Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]

Committee slides – contains [redacted] information

Technology appraisal committee D [04 March 2026]

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- ✓ **Background and key issues**
- ❑ Clinical effectiveness and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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History of larotrectinib appraisal

See appendix: TA630 conclusions

TA630
(May 2020 – recommended into CDF within full MA)

→

CDF
(April 2020 to December 2024)

→

ID6292
(2026, managed access review)

TA630 key committee uncertainties:

- Prevalence and characterisation of NTRK gene fusions in each tumour site
- Prevalence and characteristics of NTRK gene fusions by tumour type
- Prognostic significance of NTRK gene fusions
- Larotrectinib's place in the treatment pathway, including use after subsequent therapies
- Uncertain diagnostic pathway until NHSE establishes national genomic testing for all advanced solid tumours
- Limited generalisability of trial evidence to NHS practice
- Immature data preventing reliable long-term survival estimates
- Heterogeneity of response across tumour types
- Post-progression utility differences between larotrectinib and comparators
- Whether the treatment meets end-of-life criteria

CDF: Cancer Drugs Fund; MA: Marketing authorisation; NTRK: Neurotrophic Tyrosine Receptor Kinase; TA: Technology appraisal

Background on NTRK fusion-positive solid tumours

NTRK fusion-positive solid tumours are cancers driven by NTRK gene fusions and can occur in many tumour types in both adults and children

Causes

- NTRK gene fusions occur when part of an NTRK gene joins another gene, creating an always-active TRK protein ➔ this drives cancer by causing uncontrolled cell growth and tumour formation

Epidemiology

- Prevalence varies by tumour type: common cancers (<0.1–3%), rare tumours (>90%) e.g., infantile fibrosarcoma
- Overall prevalence of NTRK fusion-positive tumours tends to be low (children: 0.44–3.33%; adults: 0.03–0.7%)
    - Estimated annual UK NTRK fusion-positive tumour cases: ~11 to 82 children, ~115 to 2681 adults
    - UK SACT database (2018–2024): 39,363 tested → 404 (0.11%) positive or borderline for NTRK fusions

Diagnosis and classification

- Genomic testing, particularly Next Generation Sequencing, is gold-standard for identifying NTRK gene fusions
    - Other testing methods: FISH, IHC, RT-PCR, and whole-genome sequencing
- UK testing varies based on several factors (e.g., histology, geography, clinician awareness, urgency) and is prioritised for tumours with higher fusion prevalence or limited standard treatments options
    - NHS England confirmed that testing for NTRK gene fusions can be considered standard practice

Symptoms and prognosis

- Symptoms depend on tumour's organ of origin and there are no fusion-specific symptoms
- RWE suggests NTRK positive tumours may carry a 51% higher risk of death than NTRK negative tumours

FISH, fluorescence in situ hybridisation; IHC: Immunohistochemistry; NTRK: Neurotrophic Tyrosine Receptor Kinase; RT-PCR, reverse transcription polymerase chain reaction; RWE, real world evidence; TRK: Tyrosine receptor kinase

Patient and carer perspectives

NTRK fusion-positive cancers are rare and can profoundly affect the lives of those living with the condition and the people who care for them

Submissions from Sarcoma UK, AMMF and patient expert

- **Rare, high-burden cancers:** NTRK FP cancers occur across histologies and ages and often diagnosed late, with significant physical and psychological impact
- **Severe life disruption:** these tumours significantly affect physical, emotional, and social wellbeing, disrupting independence, work, relationships, mental health, mobility, and causing pain and anxiety
- **Impact on carers and family:** Carers face financial, emotional, and social strain, often disrupting work and severely affecting mental health
- **Limitations of standard care:** Conventional treatments often poorly tolerated and may fail to control NTRK-driven disease, particularly in rare cancers
- **Transformative role of TRK inhibitors:** provides effective disease control with manageable side effects, restoring normality and quality of life
- **Key unmet need:** Timely molecular profiling and equitable tumour-agnostic access are essential to ensure eligible patients benefit without delay

"Living with this condition has been life-changing on every level - physically, emotionally, and mentally"

"There is constant uncertainty about the future, which brings stress and anxiety not only for me but for my loved ones."

"We had very few good options, and the treatments caused unnecessary suffering."

"[Larotrectinib] provided real disease control where other options had failed"

NICE

NTRK FP: Neurotrophic Tyrosine Receptor Kinase Fusion Positive; TRK: Tyrosine receptor kinase;

Clinical perspectives

There is a clear unmet need for a highly effective, well-tolerated and life-changing targeted treatment for NTRK fusion positive tumours such as larotrectinib

Submissions from clinical experts

- **Treatment aim:** Achieve tumour eradication or meaningful shrinkage enabling surgery; where cure is not immediate, stabilise disease to prolong survival and preserve quality of life
- **Limitations of standard care:** Chemotherapy and surgery are often toxic, burdensome, and may fail to control NTRK-driven disease, with significant impact on patients and carers
- **Larotrectinib:** Delivers high and durable response rates across tumour types and ages, addressing a major unmet need
    - Oral, at-home treatment allows patients to maintain independence, work or education, and reduces carer burden
    - Generally well tolerated with mild, manageable side effects and far less intensive monitoring than chemotherapy
    - Quality of life of children and their families is incomparably better
- **Unmet need**: Equitable NHS access, including re-treatment at progression, is key to optimise outcomes in NTRK fusion-positive cancers

"For NTRK fusion-positive cancers, conventional chemotherapy and surgery often fail to address the underlying driver of disease, leaving a clear unmet need for effective targeted treatment."

"The difference compared with standard care is astonishing, both in tumour response and quality of life."

"I have not seen a single NTRK-mutated tumour that has failed to respond to larotrectinib in real-world practice"

Equality considerations raised by stakeholders

Variation in testing access may disadvantage older adults, young children, ethnic minority groups, people with severe or rare conditions, lower-income families, and those in rural areas

- **Age**
  - Older adults may be disadvantaged by variation in NTRK testing
  - Young children with NTRK-mutated tumours are particularly vulnerable if access is restricted
- **Race / ethnicity**
  - Testing variation may disadvantage ethnic minority groups
  - Bias may limit testing for Black and ethnic minority patients
  - Language barriers may further restrict access
- **Disability / long-term conditions**
  - People with incurable brain tumours or severe NTRK-related conditions are particularly vulnerable
  - Rare cancer patients already face unequal diagnosis and treatment compared with common cancers
- **Socio-economic status**
  - Lack of routine NHS funding could push patients into private care, worsening socio-economic inequality
  - Travel to specialist centres may disproportionately burden lower-income families
- **Geographic location**
  - Regional variation in NTRK testing may limit access for rural populations
  - Home-administered larotrectinib can reduce travel-related barriers

Are there any equality considerations that can be addressed by the committee in this appraisal?

NTRK: Neurotrophic Tyrosine Receptor Kinase

Health inequalities considerations raised by stakeholders

- **Variation in testing and diagnostic access:**
  - NTRK testing varies across the UK, potentially limiting access to larotrectinib
  - Regional disparities exist between smaller hospitals and major urban centres
  - Language barriers and staff bias may further restrict access for ethnic minority patients
- **Inequalities affecting specific patient groups:**
  - Sarcoma patients represent almost a quarter of those in larotrectinib trials and the CDF, highlighting reliance on this pathway
  - Conscious and unconscious biases may reduce testing for Black and ethnic minority groups
- **Socio-economic barriers:**
  - Ending NHS funding would force reliance on private care, worsening socio-economic inequalities
- **Disease rarity and HTA-related disadvantage**
  - The rarity and heterogeneity of NTRK fusions may disadvantage patients within HTA processes due to limited evidence and variable case mix

EAG critique

- No robust quantitative or qualitative evidence on the impact of larotrectinib upon health inequalities has been provided ➔ EAG does not consider larotrectinib to meaningfully address inequality or unfairness in the distribution of health across society

Are there any health inequality considerations that can be addressed by the committee in this appraisal?

CDF: Cancer Drugs Fund; HTA: Health technology assessment; NTRK: Neurotrophic Tyrosine Receptor Kinase

Larotrectinib (Vitrakvi, Bayer)

Marketing authorisation (MA)	UK conditional MA authorisation on March 2021 *"VITRAKVI 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"*
Mechanism of action	Highly selective, ATP-competitive oral inhibitor of the TRK kinases (TRKA, TRKB and TRKC) that directly targets oncogenic TRK fusion proteins resulting from NTRK gene fusions. By blocking constitutive TRK signalling that drives tumour cell proliferation and survival, it delivers targeted anti-tumour activity with minimal off-target effects
Administration	Formulations: Oral capsules (25 mg or 100 mg) or oral solution (20 mg/ml) Dosage: • Adults: 100 mg twice daily until disease progression or unacceptable toxicity • Paediatric: 100 mg/m^2 twice daily with a maximum of 100 mg per dose until disease progression or unacceptable toxicity
Price	• The list price for larotrectinib is £14,000 (56 capsules of 100 mg), £3,500 (56 capsules of 25 mg) and £5,000 (100 ml solution of 20 mg/ml) • Company has a confidential PAS discount in place

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ATP: Adenosine Triphosphate; NTRK: Neurotrophic Tyrosine Receptor Kinase; PAS: Patient access scheme; TRK: Tyrosine receptor kinase; TRKA: Tropomyosin receptor kinase A; TRKB: Tropomyosin receptor kinase B; TRKC: Tropomyosin receptor kinase C

Key issues for discussion

Issue	ICER impact
Clinical effectiveness	
Applicability of trial evidence to the NHS	Large/ unknown
Assuming common response across tumour types	Large
Magnitude of larotrectinib's survival benefit	Unknown
SACT limitations	Unknown
Validity of the MAICs and relevance to the NHS	Large/ unknown
Cost effectiveness	
Optimal approach to economic modelling	Large
Heterogeneity in cost-effectiveness estimates across key subgroups is not captured	Unknown
Modelled health state utility values	Large
Subsequent therapy effects and costs	Unknown
QALY weights for severity	Large

ICER: Incremental cost effectiveness ratio; MAICs: Matching-adjusted indirect comparisons; QALY: Quality-adjusted life year; SACT: Systemic Anti-Cancer Therapy data set

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Clinical trial evidence: pooled analyses

Pooled data from 3 single-arm trials in NTRK fusion-positive cancers

	Pooled analyses (study 20288, study 20289, study 20290) (n=364)
Design	Pooled safety and efficacy analysis of participants enrolled and treated in 1 of 3 clinical studies for larotrectinib
Population	Adults & children with locally advanced/metastatic NTRK FP solid tumours
Efficacy datasets	• ePAS9 (n=304): people with **non-CNS** NTRK FP solid tumours • SAS3 (n=60): people with **primary CNS** NTRK FP solid tumours
Tumour sites	28 (most common: soft tissue sarcoma, primary CNS cancer, infantile sarcoma, lung cancer, thyroid cancer, salivary gland tumour, and colorectal cancer)
Data cut for pooled analysis	20th July 2024
Primary outcome	ORR by IRC assessment
Secondary Outcomes	ORR (by investigator), DCR, DoR, PFS, OS, safety
Location	121 sites – no UK

CNS: Central nervous system; DCR: Disease control rate; DoR: Duration of response; ePAS9: extended primary analysis set 9; IRC: Independent review committee; NTRK FP: Neurotrophic Tyrosine Receptor Kinase Fusion Positive; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; SAS3; Supplementary analysis set 3

SACT data

	SACT data (n=60)
Study design	Real-world observational cohort study using routinely collected NHS data under CDF
Setting	England; analysis conducted by NHS England's NDRS
Population (eligibility)	People with NTRK fusion-positive advanced solid tumours who had an approved Blueteq application, met all CDF clinical criteria, and initiated larotrectinib treatment. • Eligibility: requires surgery likely to cause severe morbidity, has no satisfactory systemic therapy options funded by NHS England, no previous TRK inhibitor, baseline ECOG performance status 0–2
Inclusion period	21 April 2020 – 31 December 2024.
Intervention	Larotrectinib monotherapy, administered orally in 28-day cycles; continued until progression, toxicity, surgery, or patient choice. No treatment breaks > 6 weeks.
Primary outcome	Treatment duration and OS
Secondary outcomes	Treatment status, discontinuation, RECIST radiological and cerebral response, subsequent therapies, data completeness metrics, and NTRK testing characteristics
Data sources	Blueteq (eligibility + baseline variables), SACT dataset (treatment records), PDS (vital status), NDRS molecular dataset (NTRK testing information).

CDF: Cancer Drugs Fund; ECOG: Eastern Cooperative Oncology Group; NDRS, National Disease Registration Service; NTRK: Neurotrophic Tyrosine Receptor Kinase; OS, Overall survival; RECIST: Response Evaluation Criteria in Solid Tumours; SACT: Systemic Anti-Cancer Therapy data set

Larotrectinib ORR results: pooled analysis, SACT and BHM

Overall response rate in ePAS9 and SAS3 analysis sets and SACT

	ePAS9 (n=304)	SAS3 (n=60)	SACT (n=60)
Number (%) with objective response	198 (65)	[redacted]	43 (72)
Objective response rate, % [95% CI]	65 [59, 70]	[redacted]	72 [NR]
Any complete response, n (%)	86 (28)	[redacted]	3 (7)
Partial response, n (%)	112 (37)	[redacted]	28 (65)
Stable disease ≥16 weeks, n (%)	[redacted]	[redacted]	12 (28) (≥10 weeks)

Bayesian Hierarchical Model analyses – ORR accounting for heterogeneity

	Predicted ORR with heterogeneity % (95% prediction interval)
Main analysis: ePAS9	[redacted]
Combined ePAS9 and SAS3	[redacted]
SAS3	[redacted]
BHM without tumour types with < 2 patients	[redacted]
BHM without tumour types with < 5 patients	[redacted]
Estimated strength of heterogeneity in the data: [redacted] SD on logit scale (95% Prediction interval: [redacted])	

EAG: Any naïve comparisons between data sources are limited and should be made with caution, due to immature data, censoring, small patient numbers, study designs and differences in populations

BHM: Bayesian hierarchical model; CI: Confidence interval; ePAS9: extended primary analysis set 9; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; SACT: Systemic Anti-Cancer Therapy data set SAS3; Supplementary analysis set 3; NR, not reported; SD, standard deviation

Key issue 1: Applicability of trial evidence to the NHS

Background

EAG: Trial populations differ significantly from NHS SACT population, particularly in prior lines of therapy and distribution of tumour types (28 sites vs 14 sites) → limits direct comparability

- Differences in response and survival, alongside variation in design, disease natural history, prognosis, subsequent treatments, and data maturity, reduce confidence in applying trial outcomes to NHS practice

Company approach

- SACT findings reinforce external validity and NHS generalisability of larotrectinib trials, despite small numbers and population heterogeneity → model primarily informed by trial evidence
  - Adults/children mix, tumour types and NTRK-fusion status consistent with trial, but missing data e.g., ECOG, limits comparability
  - Outcomes consistent with trials: ORR, time to response, time on treatment, PFS and 48-month OS
- MAIC using SACT IPD not undertaken due to NHSE access restrictions, small and incomplete dataset, partial overlap between tumour populations with MAIC, and requirement for an unanchored comparison

EAG critique

- Trial evidence has limited NHS applicability given population differences versus SACT
- Scenarios incorporating SACT pseudo-IPD produced highly uncertain and ICER-sensitive results
- More advanced methods (e.g. IPD meta-regression or ML-NMR) could help but would remain constrained by small samples and unanchored comparisons

Is the clinical evidence from larotrectinib trials applicable to NHS clinical practice?

ECOG: Eastern Cooperative Oncology Group; ICER: Incremental cost effectiveness ratio; IPD: Individual patient data; MAIC: Matching adjusted indirect comparison; ML-NMR:

Large impact

Key issue 2: Assuming common response across tumour types (1)

Background

- **Company**: pooled outcomes across all tumour types to give overall average response among indications
  - Scenario addressing tumour-level variation: Bayesian hierarchical model analyses
- **EAG**: BHM analysis shows clear heterogeneity in ORR by tumour type, with most variation unexplained
  - Given prognostic heterogeneity across tumour types and several patient characteristics, pooled trial estimates are unlikely to be reliable to inform decisions across tumour types in an NHS population

Company approach

- Pooled estimates are clinically meaningful → encapsulate expected range of outcomes across the diverse population eligible for tumour-agnostic therapy in NHS practice
- Heterogeneity in outcomes is expected, as larotrectinib is utilised across populations with very different background prognoses, disease kinetics and prior therapy exposure
  - Mechanism of action consistent across histologies, so observed outcome differences are primarily explained by prognostic factors rather than differential drug activity
- Base case: adults and paediatrics modelled separately to ensure appropriate representation of clinical differences

See appendix: ORR by tumour type and BHM results for ORR

BHM; Bayesian hierarchical model; ORR: Objective response rate

Key issue 2: Assuming common response across tumour types (2)

Large impact

EAG critique

- SLR of oncology basket trials concluded response rates varied by drug target and tumour type within same molecular target → pooling results ignores potential heterogeneity in efficacy across tumour types
- BHM and subgroup analyses indicate substantial heterogeneity → pooled estimates that ignore heterogeneity across tumour types, ages, and disease settings may be misleading and of limited value
  - Clinical experts: tumour types likely to influence PFS/OS after larotrectinib due to prognosis differences
  - Pooling data from adults and children may be inappropriate due to considerable variation in PFS and OS
- Trials do not test subgroup heterogeneity → inappropriate to assume common response rate across tumour sites
- BHM analyses are more robust and appropriately reflect heterogeneity and uncertainty

EAG proposals:

- Response-based model structure using tumour-specific BHM response rates reweighted to reflect the tumour distribution observed in SACT and enabling more accurate QALY estimation
  - Results in a higher ICER ➔ highlights the impact of heterogeneity on cost-effectiveness
- Further explanation of heterogeneity (e.g. by tumour type, CNS involvement, and age group) and disaggregated survival outcomes would help reduce uncertainty and improve model robustness

Is it appropriate to assume a common treatment response across tumour types?

NICE

BHM; Bayesian hierarchical model; CNS: Central nervous system; ICER: Incremental cost effectiveness ratio; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year; SACT: Systemic Anti-Cancer Therapy data set; SLR, systematic literature review

Key issue 3: Magnitude of larotrectinib's survival benefit

Background

- **Company**: updated pooled analysis has longer follow-up, larger sample size and more mature survival data
- **EAG**: company model relies on single-arm OS data, despite data immaturity (median OS still not estimable), and high use of subsequent therapies (SAS3: [redacted]; ePAS9: [redacted]), which may confound survival outcomes

Company approach

- The latest data cut-off (20th July 2024) confirms long-term clinical effectiveness, with a [redacted]% (ePAS9, non-CNS) and [redacted]% (SAS3, CNS) probability of being alive at 72 months (July 2025 data cut still under analysis)
- Expect the impact of subsequent therapies on survival to be minimal

EAG critique

- Immature OS data may overestimate post-progression survival, inflating QALYs and lowering ICER
- High trial subsequent treatments use limits NHS applicability and risks confounding OS outcomes
  - SACT data suggest OS may be less favourable in NHS and adjustment would likely reduce QALY gains
- Lack of control arms prevents robust estimation of the true OS benefit of larotrectinib versus SoC
- Further follow-up and data cuts that adjust for subsequent treatments may reduce uncertainty, but lack of comparator remains a fundamental trial evidence limitation

Given the uncertainty from immature OS data, the subsequent treatment use and the absence of a control arm in larotrectinib trials, is the magnitude of OS benefit with larotrectinib plausible?

NICE

CNS: Central nervous system; ePAS9: extended primary analysis set 9; ICER: Incremental cost effectiveness ratio; OS: Overall survival; QALY: Quality-adjusted life year; SACT: Systemic Anti-Cancer Therapy data set; SAS3; Supplementary analysis set 3; SoC: Standard of care

Key issue 4: SACT limitations

Unknown impact

Baseline characteristics
SACT clinical effectiveness results

Background

EAG: SACT provides mature TTD and OS in an NHS setting, but the sample is small and many tumour types are sparsely represented, limiting statistical power and detection of differences

- Outcomes (ORR, TTD, OS) are pooled across heterogeneous tumours and patient characteristics, so estimates may be site-agnostic and not fully reflective of prognostic variation

Company approach

- Larotrectinib CDF criteria was highly restrictive so SACT population may not fully represent likely NHS population (key characteristics in SACT dataset have substantial missing data e.g., performance status)
  - SACT data not used in the company's base-case model

EAG critique

- SACT database is considered highly relevant to the target population NHS
- Pooled SACT estimates have limited decision utility across tumour types given heterogeneity and small numbers; applying them across all tumours implicitly assumes a common treatment effect
- Cost-effectiveness impact uncertain; reliance on a small, heterogeneous dataset risks misestimating effectiveness in unrepresented tumour types
- A BHM on SACT could quantify heterogeneity in NHS context, but current sample size is likely insufficient
  - Instead, consider synthesis methods that integrate SACT information into wider evidence network

Is it appropriate to use pooled SACT outcomes?

BHM: Bayesian hierarchical model; CDF: Cancer Drugs Fund; IPD: Individual patient data; ML-NMR: Multi-Level Network Meta-Regression; ORR: Objective response rate; OS: Overall survival; SACT: Systemic Anti-Cancer Therapy data set; TTD: Time to treatment discontinuation

MAICs: comparative evidence and methodology

Covariates matched HMF and Flatiron MAICs

Company provided 4 unanchored MAICs to inform relative effectiveness of larotrectinib vs SoC – 2 were selected for their base case and are used in the model

	VICTORIA	EPI VITRAKVI
Population	Adults with locally advanced/metastatic TRK fusion-positive cancer	People aged ≤21 years with locally advanced or metastatic infantile sarcoma
Treatments included	Chemotherapy, small molecule-targeted therapy, chemo + targeted therapy, immune checkpoint inhibitor	Chemotherapy
Countries (year)	International (1 UK site) (2013 to 2023)	Germany, France (2000 to 2022)
Tumour types and sites	**5:** NSCLC, CRC, thyroid cancer, sarcomas, and salivary gland carcinoma	**1:** Infantile sarcoma
Trial data cut (dataset)	July 2022 (ePAS7)	July 2021 (ePAS6, subset 20290)
Matching method (n matched)	IPTW (Larotrectinib: 82; Comparator: 82)	IPTW (Larotrectinib: 51; Comparator: 42)
Outcomes	Primary: OS Others: ORR, DOT, TTNT, PFS	Primary: Treatment failure Others: OS, ORR, PFS, TEA, discontinuation, DCR
Comparator IPD	Yes	Yes
Used in base case	Yes	Yes

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CRC: Colorectal cancer; DCR: Disease control rate; DOT: Duration of therapy; IPD: Individual patient data; IPTW: Inverse probability of treatment weighting; MAICs: Matching-adjusted indirect comparisons; NR: Not reported; NSCLC: Non-small-cell lung cancerORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RR: Response rate; SoC: Standard of care; TTNT: Time to next treatment;

MAIC: OS and PFS results (weighted)

Comparative overall survival estimates for larotrectinib vs comparator cohort with NTRK fusion solid tumours

VICTORIA (adults)*			
	Larotrectinib (n=82)	Comparator (n=82)	**HR (95%CI)**
OS (Median value (95% CI), months)	Not reached (42.9-NE)	37.2 (12.5-NE)	**0.44 (0.23-0.83)**
PFS (Median value (95% CI), months)	36.8 (25.8-58.2)	5.2 (3.5-6.8)	0.29 (0.18-0.46)
EPI-VITRAKVI (paediatrics)*			
	Larotrectinib (n=51)	Comparator(n=42)	**HR (95%CI)**
OS (Median value (95% CI), months)	NR	NR	**0.21 (0.02 - 2.84)**
PFS (Median value (95% CI), months)	NE	16.0 (16.0-NE)	0.80 (0.41-1.58)
* Effective sample sizes not reported			

NICE

CI: Confidence interval; HMF: Hartwig Medical Foundation; HR: Hazard ratio; MAIC: Matching-adjusted indirect comparison; NE: Not estimable; NR: Not reported; NTRK: Neurotrophic Tyrosine Receptor Kinase; OS: Overall survival; PFS: Progression-free survival

Large/unknown impact

Key issue 5: Validity of the MAICs and relevance to the NHS

Background

- **Company:** In the absence of control arms, 4 unanchored MAICs comparing larotrectinib trials with multiple real-world SoC datasets were used to estimate comparative effectiveness.
- **EAG**: All MAICs have significant internal and external validity limitations

Company approach

- Base case: VICTORIA MAIC (adults) and EPI-VITRAKVI MAIC (≤21 years), derived using full IPD, despite limited tumour coverage (other MAICs included in model scenario analyses)
- Results from MAICs included in various scenario analyses of the cost-effectiveness model

EAG critique

- **Limited NHS applicability & bias**: MAICs cover few tumour types, over-represent high-response cancers and exclude low-response groups (e.g., primary CNS)
- **Methodological issues**: unanchored MAIC assumptions unmet, key prognostic factors not fully adjusted, PHA violated, and small samples; comparator data historical and from heterogeneous non-trial sources
- **Alternatives**: ITCs using SACT and SoC evidence may help, but substantial uncertainty remains due to MAIC and trial limitations

Are the MAICs sufficiently robust to inform comparative effectiveness of larotrectinib versus SoC?

CNS: Central nervous system; IPD: Individual patient data; ITC, indirect treatment comparisons; MAIC: Matching-adjusted indirect comparison; NTRK FP: Neurotrophic Tyrosine Receptor Kinase Fusion Positive; SACT: Systemic Anti-Cancer Therapy data set; SoC: Standard of care; PHA, proportional hazard assumptions

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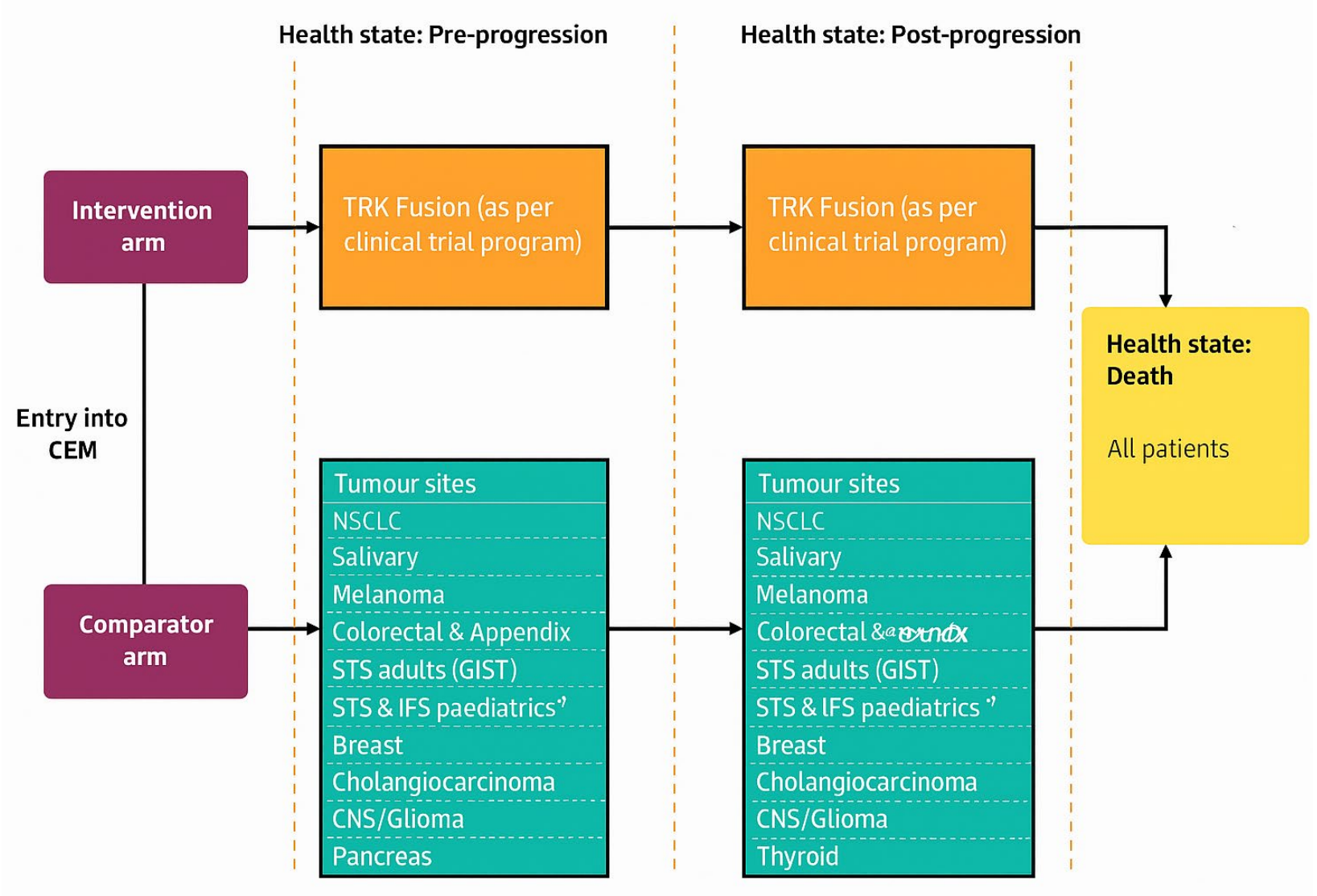
Company's model overview

See appendix: Summary of base case inputs and Tumour location distribution

- Partitioned survival model: 3 health states (progression-free survival, progressed and death)
- Life-time horizon (80 years) using 7-day cycles
- Health state occupancy:
  - **Larotrectinib:** OS and PFS curves are fitted to pooled trial data (ePAS9/SAS3)
  - **SoC:** OS and PFS curves are derived by applying MAIC-based hazard ratios (VICTORIA for adults; EPI-VITRAKVI for paediatrics) to the larotrectinib survival curves

Model schematic



CNS: Central nervous system; ePAS9: extended primary analysis set 9; HR: Hazard ratio; HRQoL: Health-related quality of life; IFS: Infantile sarcoma; MAIC: Matching-adjusted indirect comparison; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; QALYs; Quality-adjusted life years; SAS3; Supplementary analysis set 3; SoC: Standard of care; STS: Soft tissue sarcoma; TRK: Tyrosine receptor kinase

Large impact

Key issue 6: Optimal approach to economic modelling (1)

Background

- Modelling is challenging due to single-arm evidence, heterogeneity across histology and ages, and reliance on unanchored indirect comparisons

Company approach

- **Base case: MAIC-based PSM** → most robust approach and MAIC minimises bias from baseline prognostic/effect-modifying imbalances
  - Larotrectinib: independent Weibull models fit to pooled ePAS9/SAS3 data, with separate adult and paediatric curves to reduce heterogeneity and retain adequate sample size
  - SoC: MAIC HRs (adults: VICTORIA, paediatrics: EPI VITRAKVI) applied to larotrectinib OS/PFS curves

<u>Alternative model structures (different implementations of efficacy data in larortectinib and/or SoC arm)</u>

1. **Responder / non-responder analysis:** Separate curves fitted for larotrectinib responders and non-responders
   - Larotrectinib: mix of curves, weighted according to BHM-derived ORR or only use responder curves
   - SoC: larotrectinib non-responder curves → ignores stable disease benefits = overestimates SoC
2. **Intra-patient comparison (using GMI):** SoC arm – for PFS, larotrectinib's time-to-progression on prior therapy used as proxy; for OS, apply relative OS/PFS relationship observed for larotrectinib
3. **Naïve literature comparison**: SoC arm OS/PFS sourced from literature by tumour location
4. **Paediatric mixture-cure model**: assume larotrectinib may provide curative option for paediatric cohort

BHM: Bayesian hierarchical model; ePAS9; extended primary analysis set 9; HRs: Hazard ratios; MAIC: Matching-adjusted indirect comparison; ORR: Objective response rate; GMI, growth modulation index; PSM: Partition survival model; SAS3: Supplementary analysis set 3; SoC: Standard of care

Large impact

Key issue 6: Optimal approach to economic modelling (2)

EAG critique

- **Pooled MAIC-based model (company base case)**: has limited NHS applicability, as it assumes a site-agnostic treatment effect, applies MAIC HRs that violate proportional hazards, and models clinically implausible post-progression survival, especially in paediatric patients
- **Response-based model**: partially addresses heterogeneity but company's implementation does not allow tumour-specific responses or NHS-representative tumour distributions, limiting its usefulness
- **Other company scenarios:** do not resolve key uncertainties around heterogeneity, immature paediatric OS data, severity-weighting assumptions, or applicability of trial populations to the NHS
- ICERs vary substantially by model structure and comparator, demonstrating high decision uncertainty
- Analyses together are informative for decision making but do not consider any individual analysis to be a best representation of the cost-effectiveness of larotrectinib in the NHS
- Consider a model incorporating a formal population-adjusted MAIC, ideally integrating SACT data with IPD from SoC sources, to improve internal and external validity of NHS-relevant estimates
- EAG present 3 base case modelling approaches (see next slide)

HRs: Hazard ratios; ICER: Incremental cost effectiveness ratio; IPD: Individual patient data; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; SACT; Systemic Anti Cancer Therapy data set; SoC: Standard of care

Large impact

Key issue 6: Optimal approach to economic modelling (3)

Base case	Larotrectinib arm	SoC arm	Justification
Company: MAIC	OS/PFS curves fitted to pooled trial data - separate adult and paediatric curves	HRs (adults: VICTORIA, paediatrics: EPI VITRAKVI) applied to larotrectinib OS/PFS curves	Most robust approach and MAIC minimises bias from baseline prognostic /effect-modifying imbalances
EAG 1: Pooled-MAIC	OS/PFS curves fitted to pooled adult and paediatric trial data	HRs (VICTORIA MAIC) applied to larotrectinib curves	Separate immature paediatric OS curves and a flawed, uncertain MAIC led to implausible PPS and SoC outcomes
EAG 2: BHM	OS/PFS curve based on adult- and paediatric-specific responder/non-responder curves, weighted per tumour site from BHM	No response assumed (informed by larotrectinib non-responders)	Responses vary by tumour site, and reweighting is needed due to poor trial representativeness; the model is internally consistent but likely underestimates SoC efficacy.
EAG 3: SACT	Parametric models (exponential) fitted to OS and treatment duration pseudo-IPD from SACT (proxy relationship with PFS assumed). Exponential curves modelled to OS and PFS	Parametric models fitted to tumour-specific OS and PFS derived from literature sources (naïve literature comparator)	Trial data poorly reflects NHS practice; SACT offers more relevant outcomes and costs, though unanchored literature comparisons remain uncertain.

BHM: Bayesian Hierarchical model; HRs: Hazard ratios; IPD: Individual patient data; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; PPS: Post progression survival; SACT; Systemic Anti Cancer Therapy data set; SoC: Standard of care

Key issue 6: Optimal approach to economic modelling (4)

Large impact

Base case	Strengths	Limitations
EAG 1: Pooled -MAIC	• Largest evidence base; most suitable MAIC • Pools adult and paediatric data to limit influence of immature paediatric OS • Excludes flawed paediatric MAIC	• Assumes site-agnostic effects, despite heterogeneity • Does not resolve NHS generalisability issue • Assumes PHA, despite likely time-varying effects • Relies on full adjustment for all prognostic and effect-modifying factors
EAG 2: BHM	• Captures tumour-type heterogeneity and reweights to NHS-relevant SACT mix • Uses internally consistent trial population • Avoids hazard-ratio-based comparisons. • Produces tumour-specific costs, QALYs and severity modifiers	• Assumes no SoC response, despite active therapy • SoC outcomes include trial subsequent therapies use • OS remains confounded by trial subsequent therapy • Assumes equal responder OS across tumour types • Assume stable-disease rates equivalent in SoC arm • Reweighting assumes unrepresented tumour types share outcomes of those in SACT
EAG 3: SACT	• Larotrectinib outcomes aligned with NHS • Mature SACT OS data • SoC arm includes comparable tumour types • Removes bias from subsequent therapy use • Better reflects post-progression costs	• Small, limited SACT sample; assumes similar outcomes for unrepresented tumour types • Uses naïve, unadjusted comparisons with uncertain literature SoC sources • Assumes continued benefit beyond progression

What is the most appropriate approach to modelling cost-effectiveness of larotrectinib?

BHM: Bayesian Hierarchical model; HRs: Hazard ratios; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PHA: Proportional hazards assumption; QALYs: Quality-adjusted life years; SACT; Systemic Anti Cancer Therapy data set; SoC: Standard of care

Unknown impact

Key issue 7: Heterogeneity in cost-effectiveness estimates across key subgroups is not captured

Background

- **Company:** presents a single pooled ICER across all tumour types and ages, implicitly assuming that cost-effectiveness is broadly similar across subgroups
- **EAG:** single aggregated ICER risks obscuring important subgroup differences that may be highly relevant to NHS decision-making

Company approach

- Subgroup analysis not feasible: treatment is histology-independent with no identifiable subgroups.
  - Rarity and small samples limit meaningful subgroup analyses - supports pooled adult–paediatric ICER
  - Despite heterogeneity, pooled ePAS9 data shows durable responses to larotrectinib across ages, tumour types, and NTRK fusion variants, supporting a combined population result
- Larotrectinib appears less cost-effective in adults due to shorter life expectancy and lower QALY gains –
  - Should not combine separate subgroup ICERs as base case ICER is already population-weighted

ePAS9: extended primary analysis set 9; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year; NTRK: Neurotrophic Tyrosine Receptor Kinase

Unknown impact

Key issue 7: Heterogeneity in cost-effectiveness estimates across key subgroups is not captured

EAG critique

- A single ICER inappropriate due to substantial heterogeneity across identifiable subgroups which have distinct prognoses and treatment outcomes
  - Masks substantial variation in cost and clinical effectiveness across subgroups, particularly where larotrectinib efficacy is lower (notably primary CNS tumours, especially in adults)
- If larotrectinib is poorly cost-effective in identifiable subgroups, this should be explicitly presented, especially given there are more CNS tumours in the SACT data than other tumour types
  - Disaggregated results would improve transparency and better inform NHS decision-making

Analysis	EAG preference	Notes
Single pooled ICER	Pool adult and paediatric survival and use the more robust VICTORIA MAIC to estimate SoC outcomes	Methodological issues
Subgroup ICERs	For example: • Adult patients with primary CNS tumours • Paediatric patients with primary CNS tumours • Adult patients excluding those with primary CNS tumours • Paediatric patients excluding those with primary CNS tumours	Subgroup analyses may not resolve all uncertainty (ORR heterogeneity remains largely unexplained)

Is heterogeneity in cost-effectiveness estimates sufficiently captured across different subgroups?

NICE

CNS: Central nervous system; ICER: Incremental cost effectiveness ratio; MAIC: Matching-adjusted indirect comparison; ORR: Objective response rate; SACT: Systemic Anti-Cancer Therapy data set; SoC: Standard of care

Large impact

Key issue 8: Modelled health state utility values (1)

Background

- **Company:** applies treatment-specific health state utilities in the model that reflect lower toxicity and higher complete response rates for larotrectinib compared with SoC
- **EAG:** major concerns regarding the validity and representativeness of the trial HRQoL evidence

Company approach

- Assumes higher HRQoL on larotrectinib than SoC in both PFS and PD

Intervention	Base case	Notes
Larotrectinib	Utilities derived from trial HRQoL data, mapped to EQ-5D-3L and pooled across adults and children, assuming a site-agnostic HRQoL benefit	Trial data reflects the target population and uses the large sample size of ePAS9 and SAS3 datasets
SoC	Tumour-specific, sourced from NICE TAs or literature, with proxy and non-reference-case values used where data were unavailable	-

ePAS9: extended primary analysis set 9; HRQoL: Health-related quality of life; ICERs: Incremental cost effectiveness ratios; PD: Progressed disease; PFS: Progression-free survival; QALYs: Quality-adjusted life years; SAS3: Supplementary analysis set 3; SoC: Standard of care; TAs: Technology appraisals

Large impact

Key issue 8: Modelled health state utility values (2)

EAG critique

Larotrectinib:

- Size and duration of PD treatment benefit inappropriate – key driver of cost-effectiveness of larotrectinib
- Trial shows very small utility drop from PFS and PD ([redacted]), with a sustained and comparatively high PD utility
  1. Values higher than most published utilities for NTRK inhibitors and considerably higher than SoC
     - Trials may overestimate HRQoL or trial population HRQoL may not be representative
  2. PD utilities disproportionately informed by paediatrics (mostly tumour types with higher HRQoL)
  3. PD utility may be inflated by high subsequent treatment use in trials - not representative of NHS
     - PD utilities may reflect PFS2 or slowed progression from further treatment = overestimate utility

SoC utilities:

- Non-reference case PD utilities in 5 tumour sites is methodologically inappropriate and may introduce bias
- EQ-5D values applied are mostly 20+ years old - may not capture HRQoL of current NHS care

Paediatric: Pooling adult and paediatric utilities prevents appropriate age adjustment and obscures differences

EAG base case:

- SoC: utilities based on weighted values excluding those derived using non-reference case values.
- Larotrectinib: PFS – larotrectinib trials; PD – same as SoC (common PD utility across treatment arms)
  - Keeps assumption of extra HRQoL benefits in PFS → may be optimistic given potential SoC efficacy

CNS: Central nervous system; HRQoL: Health-related quality of life; NTRK: Neurotrophic Tyrosine Receptor Kinase; PD: Progressed disease; PFS: progression-free survival; SoC: Standard of care

Large impact

Key issue 8: Modelled health state utility values (3)

Larotrectinib and SoC health state utility values used in the company's base case

	Company		EAG	
Tumour location	Progression-free	Progressive disease	Progression-free	Progressive disease
Larotrectinib arm				
Tumour agnostic	[redacted]	[redacted]	[redacted]	[redacted]
SoC arm				
NSCLC	0.74	0.46	0.74	0.57
Salivary	0.75	0.60	0.75	0.57
Melanoma	0.75	0.69	0.75	0.57
Colorectal	0.73	0.59	0.73	0.57
STS adults (GIST)	0.77	0.65	0.77	0.57
STS adults (non-GIST)	0.65	0.47	0.65	0.57
STS paediatrics	0.68	0.43	0.68	0.57
Breast	0.71	0.50	0.71	0.57
Cholangiocarcinoma	0.63	0.53	0.67	0.57
CNS/Glioma	0.60	0.60	0.60	0.57
Pancreas	0.67	0.60	0.67	0.57
Thyroid	0.72	0.64	0.72	0.57

Is the company's or EAG's approach to model health state utility values more appropriate?

CNS: Central nervous system; GIST: Gastrointestinal stromal tumour; NSCLC: Non-small cell lung cancer; SoC: Standard of care; STS: Soft tissue sarcoma

Unknown impact

Key issue 9: Subsequent therapy effects and costs

Subsequent therapies

Background

- **Company:** assume all patients had best supportive care after disease progression in both treatment arms
- **EAG**: model excludes subsequent treatment costs, but their impacts on survival and HRQoL are included

Company approach

- Very few people in larotrectinib trial had subsequent NTRK therapy after larotrectinib ([redacted])
- Model assumes all patients discontinue active therapy upon progression, and no post-progression treatment costs are applied in either treatment arm

EAG critique

- Subsequent systemic therapy/radiotherapy/surgery was higher in trial ([redacted]%) than in NHS (SACT, 13%)
- Trial OS and PD utilities likely inflated by subsequent therapies not routinely used in the NHS (adjustment for subsequent treatments would reduce modelled OS and give more generalisable estimates)
- SACT outcomes are more representative of NHS practice and suggest lower post-progression benefit - using SACT materially reduces total QALYs and increases ICERs
- EAG prefers adjustment for treatment switching/informative censoring, costing subsequent therapies where data permit, and formal population-adjusted ITCs incorporating SACT
- **Proposal:** A state-transition model using SACT-derived progression-to-death relationships could mitigate confounding from subsequent therapies, provided tumour-type distribution is accounted for

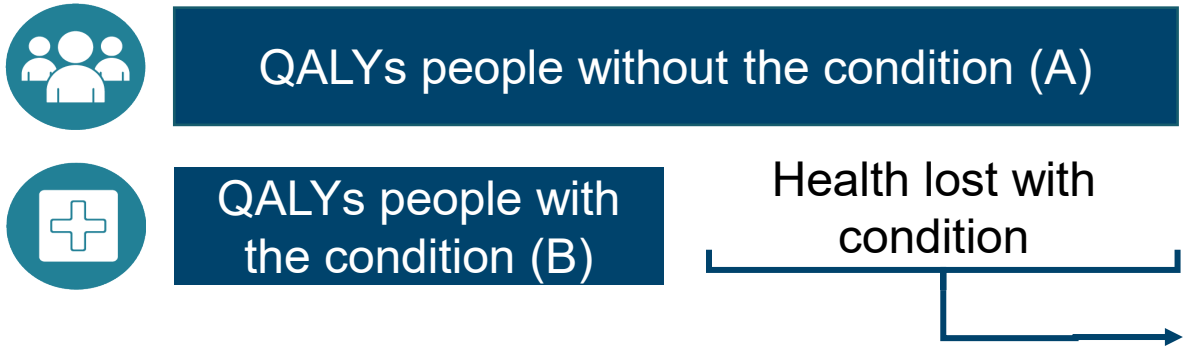
Are subsequent treatment effects and costs adequately captured in the economic model?

HRQoL: Health-related quality of life; ICERs: Incremental cost effectiveness ratios; ITCs: Indirect treatment comparisons; NTRK: Neurotrophic Tyrosine Receptor Kinase; OS: Overall survival; PD: Progressed disease; QALYs: Quality-adjusted life years; SACT: Systemic Anti Cancer Therapy data set; SoC: Standard of care

Large impact

Severity inputs

Key issue 10: QALY weighting for severity (1)



QALY weight	Absolute shortfall (A-B)	Proportional shortfall (A - B) / A
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Analysis	Expected total QALYs for general population	Expected total QALYs for people living with condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case inputs + method	[redacted]	[redacted]	[redacted]	[redacted]	1.60*
Company's base case inputs + EAG method	[redacted]	[redacted]	[redacted]	[redacted]	1.2
EAG base case 1 (MAIC)	[redacted]	[redacted]	[redacted]	[redacted]	1.2
EAG base case 2 (BHM)	[redacted]	[redacted]	[redacted]	[redacted]	1.2 1.39†
EAG base case 3 (SACT)	[redacted]	[redacted]	[redacted]	[redacted]	1.2

* Implied average QALY weighting when tumour-site specific severity modifiers applied

† EAG exploratory analyses

NICE

BHM: Bayesian hierarchical model; MAIC: Matching-adjusted indirect comparison; QALY: Quality-adjusted life year; SACT: Systemic Anti-Cancer Therapy data set

Large impact

Key issue 10: QALY weighting for severity (2)

Company approach to calculating severity

Illustrative numbers

Larotrectinib arm: tumour-agnostic QALYs = 1.00

Tumour site 1
QALY weight = 1.7
Distribution = 40%
QALY gain = 1.00

Tumour site 2
QALY weight = 1.7
Distribution = 40%
QALY gain = 1.00

Tumour site 3 etc
QALY weight = 1.2
Distribution = 20%
QALY gain = 1.00

Severity weighting x tumour prevalence x tumour-agnostic QALYs

E.g., 1.7 x 0.4 x 1.00 [tumour site 1]

Add weighted tumour-site QALYs = total Larotrectinib QALYs

Comparing incremental QALYs with and without severity modifier show an implied average severity weight of 1.6 is applied

Inputs	Source
SoC QALY weightings	Naïve literature-based comparator estimates • Closest absolute estimate of QALYs that has been used in previous NICE TAs to determine severity modifiers and end-of-life
Starting age and sex distribution	ePAS9 and SAS3
Tumour prevalence	ePAS9 and SAS3

EAG note

- Derived QALY weight from company's preferred inputs and using EAG preferred methodology
  - ➢ Average weighted QALY shortfall: 1.2 (Absolute shortfall: [redacted]; Proportional shortfall: [redacted]%)

ePAS9: extended primary analysis set 9; QALY: Quality-adjusted life year; SAS3: Supplementary analysis set 3; SoC: Standard of care

Large impact

Key issue 10: QALY weighting for severity (3)

EAG critique

Ignores heterogeneity: Applying tumour-specific severity weights to prevalence-weighted pooled QALY rather than tumour-specific QALY gains → implicitly assumes equal benefit across tumour types → over-inflates benefit

- Disproportionately inflates benefits in high-severity, low-response, low prevalence (in trial) tumours (e.g. CNS)

SoC QALYs: SoC utilities likely to underestimate HRQoL in NHS (outdated data) - overestimates QALY shortfall

- Internal inconsistency: severity based on naïve SoC literature, while treatment outcomes based on MAIC-adjusted survival curves = different evidence bases for severity and cost-effectiveness

Age/sex distributions: Trial population much younger than literature SoC cohorts – can inflate QALY shortfall

Application: Severity modifiers should be applied to incremental QALYs, not total QALYs – corrected by EAG

CNS: Central nervous system; HRQoL: Health-related quality of life; MAIC: Matching-adjusted indirect comparison; QALY: Quality-adjusted life year; SoC: Standard of care

Large impact

Key issue 10: QALY weighting for severity (4)

EAG approach to calculating severity

Tumour site 1	Tumour site 2	Tumour site 3 etc
Absolute shortfall: A Proportional shortfall: B	Absolute shortfall: C Proportional shortfall: D	Absolute shortfall: E Proportional shortfall: F

Weight absolute and proportional QALY shortfalls by tumour prevalence

Overall weighted absolute and proportional QALY shortfall

Apply single population-level severity modifier to incremental QALYs

Input	Source
SoC QALYs	Model generated SoC QALY estimates
Tumour prevalence	SACT data
Starting age and sex	Base case 1 & 2: ePAS9 and SAS3 Base case 3: SACT

- Summary of base case: apply a single population-level severity modifier derived from weighted mean QALY shortfall, using consistent efficacy, utilities, and baseline characteristics (preferably SACT-based)
- BHM base case: explore applying tumour-specific QALY weightings

1. What inputs should be used to generate absolute and proportional shortfall?
2. What methodology of generating absolute and proportional shortfall is preferred?

BHM: Bayesian hierarchical model; ePAS9: extended primary analysis set 9; QALYs: Quality-adjusted life years; SACT: Systemic Anti-Cancer Therapy data set; SAS3: Supplementary analysis set 3; SoC: Standard of care

Other issues

Issue	Company approach	EAG approach	ICER Impact
Primary CNS tumours/glioma disease management costs	Primary CNS tumours: TA23 • Assume single MRI cost in PFS with no ongoing disease-management costs	Costs based on TA977, which includes regular clinical monitoring in PFS and multidisciplinary and specialist nurse input in PD, aligning CNS tumours with other modelled sites	Small
Oral administration costs	No cost associated with orally administered therapies	Include SB11Z tariff (£247) once per treatment cycle to account for dispensing • NHSE and TA630: should be included	Small
Time on treatment (ToT)	Assume ToT equals PFS for larotrectinib ➔ no PD treatment costs modelled	SACT data PFS is based on ToT data • Base case 3 captures post-progression costs and benefits of larotrectinib	Small

CNS: Central nervous system; ICER: Incremental cost effectiveness ratio; MRI: Magnetic resonance imaging; OS: Overall survival; PD: Progressed disease; PFS: Progression-free survival; SACT: Systemic Anti-Cancer Therapy data set; TA: Technology appraisal

Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]

- ❑ Background and key issues
- ❑ Clinical effectiveness and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ✓ **Base case assumptions and cost-effectiveness results**
- ❑ Other considerations
- ❑ Summary

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Differences between company and EAG base cases (1)

Assumption	Company base case	EAG base cases
Model structure (modelling of OS/PFS)	• **Larotrectinib:** Independent OS/PFS models fitted to adult and paediatric larotrectinib data. HR from EPI-VITRAKVI MAIC applied to paediatric curves to derive SoC. Adult curves adjusted using VICTORIA MAIC • **SoC:** VICTORIA and EPI-VITRAKVI MAICs used to generate SoC arm OS and PFS using ePAS9 and SAS3 data	**EAG base case 1 – Pooled MAIC:** • Larotrectinib: OS and PFS curves fitted to pooled adult and paediatric larotrectinib trial data • SoC: HRs from VICTORIA MAIC applied to larotrectinib curves **EAG base case 2 – BHM / Response-based:** • Larotrectinib: OS and PFS curve for larotrectinib based on adult- and paediatric-specific responder- and non-responder curves weighted for each tumour site from the BHM • SoC: no response to SoC is assumed (informed by non-responders to larotrectinib) **EAG base case 3 – SACT-based:** • Larotrectinib: parametric models fitted to OS and treatment duration pseudo-IPD from SACT (proxy relationship with PFS assumed). Exponential curves modelled to OS and PFS • SoC: parametric models fitted to tumour-specific OS and PFS derived from literature sources (naïve literature comparator)

BHM: Bayesian Hierarchical Model; ePAS9: extended primary analysis set 9; HR: Hazard ratio; IPD: Individual patient data; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; SACT: Systemic Anti-Cancer Therapy data set; SAS3: Supplementary analysis set 3; SoC: Standard of care

Differences between company and EAG base cases (2)

Assumption	Company base case	EAG base cases
Tumour site distribution and baseline characteristics	Larotrectinib trials	SACT data
Utilities	• Larotrectinib: trial data • SoC: Tumour site-specific utilities from previous NICE appraisals and published literature	• Larotrectinib: PD utility based on weighted SoC average, excluding non-reference case values • SoC: Based on weighted estimates consistent with the NICE reference case, excluding utilities derived using TTO or SG methods.
CNS/glioma resource use	• PFS: Single MRI-based • PD: No ongoing disease management	• Costs assumed to follow TA977 • PFS: Monthly oncologist review, blood tests and echocardiogram • PD: Monthly multidisciplinary and specialist nurse visits
Oral administration costs	Excluded	Include SB11Z tariff once per treatment cycle
Severity	1.6	EAG base case 1 – Pooled MAIC: 1.2 EAG base case 2 – BHM / Response-based: 1.2* EAG base case 3 – SACT-based: 1.2
*Severity modifier of 1.39 when tumour-site specific severity modifiers applied		

BHM: Bayesian hierarchical model; MAIC: Matching-adjusted indirect comparison; PD: Progressed disease; PFS: Progression-free survival; SACT; Systemic Anti Cancer Therapy data set; SG: Standard gamble; SoC: Standard of care; TA: Technology appraisal; TTO: Time trade-off

Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- When comparator PAS discounts are included, the company's probabilistic base case is above the range normally considered a cost-effective use of NHS resources
- The EAG probabilistic base cases 1, 2 and 3 are also above this range
- Scenarios presented in Part 2 include alternative baseline characteristics, model structures, utility values, resource use and costs

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme

Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]

- ❑ Background and key issues
- ❑ Clinical effectiveness and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Other considerations**
- ❑ Summary

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Uncaptured benefits

Company

- Larotrectinib offers uncaptured benefits:
  - **Quality of life improvement:** Patients' health and daily functioning improves markedly
  - **Reduces caregiver burden:** Oral administration and lower toxicity reduces treatment-related time with fewer hospital visits, emotional stress, and long-term demands, especially in paediatric care
  - **Well-tolerated, simple oral regimen ➔** Minimal side effects allows return to normal life
  - **Emotional relief and stability:** Larotrectinib provides hope and reduces anxiety
  - **Adult patient benefit:** Transition from chemotherapy improved physical/mental well-being, autonomy, social life, and return to work
  - **Avoidance of chemotherapy toxicity**, especially in children, adds long-term value
- Base-case ICER is therefore conservative

EAG critique

- These benefits are subjective, unquantified, and outside the NICE reference case
- No robust evidence of meaningful carer HRQoL gains
- Option value and reduced toxicity are already captured via PFS, OS, and utilities
- No material uncaptured benefits warrant ICER adjustment

Are all benefits and disadvantages of larotrectinib captured adequately?

HRQoL: Health-related quality of life; ICER: Incremental cost effectiveness ratio; OS: Overall survival; PFS: Progression-free survival

Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]

- ❑ Background and key issues
- ❑ Clinical effectiveness and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Equality, managed access and severity
- ✓ **Summary**

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Summary of key issues for committee consideration

Issue	ICER impact
Clinical effectiveness	
Applicability of trial evidence to the NHS • Is the clinical evidence from larotrectinib trials applicable to NHS clinical practice?	Large/ unknown
Assuming common response across tumour types • Is it appropriate to assume a common treatment response across tumour types?	Large
Magnitude of larotrectinib's survival benefit • Given the uncertainty from immature OS data, the subsequent treatment use and the absence of a control arm in larotrectinib trials, is the magnitude of OS benefit with larotrectinib plausible?	Unknown
SACT limitations • Is it appropriate to use pooled SACT outcomes?	Unknown
Validity of MAICs and relevance to the NHS • Are the MAICs sufficiently robust to inform comparative effectiveness of larotrectinib versus SoC?	Large/ unknown

ICER: Incremental cost effectiveness ratio; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; SACT: Systemic Anti-Cancer Therapy data set; SoC: Standard of care

Summary of key issues for committee consideration

Issue	ICER impact
Cost-effectiveness	
Optimal approach to economic modelling • What is the most appropriate approach to modelling cost-effectiveness of larotrectinib?	Large
Heterogeneity in cost-effectiveness estimates across key subgroups is not captured • Is heterogeneity in cost-effectiveness estimates sufficiently captured across different subgroups?	Unknown
Modelled health state utility values • Is the company's or EAG's approach to model health state utility values more appropriate?	Large
Subsequent therapy effects and costs • Are subsequent treatment effects and costs adequately captured in the economic model?	Unknown
QALY weighting for severity 1. What inputs should be used to generate absolute and proportional shortfall? 2. What methodology of generating absolute and proportional shortfall is preferred?	Large

ICER: Incremental cost effectiveness ratio; QALYs: Quality-adjusted life years

Larotrectinib for treating NTRK fusion-positive solid tumours (Managed access review of TA630) [ID6292]

Supplementary appendix

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Relevant conclusions from TA630

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TA630 committee conclusions	ID6292: company's updated base case	Resolved?
Utility values equal between post-progression treatment arms	• Larotrectinib: utility based on trial data • SoC: tumour site-specific values sourced from previous NICE appraisals and literature	No
Include oral chemotherapy administration cost for larotrectinib	No cost associated with orally administering therapies	No
Include drug wastage costs	No drug wastage included	No
Response rate using the more generalisable response rate from the BHM	Base case: apply common response rate across all tumour sites and within the adult and paediatric populations Scenario: BHM to estimate a pooled ORR that statistically accounts for variation in response across tumour types	No
Include diagnostic testing costs as proposed by NHSE	Testing costs are not included in the base case analysis but are explored in sensitivity analyses	Yes - NHSE confirms company approach
Include costs of post-progression larotrectinib	Assumes that time on treatment is equal to PFS	No
Different model structure should be used to explore the effect of a cure	Explored different model structure, including mixture-cure model	Yes

BHM: Bayesian Hierarchical Model; ORR: Objective response rate; PFS: Progression-free survival; SoC: Standard of care; TA: Technology appraisal

Clinical trial evidence: 3 single arm trials

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3 single-arm trials in NTRK fusion-positive cancers

	Study 20288 (n=13)	Study 20289 (n=210)	Study 20290 (n=141)
Design	Phase 1, open-label, dose escalation	Phase 2, open-label, basket	Phase 1/2, open-label
Population	Adults, locally advanced/metastatic solid tumours	Adults & adolescents (≥12y) with NTRK FP tumours	Children (≤21y) advanced solid & primary CNS tumours
N in pooled dataset	ePAS9: 13; SAS: 0	ePAS9: 191; SAS: 19	ePAS9: 100; SAS: 41
Primary outcome	Safety	ORRc (CR+PR)	Phase 1: safety Phase 2: ORR
Secondary Outcomes	ORR, DoR	DoR, PFS, OS, safety	Phase 1: ORR, DoR, HRQoL, safety Phase 2: DoR, OS, PFS, safety
Location	8 sites - USA	98 sites – no UK	45 sites – no UK

CNS: Central nervous system; CR: Complete response; DoR: Duration of response; ePAS9: extended primary analysis set 9; HRQoL: Health-related quality of life; IRC: Independent review committee; NTRK FP: Neurotrophic Tyrosine Receptor Kinase Fusion Positive; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SAS; Supplementary analysis set

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OS and PFS: pooled analyses vs SACT

PFS and OS for adults and paediatric populations in ePAS9 and SAS3 (data cut 20th July 2024)

	ePAS9		SAS3		SACT
	Adults (n=[redacted])	Paediatrics (n=[redacted])	Adults (n=[redacted])	Paediatrics (n=[redacted])	Overall (N=60)
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	-
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	45.2 (NE)

OS rates at time intervals in SACT, ePAS9 and SAS3

	SACT [% (95% CI)] (N=60)	ePAS9 [% (95% CI)] (N=304)	SAS3 [% (95% CI)] (N=60)
≥6 months	93 [87, 100]	[redacted]	[redacted]
≥12 months	86 [77, 95]	[redacted]	[redacted]
≥18 months	69 [57, 83]	[redacted]	[redacted]
≥24 months	69 [57, 83]	[redacted]	[redacted]
≥36 months	60 [47, 77]	[redacted]	[redacted]
≥48 months	49 [34, 69]	[redacted]	[redacted]
≥60 months	NE	[redacted]	[redacted]
≥72 months	NE	[redacted]	[redacted]
≥84 months	NE	[redacted]	[redacted]

Note: Any naïve comparisons between data sources are limited and should be made with caution, due to immature data, censoring, small patient numbers, study designs and differences in populations

NICE

CI: Confidence interval; ePAS9: extended primary analysis set 9; NE: Not estimable; OS: Overall survival; PFS: Progression-free survival; SACT: Systemic Anti-Cancer Therapy data set; SAS3; Supplementary analysis set 3

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Pooled trial results: ORR by tumour type

IRC Assessment (ePAS9, data cut-off July 2024)

	N	CR/pCR/PR (N)	ORR% [95% CI]		N	CR/pCR/PR (N)	ORR% [95% CI]
Overall	[redacted]	[redacted]	[redacted]	Cholangiocarcinoma	[redacted]	[redacted]	[redacted]
Soft tissue sarcoma	[redacted]	[redacted]	[redacted]	Bone sarcoma	[redacted]	[redacted]	[redacted]
Infantile sarcoma	[redacted]	[redacted]	[redacted]	Gastric	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]	Cancer of unknown primary	[redacted]	[redacted]	[redacted]
Thyroid	[redacted]	[redacted]	[redacted]	Cervix	[redacted]	[redacted]	[redacted]
Differentiated	[redacted]	[redacted]	[redacted]	CMN	[redacted]	[redacted]	[redacted]
Non-differentiated	[redacted]	[redacted]	[redacted]	Prostate	[redacted]	[redacted]	[redacted]
Salivary gland	[redacted]	[redacted]	[redacted]	Appendix	[redacted]	[redacted]	[redacted]
Colorectal	[redacted]	[redacted]	[redacted]	Duodenal	[redacted]	[redacted]	[redacted]
Colon	[redacted]	[redacted]	[redacted]	Oesophageal	[redacted]	[redacted]	[redacted]
Rectal	[redacted]	[redacted]	[redacted]	External auditory canal	[redacted]	[redacted]	[redacted]
Breast	[redacted]	[redacted]	[redacted]	Hepatic	[redacted]	[redacted]	[redacted]
Non-secretory	[redacted]	[redacted]	[redacted]	Lipofibromatosis	[redacted]	[redacted]	[redacted]
Secretory	[redacted]	[redacted]	[redacted]	Testes	[redacted]	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]	[redacted]	Thymus	[redacted]	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]	[redacted]	Urothelial	[redacted]	[redacted]	[redacted]
GIST	[redacted]	[redacted]	[redacted]	Uterus	[redacted]	[redacted]	[redacted]

Company: BHM predicted response rates per tumour type were in principle similar to main model, with negligible differences (<2.3%) across all tumour types

BHM: Bayesian hierarchical model; CI: Confidence interval; CMN: Congenital Mesoblastic Nephroma; CR: Complete response; GIST: Gastrointestinal Stromal Tumour; IRC: Independent review committee; ORR: Objective response rate; PR: Partial response

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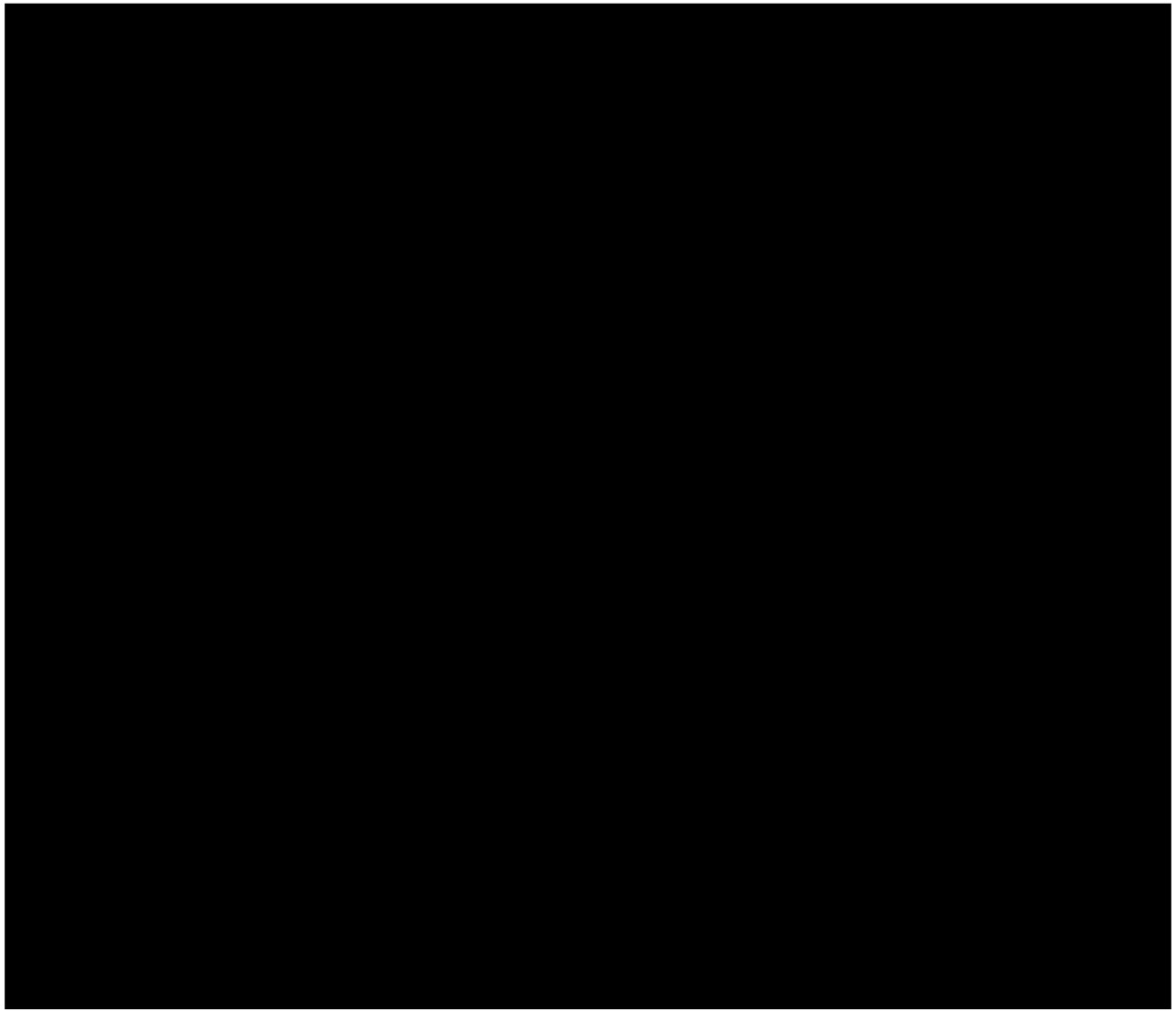
BHM analyses: predicted response rate by tumour type

Forest plot of predicted response rates (with 95% Prediction interval), by tumor type



BHM: Bayesian hierarchical model; CUP: Cancer of Unknown Primary Origin; GIST: Gastrointestinal Stromal Tumour; IFS: Infantile sarcoma

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Comparison of trial and SACT baseline characteristics

Characteristic	Categories	ePAS9 (n=304)	SAS3 (n=60)	SACT (n=60)
Age (yrs)	Median age	44.5 (0.0-90.0)	[redacted]	-
	0 to <20 for SACT [0 to <18 for trials]	[redacted]	[redacted]	22 (37%)
	20 to <50 for SACT [18 to 45 for trials]	[redacted]	[redacted]	17 (28%)
	>50 for SACT [>45 for trials]	[redacted]	[redacted]	21 (35%)
Sex	Female	[redacted]	[redacted]	26 (43%)
Priori lines of systemic therapy	0 (larotrectinib 1st line)	[redacted]	[redacted]	1 (2%)
	1	[redacted]	[redacted]	47 (78%)
	2	[redacted]	[redacted]	5(8%)
	≥3	[redacted]	[redacted]	6 (10%)
Type of disease	Metastatic	[redacted]	[redacted]	24 (40%)
	Locally advanced with systemic therapy	[redacted]	[redacted]	18 (30%)
	Locally advanced with resection resulting in morbidity	[redacted]	[redacted]	17 (28%)
	Not captured	[redacted]	[redacted]	1 (2%)
Brain metastases	None	[redacted]	[redacted]	51 (85%)
	Brain metastases	[redacted]	[redacted]	8 (13%)
	Not captured	[redacted]	[redacted]	1 (2%)
NTRK gene	NTRK1	[redacted]	[redacted]	22 (37%)
	NTRK2	[redacted]	[redacted]	18 (30%)
	NTRK3	[redacted]	[redacted]	19 (32%)

NICE

ePAS9: extended primary analysis set 9; NTRK; Neurotrophic Tyrosine Receptor Kinase; SACT: Systemic Anti-Cancer Therapy data set; SAS3; Supplementary analysis set 3

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Primary tumour type in the trial evidence and SACT population

	ePAS9 and SAS3 (n=364)	SACT (n=60)		ePAS9 and SAS3 (n=364)	SACT (n=60)
Primary CNS	[redacted]	21 (35%)	Pancreas	[redacted]	0
Soft tissue sarcoma	72 (24%)	12 (20%)	GIST	[redacted]	0
Infantile fibrosarcoma	49 (16%)	4 (7%)	Cholangiocarcinoma	[redacted]	0
Lung adenocarcinoma	32 (11%)	4 (7%)	Gastric	[redacted]	0
Non-squamous NSCLC		4 (7%)	Cervix	[redacted]	0
Lung (other)		2 (3%)	CMN	[redacted]	0
Thyroid	31 (10%)	3 (5%)	Prostate	[redacted]	0
Papillary thyroid carcinoma		2 (3%)	Appendix	[redacted]	0
Colorectal	[redacted]	2 (3%)	Duodenal	[redacted]	0
Forearm spindle cell sarcoma	[redacted]	1 (2%)	External auditory canal	[redacted]	0
Head adenocarcinoma	[redacted]	1 (2%)	Hepatic	[redacted]	0
Oesophagus	[redacted]	1 (2%)	Lipofibromatosis	[redacted]	0
Salivary gland carcinoma	[redacted]	1 (2%)	Testes	[redacted]	0
Salivary gland adenocarcinoma	[redacted]	1 (2%)	Thymus	[redacted]	0
Breast	[redacted]	0	Urothelial	[redacted]	0
Melanoma	[redacted]	0	Uterus	[redacted]	0

NICE

EAG: Nearly [redacted] of tumour types ([redacted] of 28) in trial evidence were not included in SACT database although these represented typically rarer types, and [redacted] of the trial evidence population.

CMN: Congenital Mesoblastic Nephroma; CNS: Central nervous system; ePAS5: extended analysis set 5; GIST: Gastrointestinal Stromal Tumour; NSCLC: Non small cell lung

Maturity of clinical evidence

	TA630 – Original submission	ID6292 – Review of TA630
Sample size	102	364
Patients with CNS tumours	9	60
Number of tumour types	15	28
Data cut	30th July 2018	20th July 2024
Median follow-up	[redacted] months	[redacted] months
OS data maturity	Median OS not reachedestimable 12-month OS rate: [redacted]	Median OS not estimable 72-month OS rate: [redacted] (ePAS9), [redacted] (SAS3)

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ePAS9: extended primary analysis set 9; OS: Overall survival; SAS3; Supplementary analysis set 3; TA: Technology appraisal

Summary of trial subsequent therapies

ePAS9			
Subsequent Therapy	Children (Age < 18 years) N=99	Adults (Age ≥18 years) N=205	Total N=304
NTRK inhibitor therapies	[redacted]	[redacted]	[redacted]
Other systemic therapies	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]
Cryoablation of tumour	[redacted]	[redacted]	[redacted]
Radioactive iodine therapy	[redacted]	[redacted]	[redacted]

SAS3			
Subsequent Therapy	Children (Age < 18 years) N=[redacted]	Adults (Age ≥18 years) N=[redacted]	Total N=[redacted]
Other systemic therapies	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Radioactive iodine therapy	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]
Systemic and radiotherapy	[redacted]	[redacted]	[redacted]

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ePAS9: extended primary analysis set 9; NTRK; Neurotrophic Tyrosine Receptor Kinase; SAS3; Supplementary analysis set 3

Additional SACT clinical effectiveness results

Outcomes	SACT 2025 (n=60)
Median duration of follow up for OS (95% CI) months	19.4 [min: 3.7, max: 59.5]
Median OS (95% CI) months	45.2
Overall mortality (%)	22/60 at end of FU (36.7)
Median PFS (95% CI) months	-
Time to treatment discontinuation (95% CI) months	26.9 (14.4, 45.4)
Progressive Disease (PD)	0
Median duration of Response (95% CI) months	-
Treatment cessation due to disease progression [disease progression and death)]	10/60 (17%) [32/60 (53%)]
Post-larotrectinib targeted drug therapy	4/60 (6.7%)

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CI: Confidence interval; FU: Follow up; PFS: Progression-free survival; SACT: Systemic Anti-Cancer Therapy data set

MAICs - main deck

HMF and Flatiron MAICs results

	FLATIRON	HMF
Population	Adults with locally advanced/metastatic TRK fusion-positive cancer	
Treatments included	Chemotherapy, Chemo + targeted therapy, Chemo + hormone, others / NR	NR
Countries (year)	USA (2011-2019)	Netherlands (2012-2020)
Tumour types and sites	**10 -** Uterine, biliary, stomach, endometrial, breast, salivary gland, NSCLC, STS, colorectal cancer, primary cancer unknown	**9 -** Bone/soft tissue, breast, pancreas, colon/rectum, head & neck, lung, prostate, skin, urinary tract
Trial data cut (dataset)	July 2020 (ePAS5)	July 2023 (NR)
Matching method (n matched)	NR (sarotrectinib: 85; SoC: 28)	IPTW (larotrectinib:120; SoC: 24)
Outcomes (used in base case)	Primary: OS (No – no comparator IPD available)	

FLATIRON – weighted results	**Larotrectinib (n=85)**	**Comparator (n=28)**	**HR (95%CI)**
Median OS, months (95% CI)	39.7 (16.4, NE)	10.2 (7.2, 14.1)	**0.22 (0.09, 0.52)**
Effective sample size	13.1		
HMF – weighted	**Larotrectinib (n=120)**	**Comparator (n=24)**	**HR (95%CI)**
Median OS, months (IQR), months)	50.3 (23.3-NE)	13.0 (6.4-18.3)	**0.16 (0.07-0.36)**
Effective sample size	36		

CI: Confidence interval; ePAS5: extended analysis set 5; HMF: Hartwig Medical Foundation; HR: Hazard ratio; IPD: Individual patient data; IPTW: Inverse probability of treatment weighting; IQR: Interquartile range; MAIC: Matching-adjusted indirect comparison; NE: Not estimable; NR: Not reported; NSCLC: Non small cell lung cancer; NTRK: Neurotrophic Tyrosine Receptor Kinase; OS: Overall survival; STS: Soft tissue sarcoma; TRK: Tyrosine receptor kinase

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MAICs – covariates matched

Covariates matched for in indirect comparisons of NTRK fusion positive patients

	VICTORIA	FLATIRON	HMF	EPI-VITRAVKI
Age	X	X	X	X
Line of therapy	X	X	X	X
Tumour location/type	X	X	X*	X
Brain metastases		X		
Disease stage/baseline metastases	X	X		X
ECOG PS	X	X		
Time from diagnosis to treatment initiation				X
NTRK1-gene		X	X	
Smoking history		X		
Practice type		X		
Race	X			
Year of treatment initiation			X	
Others	X**		X***	X****

* Only matched for in sensitivity analyses
** Sex considered as additional covariate
*** Year of biopsy also included
****Additional covariates were considered such as sex, disease history, and treatment-related information.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; HMF: Hartwig Medical Foundation; MAIC: Matching-adjusted indirect comparison; NTRK: Neurotrophic Tyrosine Receptor Kinase

Company's model overview – Summary of base case inputs (1)

Variable	Input	Justification
Patient characteristics	Larotrectinib clinical trials and literature	Reflect target population and align with survival inputs
Weighting of tumour locations	Larotrectinib clinical trial programme	Reflect target population and align with survival inputs
OS and PFS	**Larotrectinib:** Survival analysis of ePAS9+SAS3 split by adult and paediatric patients Adults: Weibull for both OS and PFS Paediatric: Weibull for both OS and PFS	Stratification by adult and paediatric patients reduces heterogeneity for the survival extrapolations
	SoC: MAIC HR applied to larotrectinib survival curves • Adults: VICTORIA • Paediatric: EPI VITRAKVI	MAIC approach minimises bias from prognostic or effect-modifying baseline characteristics. Using HRs from MAIC allowed the maturity and large sample size of the ePAS9 and SAS3 datasets to be leveraged
TTD	**Larotrectinib:** Treat to progression **SoC:** Teat to progression	Observed TTD and PFS from the ePAS9 and SAS3 datasets were similar confirmed by clinical experts
Treatment waning	No waning of the treatment effect	Assumed given data maturity in VICTORIA MAIC

ePAS9: extended primary analysis set 9; HR: Hazard ratio; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; SAS3; Supplementary analysis set 3; SoC: Standard of care; TTD: Time to treatment discontinuation

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Company's model overview – Summary of base case inputs (2)

Variable	Input	Justification
Costs	Excludes cost of drug wastage	Excluded for both larotrectinib and SoC to avoid introducing bias, consistent with the approach used in the previous appraisal
	No testing costs included	Genomic and NTRK testing already commissioned and embedded in routine NHS cancer care, representing standard practice rather than a new resource need; costs examined in scenario analyses.
	Health state costs • **Larotrectinib:** average of SoC tumour location inputs • **SoC:** literature costs per tumour location	Health state costs for larotrectinib were assumed to equal the average SOC tumour-location costs, as a conservative assumption in the absence of specific healthcare resource use data, consistent with the prior appraisal
Utilities	**Larotrectinib: using** EQ-5D-3L data from larotrectinib trials (PF: [redacted], PD: [redacted]) **SoC:** Utilities from literature per tumour site	**Larotrectinib**: trial data reflects target population and uses large sample size of ePAS9 and SAS3 datasets **SoC:** sourced from literature as no utilities were obtained for comparators in the larotrectinib trials
Severity modifier	Included by tumour location, calculated using naïve literature-based comparator	The naïve literature-based comparator scenario was chosen to estimate severity modifier as it is the closest absolute estimate of QALYs that has been used in previous NICE TAs to determine severity modifiers and end-of-life criteria

ePAS9: extended primary analysis set 9; NTRK: Neurotrophic Tyrosine Receptor Kinase; PD: Progressed disease; PF: Progression-free; QALYs: Quality-adjusted life years; SAS3: Supplementary analysis set 3; SoC: Standard of care; TAs: technology appraisals

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Tumour location distribution in company's economic model

Tumour location	No. in ePAS9 and SAS3	Calculated weighting (%)	No. patients in SACT	Calculated weighting (%)
NSCLC	[redacted]	[redacted]	10	17.2
Salivary	[redacted]	[redacted]	3	5.2
Melanoma	[redacted]	[redacted]	0	0.0
Colorectal (used as proxy for appendix)	[redacted]	[redacted]	2	3.4
STS adults (GIST)	[redacted]	[redacted]	0	0.0
STS adults (non-GIST) (used as proxy for bone sarcoma)	[redacted]	[redacted]	13	22.4
STS paediatrics*	[redacted]	[redacted]	4	6.9
IFS (used as proxy for IFS)	[redacted]	Added to STS paediatrics	0	Added to STS paediatrics
Appendix	[redacted]	Added to colorectal	0	0
Breast	[redacted]	[redacted]	0	0
Bone sarcoma	[redacted]	Added to STS adults (non-GIST)	0	0
Cholangiocarcinoma	[redacted]	[redacted]	0	0
CNS/Glioma	[redacted]	[redacted]	21	36.2
Pancreas	[redacted]	[redacted]	0	0
Thyroid	[redacted]	[redacted]	5	8.6
Other	[redacted]	Redistributed evenly	0	0
Total	[redacted]	100	58	100

NICE

CNS: Central nervous system; ePAS5: extended analysis set 5; GIST: Gastrointestinal Stromal Tumour; IFS: Infantile sarcoma; NSCLC: Non small cell lung cancer; SACT: Systemic Anti-Cancer Therapy data set; SAS: Supplementary analysis set 3; STS: Soft tissue sarcoma; TRK: Tyrosine receptor kinase

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Severity inputs

Factor	Company	EAG Base Case 1	EAG Base Case 2	EAG Base Case 3
Sex distribution (% female)	Larotrectinib trial tumour-specific distribution	Larotrectinib trial tumour-specific distribution	Larotrectinib trial tumour-specific distribution	43% (SACT)
Starting age (years)	Larotrectinib trial tumour-specific ages	Larotrectinib trial tumour-specific ages	Larotrectinib trial tumour-specific ages	37.5 years (SACT)
Tumour type distribution	Larotrectinib trial	SACT dataset	SACT dataset	SACT dataset
Expected years of life (SoC)	Naïve SoC literature value	SoC arm (MAIC-adjusted) tumour-specific values	SoC arm (larotrectinib trial non-responders)	Naïve literature SoC arm weighted by SACT tumour types
Quality of life by age	Naïve SoC literature value	Age-adjusted utilities	Age-adjusted utilities	Naïve literature SoC arm weighted by SACT tumour types. Non-reference case utilities excluded.
Discount rate	3.5%	3.5%	3.5%	3.5%

MAIC: Matching-adjusted indirect comparison; SACT: Systemic Anti-Cancer Therapy data set; SoC: Standard of care