIC-based hazard ratios (VICTORIA for adults; EPI-VITRAKVI for people 21 years or younger) to the larotrectinib survival curves. The modelled cohort remained on treatment until disease progression or death and the analysis assumed no treatment effect waning. The company presented 4 additional modelling approaches used in scenario analyses:

- Responder and non-responder analysis: separate progression-free survival and overall survival curves were fitted for responders and non-responders. For larotrectinib, outcomes were estimated by combining these curves using weights based on the expected response rate in selected tumour types from the BHM. For standard care, outcomes were assumed to be equal to those of non-responders.
- Intra-patient comparison (using growth modulation index): time-to-progression on previous therapy served as a proxy for standard care progression-free survival. Standard care overall survival was informed by applying the relative progression-free survival and overall survival relationship for larotrectinib.

- Naive literature comparison: overall survival and progression-free survival for standard care was informed from literature by tumour location.
- Mixture-cure model: a cure fraction was assumed for children (0 to 17 years) who had larotrectinib. The adult cohort (18 years and over) was modelled as per the company's base-case model.

EAG's alternative modelling approaches

3.12 The EAG highlighted that the company's base-case model did not address the heterogeneity in response across tumour types as it assumed a histology-independent treatment effect. It also noted that the approach had limited NHS applicability. The EAG said that the MAIC hazard ratios implied a clinically implausible post-progression survival, especially in children, and violated the proportional hazards assumption. The EAG explained that the company's response-based BHM model had advantages in capturing heterogeneity in response across tumour types but noted that the way it was implemented did not allow tumour-specific responses or NHS tumour distributions to be incorporated, limiting its usefulness. Overall, the EAG thought that none of the company's modelling approaches resolved the uncertainties around heterogeneity, immature overall survival data in children, or applicability of trial populations to the NHS. So, the EAG explored 3 different modelling approaches:

- Pooled-MAIC model (EAG base case 1): for the larotrectinib arm, progression-free survival and overall survival curves were fitted to pooled adult (18 years and over) and child (0 to 17 years) data from the trials. For the standard care arm, hazard ratios from a MAIC using VICTORIA data were applied to the larotrectinib curves. The EAG highlighted that this approach used the largest evidence base available, removed the flawed EPI VITRAKVI MAIC, and pooled adult and child trial data to reduce the impact of immature paediatric data on post-progression survival. But it assumed histology-independent treatment

effects, did not resolve trial generalisability concerns, and relied on assumptions of proportional hazards and full adjustments for prognostic and effect-modifying factors.

- Response-based model informed by BHM (EAG base case 2): for the larotrectinib arm, progression-free survival and the overall survival curve were based on adult- and child-specific responder and non-responder curves, weighted by tumour site from the BHM analyses. For the standard care arm, no response was assumed and it was informed by people having larotrectinib whose tumours did not respond. The EAG highlighted that this approach accounted for differences between tumour types and adjusted the distribution of tumour sites to reflect the SACT NHS data. But it assumed no tumour response with standard care, included trial-based subsequent therapy use and relied on several strong assumptions about tumour-site outcomes, responder survival and stable disease rates, which may have biased survival estimates.
- SACT model (EAG base case 3): for the larotrectinib arm, exponential parametric models were fitted to overall survival and treatment duration pseudo-individual patient data from SACT (assuming a proxy relationship with progression-free survival). For the standard care arm, parametric models were fitted to tumour-specific progression-free survival and overall survival data derived from literature sources. The EAG highlighted that this approach used tumour types and patient characteristics aligned with NHS clinical practice, and mature SACT overall survival data, and avoided biases from trial-based subsequent therapies. But it was based on a small sample size and unadjusted comparisons with uncertain literature sources. It also assumed similar outcomes for tumour types not represented and treatment benefit that continued beyond progression.

  The EAG highlighted that although analyses using different modelling approaches were informative for decision making, neither the

company's or EAG's modelling approaches accurately reflected the cost effectiveness of larotrectinib in the NHS.

Most appropriate modelling approach for decision making

3.13 The committee considered the different modelling approaches used by the company and the EAG to model the cost effectiveness of larotrectinib. The committee noted that modelling in this evaluation was particularly challenging because the clinical evidence came from single-arm trials, the population included people of all ages with a wide range of tumour types, and it relied on indirect comparisons alongside limited real-world evidence from the SACT dataset. The committee noted that each modelling approach had important limitations and that the cost-effectiveness estimate varied substantially depending on the model structure and comparator assumptions, indicating substantial decision uncertainty (see sections 3.11 and 3.12). The committee noted that the company's base-case approach and EAG's pooled-MAIC approach both relied on a histology-independent treatment effect using clinical trial data. It recalled that this was highly uncertain (see section 3.7). It also recalled the generalisability concerns with the trial data and that it had thought that the MAICs were not appropriate for decision making (see sections 3.6 and 3.10).

The committee considered the EAG's SACT model and noted that although it was more generalisable to NHS clinical practice, it relied on unadjusted naive comparisons in the absence of comparator data for the standard care arm in SACT. It was concerned that the comparator data did not reflect the target population of interest, recalling similar issues about the comparator data used in the MAICs (see section 3.10). It also noted that this approach maintained the assumption of treatment benefit beyond progression. The committee then considered the appropriateness of the EAG's BHM approach. The company said that although the BHM was useful, it introduced additional assumptions that could not be directly

tested and may have been particularly sensitive to tumour site in the context of sparse data. The committee noted that the other modelling approaches that used a common effect across tumour sites also relied on a strong assumption that all tumour sites respond equally. It thought that using response estimates from tumour sites with available data to inform estimates for those with limited or no data in the BHM model may not be a stronger assumption than assuming a common response across all sites. The committee questioned the plausibility of assuming that overall survival would be the same for all people who experience a response regardless of tumour type in the BHM model. The clinical experts highlighted that response to larotrectinib and survival outcomes may differ substantially between tumour types and between people with locally advanced and metastatic disease, meaning that assuming identical survival outcomes across tumour types for people who experience a response may not be clinically plausible.

The committee felt that no single modelling approach fully resolved the uncertainties associated with the available evidence and that all of the approaches relied on strong assumptions because of the rarity and heterogeneity of NTRK fusion-positive cancers. But it thought that the different modelling approaches together provided informative scenarios to explore the potential cost effectiveness of larotrectinib in the NHS, although substantial uncertainty remained. The committee thought that the EAG's BHM model addressed some of the heterogeneity in pooled tumour response across tumour types. It acknowledged that this approach also used the trial data. But, it thought that the EAG's adjustment to the tumour-site distribution to reflect the NHS population in the SACT dataset addressed some of these concerns. The committee felt that neither the company's base case nor EAG's alternative modelling approaches were optimal for informing the cost effectiveness of larotrectinib. The committee concluded that the BHM response-based model was likely the most appropriate, in the absence of a more appropriate alternative.

Health state utility values

3.14 The company model used treatment-specific utility values. It assumed that people having larotrectinib would have a higher quality of life than those having standard care, in both the progression-free and progressed disease states, reflecting lower toxicity and higher complete response rates. Utility data was collected in the larotrectinib clinical trials using the EQ-5D-5L, which was mapped to the EQ-5D-3L. These utility values were then pooled across adult and paediatric populations, assuming tumour site-agnostic utilities for larotrectinib. For standard care, tumour-specific utilities were taken from previous NICE technology appraisals and various published literature, including proxy and non-reference case estimates where EQ-5D data was unavailable. The EAG highlighted several concerns with company's approach to modelling health state utility values:

- The trial-derived utilities showed only a small decline in quality of life after progression, resulting in relatively high utilities in the progressed disease health state, which were sustained over a long period. These were higher than most published estimates for NTRK inhibitors and were considerably higher than those used for standard care.
- Pooled utility values may have overestimated quality of life because the trial population may not have been representative of the NHS population. For example, children, who tended to have higher utilities in the trial, may have disproportionately influenced the long-term post-progression utility values. Also, high rates of subsequent treatment use in the trials may have inflated post-progression quality of life compared with what would be expected in NHS practice.
- In the standard care arm, the company relied on non-reference case utility estimates in 5 tumour types and on EQ-5D values that were more than 20 years old, so may not have reflected current NHS care.
- Pooling adult and paediatric utilities prevented appropriate age adjustment and may have obscured meaningful differences between populations.

In the EAG's base-case approach, standard care utilities in both the progression-free and progressed disease health states were based on weighted EQ-5D utility values only from literature and excluded non-reference case estimates. For the larotrectinib arm, the progression-free utility values were based on trial data. For the progressed disease health state, the same utilities as the standard care arm were applied, assuming a common progressed disease utility value across treatment arms. The EAG said that this approach retained the assumption of an additional quality-of-life benefit for larotrectinib in the progression-free health state, which it considered optimistic but plausible. But it removed the treatment benefit in the progressed disease health state because it deemed the size and duration to be inappropriate.

The committee was concerned with assuming treatment-specific utilities based on naive comparisons between trial data for larotrectinib and heterogeneous sources from literature and previous appraisals rather than direct comparative evidence. It also questioned the company's justification for higher progressed disease utilities in the larotrectinib arm despite progression in both treatment arms. The company argued that:

- the progressed disease health state reflected treatment experience rather than progression alone
- progression may be radiographic rather than symptomatic, so people may progress without feeling any worse
- larotrectinib may allow people to avoid mutilating surgeries and these benefits remain even after progression
- better tumour responses with larotrectinib compared with standard care may delay symptomatic deterioration even if radiographic progression occurs

- for people on standard care such as chemotherapy, toxicities may persist after disease progression.

The EAG said that differences in progressed disease utilities accounted for a substantial proportion of the quality-adjusted life years (QALYs) gained. This was because people spent a long time in the progressed disease health state in the model. The EAG further explained that the progressed disease utility was intended to represent quality of life from progression until death and that evidence from other sources for people who had NTRK inhibitors typically showed a larger decline in quality of life after progression. The EAG stated that attrition in the long-term trial follow up may have increased the influence of paediatric observations over time and that some responses classified as progressed disease in the trials may have reflected people having subsequent treatments rather than remaining in a true post-progression state. The committee noted that the EAG's approach resulted in a much lower progressed disease utility value for larotrectinib, which was more consistent with what would be expected in clinical practice and from existing evidence.

The committee remained concerned that the assumption of treatment-specific utilities, particularly in the progression-free health state, was highly uncertain and not supported by robust comparative evidence. It thought that the utility benefit in the larotrectinib arm may be plausible, but noted that no clear evidence had been presented to show this. So, the committee felt that the treatment-specific utility values used in the economic modelling were not well justified. The committee concluded that it would like to see cost-effectiveness analyses without a treatment-specific utility benefit for larotrectinib in the progression-free or the progressed disease health states. It noted that plausible treatment benefits in the larotrectinib arm could be explored as an uncaptured benefit of larotrectinib.

Subsequent treatment effects and costs

3.15 The company assumed that all people in the model would stop active treatment and have best supportive care after disease progression in both the larotrectinib and standard care treatment arms. So, no post-progression subsequent treatment costs were applied in the model. It based this assumption on the small number of people having subsequent treatments in the SACT data and trial data, and very few people in the larotrectinib arm had a subsequent NTRK inhibitor after progression. So the company said that subsequent therapy use in NHS practice is rare and that any associated costs would 'cancel out' between the larotrectinib and standard care arms. The EAG raised concerns with this approach, highlighting that the company had used the larotrectinib trial data to inform outcomes in the model. This data included a large proportion of people who had subsequent treatments, including other NTRK inhibitors, which are not available in the NHS. So, the effects of these treatments were embedded in the survival and health-related quality-of-life outcomes in the model, but were not costed or adjusted for. The EAG thought this was an issue because the use of subsequent treatments such as chemotherapy, radiotherapy and surgery was much higher in the clinical trials than was observed in the SACT data, which reflects NHS practice, but was not costed. It also highlighted that in the SACT data, only around 13% of people had subsequent treatment after progression, but this was much higher in the trials. So, the trial-based estimates of overall survival and progressed disease utilities may have been inflated by the effects of subsequent treatments that are not typically used in the NHS.

The committee recalled that this issue was related to the post-progression survival and quality-of-life estimates (see sections 3.8 and 3.14). The EAG further highlighted that adjusting for the impact of subsequent therapies would likely reduce the estimated overall survival benefit and produce results that were more generalisable to NHS clinical practice. The committee questioned if the company's approach may bias the cost-

effectiveness results. The company explained that there was no robust evidence to quantify the independent survival benefit associated with the wide range of treatments used after progression in this heterogeneous population. So, any adjustment would rely on strong assumptions about the magnitude and duration of treatment effects and might introduce additional bias. The committee questioned why neither the company nor the EAG included the costs of subsequent treatments given that their survival benefits were included in the economic model. The EAG said that in the SACT dataset, only a small number of people had subsequent treatment. So the cost impact of these was likely limited. The committee felt that the subsequent treatment effects and costs were inconsistently accounted for in the company's and EAG's modelling approaches. It concluded that if subsequent treatment effects are modelled, then the costs of subsequent treatments should also be accounted for in the economic model.

Effects of heterogeneity on the cost-effectiveness estimates

3.16 The company presented a single pooled cost-effectiveness estimate across all tumour types and age groups. It said that this was appropriate because larotrectinib is a tumour-agnostic treatment based on a NTRK fusion mutation across many solid tumours, with no clearly defined clinical subgroups. So, a pooled estimate maximised statistical power and best reflected the licensed population. The EAG cautioned that using a single pooled cost-effectiveness estimate may obscure important differences between patient groups because the population is highly heterogeneous and includes tumour types with different prognoses and treatment outcomes. The EAG noted that it requested disaggregated subgroup results by tumour type and age at clarification, but the company thought that subgroup analyses were not appropriate. The company explained that the rarity of NTRK fusion-positive cancers and the small sample sizes of the trial data and SACT data limited the feasibility and robustness of subgroup analyses. It also highlighted that the pooled trial evidence

suggested a durable response to larotrectinib across tumour types, age groups and NTRK fusion variants. The company further explained that differences in apparent cost effectiveness between adults and children may largely have reflected differences in life expectancy and baseline prognosis rather than clear differences in relative treatment effect. The CDF lead said that differences between the trial populations and SACT data may have partly reflected initial differences in testing practices across tumour sites and the evolving use of genomic testing in clinical practice. But they noted that genomic testing is now considered standard practice. The EAG thought that exploring the heterogeneity in cost effectiveness and presenting disaggregated cost-effectiveness estimates could improve transparency and support decision making, even though the analyses would be subject to substantial uncertainty.

The committee acknowledged that doing robust subgroup analyses would be difficult because of small sample sizes and limited comparative data. But it noted that there was substantial heterogeneity in the tumour types, outcomes and treatment pathways, so a single pooled cost-effectiveness estimate might have masked important differences in cost effectiveness between subgroups. The committee also thought that subgroup analyses could help assess whether the cost effectiveness estimates would be broadly similar despite differences between these subgroups. The committee concluded that further exploration of the effects of heterogeneity in cost-effectiveness analyses would help with understanding the impact of heterogeneity on the range of cost effectiveness estimates. This may reduce the uncertainty in the overall cost-effectiveness results and support decision making.

Severity and QALY weighting

3.17 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity

modifier) if technologies are indicated for conditions with a high degree of severity. The committee recognised the challenges of calculating and applying a QALY weight because larotrectinib was being evaluated across multiple tumour types within a tumour-agnostic population. The company and EAG both applied a severity modifier in their base cases, but used different approaches to calculate and apply the QALY weighting.

The company estimated severity at the tumour-site level, calculating a severity weighting separately for each tumour type based on the tumour-specific QALY shortfall. The tumour-site severity weight was then applied to total QALYs in each treatment arm. The severity-weighted QALYs from each tumour site were then aggregated according to the tumour prevalence distribution. This approach produced an overall implied QALY weighting of 1.6. The company used literature-based estimates of standard care outcomes that had been used in previous NICE technology appraisals, together with the age and sex distribution and tumour-type prevalence observed in the larotrectinib clinical trials. This approach was also explored by the EAG in a scenario using its BHM modelling approach, which resulted in a overall implied QALY weighting of 1.39. The EAG raised several concerns with the company's approach. First, it thought it was inappropriate to aggregate the tumour-specific severity-weighted QALYs by tumour prevalence rather than by the distribution of QALYs across tumour types. It said that this assumed an equal benefit of larotrectinib across tumour types, regardless of response rate, natural history, or prognosis on treatment. This may have overestimated benefits in tumour types that are associated with higher severity but have lower response rates and had a low prevalence in the trial, for example CNS tumours. The EAG also highlighted an internal inconsistency in the standard care QALY estimation. This was because the severity calculation relied on naive literature-based estimates of standard care outcomes, whereas treatment effects in the cost-effectiveness model were derived from MAIC-adjusted survival estimates. The EAG also noted that the

standard care QALY estimates used in the company's analysis were largely derived from older literature sources. This may have underestimated health-related quality of life under current NHS care, and inflated the estimated QALY shortfall. Similarly, it thought that using the relatively young trial population to estimate starting age may also have increased the calculated QALY shortfall compared with what would be expected in the NHS population. Finally, the EAG noted that the severity modifier should be applied to incremental QALYs only, rather than to total QALYs, and adjusted the modelling approach accordingly.

The EAG proposed an alternative method that calculated the absolute and proportional QALY shortfalls separately for each tumour site. The shortfalls were weighted by tumour prevalence to derive population-level absolute and proportional shortfalls. A single population-level severity modifier was then applied to the incremental QALYs in the model. In all of the EAG base cases, this resulted in a 1.2 QALY weighting. In its preferred analyses, the EAG's standard care QALY estimates came directly from the model and it used tumour prevalence distributions informed by SACT data. It explored alternative age and sex distributions from the trials and the SACT dataset, depending on the modelling approach taken (see section 3.12). The company emphasised that applying an overall severity weighting may not account for the fact that many tumour types included in the indication are associated with poor prognosis, limited treatment options and, in some cases, the risk of highly morbid interventions such as mutilating surgery. It argued that these factors supported the higher severity weighting.

The committee noted that some aspects of the company's model pooled tumour types, while other aspects considered tumours separately, which was inconsistent. It thought that the EAG's approach of calculating absolute and proportional QALY shortfall separately for each tumour site and then weighting these by tumour prevalence to derive a single

population-level severity modifier was more appropriate. So, the committee concluded that the severity weight of 1.2 applied to the incremental QALYs was appropriate for decision making.

Costs of primary CNS tumour management, oral administration, formulation and drug wastage

3.18 The committee noted differences in assumptions around disease management costs for primary CNS tumours and oral administration costs. The company based costs for these on values in NICE's technology appraisal guidance on temozolomide for the treatment of recurrent malignant glioma (brain cancer) [from here, TA23]), assuming a single MRI cost in the progression-free survival health state with no further ongoing disease management costs. The EAG highlighted that this did not accurately capture all of the costs of managing CNS tumours and that TA23 is nearly 25 years old. So it included regular clinical monitoring costs for the progression-free survival health state from NICE's technology appraisal guidance on dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 year and over and multidisciplinary and specialist nurse input in progressive disease, aligning CNS tumours with other modelled tumour sites. The patient and clinical experts at the committee meeting also said that most people with NTRK fusion-positive tumours have follow-up MRI scans every 3 months as part of monitoring the disease progression. The company did not include any costs for orally administered therapies. The EAG recommended including the SB11Z tariff (£247) per treatment cycle to account for dispensing, consistent with NHS England and TA630. The committee noted that the company assumed that all adults in the model would have oral capsules, and children could have oral capsules or oral solution. The clinical experts at the committee meeting said that they would expect most adults to have capsules and children to have oral solution in NHS clinical practice. The EAG highlighted that the company's base-case model excluded drug wastage for both larotrectinib and

standard care arms. The committee preferred drug wastage to be included by assuming that the full cost of the final pack of capsules or bottles of oral solution would be incurred unless partially used packs or bottles can be reallocated. The committee considered these differences in the modelling of costs and resource use and concluded that, to help with decision making, it would like to see the following included in the model:

- for larotrectinib, all adults having oral capsules and all children having oral solution
- the full cost of the final pack of capsules or bottles of oral solution, unless partially used packs or bottles can be reallocated
- costs and resource use for managing CNS tumours, and oral administration costs to reflect costs paid by the NHS.

Cost-effectiveness estimates

Acceptable ICER

3.19 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will take into account other aspects including uncaptured health benefits. The committee was also aware of its duties to consider a higher degree of uncertainty in technologies for which evidence generation is difficult, for example in rare diseases or populations including children. The committee noted the high level of uncertainty, including the:

- generalisability of clinical-effectiveness evidence from the larotrectinib trials to NHS clinical practice (see sections 3.4 to 3.6)
- pooling of outcomes across tumour types (see section 3.7)

- size of overall survival benefit with larotrectinib in the clinical trials (see section 3.8)
- validity of the MAICs to inform the comparative effectiveness of larotrectinib and standard care (see sections 3.9 and 3.10)
- most appropriate modelling approach (see sections 3.11 to 3.13)
- health state utility values used in the economic model (see section 3.14)
- differences in subsequent treatments used after progression in the trial and SACT data (see section 3.15)
- effects of heterogeneity in the single pooled cost-effectiveness estimate for a population with different tumour types, outcomes and treatment pathways (see section 3.16).

The committee noted that, based on the evidence and analyses it had seen, there were substantial uncertainties. So it would like to see further evidence and updated analyses to better assess and explore these uncertainties. So the committee concluded that it was unable to determine an acceptable ICER.

Company and EAG cost-effectiveness estimates

3.20 The company's and EAG's base cases differed because of the following:

- the clinical evidence used to inform tumour-site distribution and baseline characteristics in the model (see section 3.6)
- the approach to modelling health state occupancy (see section 3.13)
- the health state utility values applied in the model (see section 3.14)
- the approach to calculating and applying the severity modifier (see section 3.17)
- the health state resource use for primary CNS tumours (see section 3.18)
- the inclusion of oral treatment administration costs (see section 3.18).

Because of confidential commercial arrangements for larotrectinib and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here.

Committee's preferred assumptions and request for additional analyses

3.21 The committee's preferred assumptions were to model:

- the tumour-site distribution and baseline characteristics based on the SACT dataset population (see section 3.6)
- health state occupancy using the EAG's BHM responder-based analyses (see section 3.13)
- no treatment-specific utility benefit for larotrectinib in the progression-free or the progressed disease health states (see section 3.14)
- costs associated with subsequent treatment use (see section 3.15)
- a severity weighting of 1.2 applied to incremental QALYs (see section 3.17)
- the oral capsule formulation in adults and the oral solution formulation in children (see section 3.18)
- drug wastage by including the cost of the whole of the final pack or bottle, unless partially used packs or bottles can be reallocated (see section 3.18)

  costs and resource use for managing CNS tumours, and oral administration costs to reflect costs paid by the NHS (see section 3.18).

The committee requested that the company provide further exploration of heterogeneity, including more disaggregated outcomes, to help better assess the uncertainty in the clinical effectiveness estimates and understand the drivers of the cost-effectiveness estimates (see section 3.7 and section 3.16).

The committee considered its preferred assumptions and the potential uncaptured benefits (see section 3.24). But it concluded that because it was unable to fully assess the uncertainties in the clinical-effectiveness

evidence and in the economic model based on the evidence and analyses it had seen, it could not determine the most likely cost-effectiveness estimates for larotrectinib compared with standard care.

Other factors

Equality

3.22 The committee noted several equality considerations raised by the company and stakeholders. The submissions highlighted that there is a large variation in diagnostic testing practices across regions and between smaller hospitals and specialist centres, which may limit identification of eligible patients and delay access to treatment. A clinical expert at the meeting said that this unequal access to genomic testing for NTRK fusions may disadvantage certain groups, including older adults, young children, ethnic minority groups, people with rare or severe conditions, and people living in rural or deprived areas. The committee acknowledged that there might be variations in access to genomic testing for NTRK fusion tumours that could affect access to larotrectinib if recommended. But it explained that access to testing, which is now considered standard NHS practice, is an implementation issue that cannot be addressed by a recommendation in a NICE technology appraisal. It considered whether there were any equality issues relevant to protected characteristics that could be addressed by the evaluation process. But the committee noted that its recommendation does not restrict access to treatment for some people over others. So, the committee agreed that there were not equality issues in this evaluation. The committee then considered whether any of the issues raised were considered health inequality issues (see section 3.23).

Health inequalities

3.23 The committee considered health inequalities raised by the company and stakeholders in relation to access to larotrectinib. The submissions highlighted that variation in access to genomic testing and diagnostic

pathways may contribute to inequalities in identifying patients with NTRK fusion-positive tumours. In particular, differences in testing practices between regions and between specialist centres and smaller hospitals may limit or delay identification of eligible patients. The clinical experts said that people with rare cancers may already experience delays in diagnosis, and if genomic testing occurs late in the diagnostic pathway this may further delay access to targeted treatments such as larotrectinib. The committee acknowledged these concerns but noted that many of the issues raised related to broader service delivery and diagnostic pathways rather than the evaluation of larotrectinib. The committee felt that although these concerns were plausible, no robust qualitative or quantitative evidence had been provided to demonstrate that this evaluation would directly worsen or address health inequalities. So it could not consider how potential health inequalities could impact its decision making and consider accepting a higher level of uncertainty.

Uncaptured benefits

3.24 The committee considered whether there were any uncaptured benefits of larotrectinib not fully reflected in the economic model. The company submission highlighted that larotrectinib provides broader benefits beyond those included in the modelled outcomes, including:

- better quality of life, because of larotrectinib's favourable safety profile and simple oral administration
- reduced caregiver burden, because treatment with larotrectinib reduces treatment-related time, including time in hospital
- psychological benefits for patients and their families and carers, including reduced anxiety, especially for people caring for children.

The clinical experts emphasised that the improvements in treatment experience (including oral administration benefit, better outcomes and better safety profile) and quality of life described by the company are meaningful for patients and their families and carers. The EAG

highlighted that many of these benefits described were subjective or unquantified. It also said that the company had not presented robust evidence to demonstrate a measurable carer health-related quality-of-life benefit. It thought that most of these benefits with larotrectinib were likely already reflected in the model through progression-free survival, overall survival and utility values. The committee acknowledged the perspectives on uncaptured benefits and noted that such factors may be considered qualitatively when interpreting the cost-effectiveness results. It recognised that some benefits may already be reflected in the modelled outcomes, but that others may not be fully captured. In particular, the committee noted that some people expected to have larotrectinib are young children. So treatment with larotrectinib could have wider effects on the quality of life of their parents or carers, for example by reducing time spent in hospital or avoiding more extensive surgery. The committee also recalled its conclusion about providing evidence for the quality-of-life benefits of being on larotrectinib, in the absence of robust comparative evidence (see section 3.14) The committee concluded that potential additional benefits were likely relevant, but the extent to which they should be taken into account for decision making remained uncertain.

Conclusion

Recommendation

3.25 The committee recalled the uncertainties in the clinical-effectiveness evidence and the economic modelling assumptions. The committee thought that the cost-effectiveness estimates presented by the company and the EAG were highly uncertain and did not reflect its preferences, including how to explore the impact of the existing uncertainty. So it agreed that more exploration was needed before it could determine the most appropriate cost-effectiveness estimates for larotrectinib. So, larotrectinib should not be used.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Raju Reddy
Interim chair, technology appraisal committee D

NICE project team

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

Zain Hussain
Technical lead

Cara Gibbons
Technical adviser

Kate Moore
Project manager

Elizabeth Bell

Principal technical adviser

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