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CADTH Reimbursement Recommendation

Larotrectinib (Vitrakvi)

Indication: Solid tumours with *NTRK* gene fusion

Sponsor: Bayer Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What is the CADTH reimbursement recommendation for Vitrakvi?

CADTH recommends that Vitrakvi be reimbursed by public drug plans for treating adult and pediatric patients with locally advanced or metastatic solid tumours who have a *neurotrophic tyrosine receptor kinase* (*NTRK*) gene fusion without a known acquired resistance mutation, or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options, but only if certain conditions are met.

Which patients are eligible for coverage?

Vitrakvi should only be covered to treat patients with advanced solid tumours who have an *NTRK* gene fusion, who have previously failed on all standard treatments for their current tumour site, and who will be able to tolerate the treatment.

What are the conditions for reimbursement?

Vitrakvi should only be reimbursed as single-agent therapy if it is prescribed by a clinician with expertise in the use of antineoplastic drugs and if the cost of Vitrakvi is reduced.

Why did CADTH make this recommendation?

Evidence from a clinical trial demonstrated that Vitrakvi improves disease control, has a manageable toxicity profile, and may meet the needs of patients with no other effective treatment options.

Based on public list prices, Vitrakvi is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population. A price reduction is therefore required. Economic evidence suggests that, if a patient's *NTRK* mutation status is unknown and testing is required to determine eligibility for treatment with Vitrakvi, price reductions alone are not sufficient to ensure cost-effectiveness at a $50,000 per QALY threshold. If additional testing costs are not incurred by public payers, then Vitrakvi would require a price reduction of more than 90% to be considered cost-effective.

Based on public list prices, the 3-year budget impact is $35,735,142.

Additional Information

What is a solid tumour with *NTRK* gene fusions?

Solid tumours with an *NTRK* gene fusion are cancers that produce a protein called tropomyosin receptor kinase that speeds up tumour growth. *NTRK* fusions have been reported in many different types of solid tumours in adults and children including breast, colorectal, gynecological, bile duct, pancreas, lung, brain, salivary gland, and thyroid cancers; and sarcomas, with the frequency of *NTRK* gene fusion varying across these tumour types.

Unmet needs in patients with *NTRK*-positive solid tumours

There are no effective treatments available for patients with advanced *NTRK*-positive tumours whose tumours cannot be removed by a safe and non-mutilating surgery, or for patients who have failed on all other treatment options.

How much does Vitrakvi cost?

Treatment with Vitrakvi is expected to cost approximately $8,207 per 28-day cycle for pediatric patients and $11,724 for adult patients.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that larotrectinib should be reimbursed for the treatment of adult and pediatric patients with metastatic or locally advanced solid tumours who have a *neurotrophic tyrosine receptor kinase* (*NTRK*) gene fusion only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

A pooled analysis (ePAS4; N = 164) of data from 3 open-label, single-arm studies of larotrectinib in adult and pediatric patients with advanced or metastatic solid tumours, including 1 phase I trial (LOXO-TRK-14001), 1 phase I/II trial (LOXO-TRK-15003; SCOUT), and 1 phase II basket trial (LOXO-TRK-15002; NAVIGATE) demonstrated that patients with non‐central nervous system solid tumours that harbour an *NTRK* gene fusion exhibited an objective response rate (ORR) of 73% after treatment with larotrectinib. ORR was defined as the proportion of patients with a best overall response of either a complete response or a partial response (CR and PR, respectively), according to the Response Evaluation Criteria in Solid Tumours (RECIST), version1.1, and determined by an independent review committee (IRC). The overall median time to achieve an ORR was 1.84 months (range: 0.92 to 14.55) and the percentage of patients experiencing a time to response of 2 months or shorter was 81%. pERC noted that there was a considerable heterogeneity in the antitumour activity of larotrectinib on tumours in different sites and substantial uncertainty in the magnitude of the observed response rate and longer-term effects of larotrectinib on patients' survival and quality of life. However, the Committee acknowledged that tumours with an NTRK gene fusion are rare, which makes the collection of evidence particularly challenging; the correspondingly small numbers of patients in the included studies contributes to the uncertainty in the clinical evidence available to assess the effects of larotrectinib. pERC also considered that the patients for whom larotrectinib is indicated often have a substantial burden of disease and no other treatment options. While the response to larotrectinib treatment varied considerably across different tumour sites, pERC evaluated the available evidence from a tumour-agnostic perspective. pERC concluded that the benefits demonstrated in certain types of tumours outweighed the absence of definitive clinical evidence in other tumour types. pERC also noted that larotrectinib may meet the needs of patients with no other effective treatment options for a treatment that can control disease symptoms, provides disease control, has a manageable toxicity profile, and is relatively easy to administer.

At the submitted price, larotrectinib is not cost-effective at a $50,000 per QALY threshold relative to current standards of care. To be cost-effective, the price of larotrectinib would need to be reduced by more than 90% and this assumes that the public payer will incur no costs associated with identifying treatment-eligible patients with *NTRK* fusion mutations. If the costs associated with identifying treatment-eligible patients are incurred by the public payer, then larotrectinib would not be cost-effective at a $50,000 per QALY threshold at any price. CADTH was unable to address many limitations of the sponsor's model. Therefore, it is possible that further limitations exist beyond those identified, which may result in an underestimation of the true incremental cost-effectiveness ratio (ICER) for larotrectinib.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients should have the following: 1.1. *NTRK* gene fusion without a known acquired resistance mutation 1.2. Metastatic or locally advanced unresectable solid tumour 1.3. Good performance status defined as: 1.3.1. ECOG PS 0 to 2 (adults) 1.3.2. ECOG PS 0 to 3 (pediatrics)	The pivotal trials included patients with locally advanced or metastatic tumours who had relapsed or progressed following standard systemic therapy or would have required surgery with significant morbidity, and patients for whom no standard therapies existed. The LOXO-TRK-14001 trial included adults 18 years of age and older with an ECOG PS of 2 or less; the SCOUT trial included pediatric patients aged 1 month to 21 years with an ECOG PS of 2 or less; and the NAVIGATE trial included patients aged 12 years or older with an ECOG PS of 3 or less (or pediatric equivalent).
2. All available standard treatments for that tumour site should have been previously used and exhausted and surgery and/or radiation would lead to substantial morbidity	This condition reflects the eligibility criteria of the pivotal studies.
3. Treatment with larotrectinib should not be initiated in patients who: 3.1. have symptomatic brain metastases, 3.2. have unstable cardiovascular disease, or 3.3. are unable to discontinue treatment with a strong CYP3A4 inhibitor or inducer before treatment initiation	This condition reflects the eligibility criteria of the pivotal studies.
Renewal	
4. Treatment with additional cycles of larotrectinib should be permitted unless either of the following occurs: 4.1. radiographic disease progression 4.2. unacceptable toxicity	There is no evidence that re-treatment with larotrectinib of patients whose disease has progressed after treatment is effective. Patients who are unable to complete treatment with larotrectinib due to unacceptable toxicity would likely not be able to receive further treatment with larotrectinib.
5. Assessment for renewal of larotrectinib should be based on radiographic evaluation (CT and/or MRI) every 3 to 4 months for the first year after treatment initiation. Longer interval follow-up may be continued thereafter based on clinical judgment	Long-term follow-up assessments occurred every 3 months (± 1 month) in the 3 LOXO trials. In addition, this interval is used widely for assessment and radiographic monitoring in oncology. For patients with a sustained response to larotrectinib, increasing the imaging interval would be acceptable based on the clinical judgment to avoid exposure to radiation.
Discontinuation	
6. Treatment with larotrectinib should be discontinued upon the occurrence of any of the following: 6.1. radiographic disease progression 6.2. unacceptable toxicity 6.3. development of adverse reactions that do not resolve within 4 weeks of withholding the drug	These conditions correspond to the criteria used to determine whether treatment with larotrectinib should be discontinued in the pivotal studies, and also correspond to the dosing instructions within the Product Monograph.

Reimbursement condition	Reason
Prescribing	
7. Larotrectinib should only be prescribed by a clinician experienced in diagnosing and treating patients with *NTRK* gene fusions	This condition is required to ensure that larotrectinib is used appropriately and only in eligible patients.
8. Larotrectinib should only be administered under the supervision of a health professional experienced in the use of antineoplastic drugs	This condition is required to ensure that larotrectinib is used most effectively and that patients receive optimal care.
9. Larotrectinib should be administered as monotherapy	The pooled analysis of data from the 3 pivotal trials used data from patients who received larotrectinib as monotherapy.
10. Dosing of larotrectinib should be as follows: 10.1. 100 mg (oral dose) twice daily in individuals with BSA ≥ 1 m^2, or 10.2. 100 mg/m^2 (oral dose) twice daily for children with a BSA < 1 m^2	These conditions correspond to the dosing regimens used in the pivotal studies.
Pricing	
11. Price reduction is needed	If testing is required to determine eligibility based on NTRK status, then there is no price at which larotrectinib could be considered cost-effective at a $50,000 per QALY threshold. If the cost of testing to determine eligibility based on NTRK status is excluded from the total treatment cost, then larotrectinib would require a price reduction of greater than 90% to be considered cost-effective at a $50,000 per QALY threshold.

BSA = body surface area; ECOG PS = Eastern Cooperative Oncology Group Performance Status; *NTRK = neurotrophic tyrosine receptor kinase*.

Implementation Guidance

1. Testing for *NTRK* Gene Fusion Status

   Because a confirmed diagnosis of *NTRK* fusion status is a condition for reimbursement of larotrectinib, *NTRK* testing should be completed at diagnosis or in the first-line treatment setting. However, pERC noted that *NTRK* testing is not used universally across all public drug programs and cancer agencies in Canada. If testing is required to determine eligibility based on *NTRK* status, then there is no price at which larotrectinib could be considered to be cost-effective at a $50,000 per QALY threshold. pERC discussed examples of the *NTRK* testing methods that are commonly used in current practice. However, pERC noted that, as testing methods for *NTRK* gene fusions are rapidly evolving, upon implementation of the reimbursement recommendation the jurisdictions may need to consider a common approach to define their *NTRK* testing strategies to ensure equitable patient access and cost-effectiveness (e.g., through health technology assessments of companion diagnostic testing).

2. Collection of Additional Data

   Given the rarity *NTRK* gene fusions in many advanced solid tumours, jurisdictions may wish to work collaboratively with the sponsor to pursue additional real-world evidence to help further inform the effectiveness and safety of larotrectinib in these patients.

Discussion Points

- pERC deliberated on the results of the pooled efficacy analysis that included data from LOXO-TRK-14001, LOXO-TRK-15003 (SCOUT), and LOXO-TRK-15002 (NAVIGATE) trials, which evaluated the effects of larotrectinib in adult and pediatric patients with non-central nervous system (CNS)–advanced or metastatic solid tumours (ePAS4; July 2019 data cut-off; N = 164). Larotrectinib treatment was associated with an ORR of 73% (95% confidence interval [CI], 65% to 79%) in a mixed group of adult and pediatric patients with advanced or metastatic solid tumours with *NTRK* gene fusion; with 49% of the responders achieving a PR, 19% achieving a CR, and 5% achieving a pathological CR. pERC also reviewed the results of the updated pooled efficacy analysis (ePAS5; July 2020 data cut-off; N = 192) that revealed consistent results, with an ORR of 72% (95% CI, 65% to 79%); 23% of patients achieved a CR and 7% achieved a pathological CR.
- pERC additionally discussed the results of a separate pooled analysis (SAS3 dataset; July 2019 data cut-off date) that included 24 patients with primary CNS tumours. ORR by investigator assessment was 21% (95% CI, 7% to 42%); 8% of patients achieved a CR and 13% achieved a confirmed PR. At the latest data cut-off date of July 2020, the ORR was 24% (95% CI, 11% to 42%), with 9% and 15% of patients achieving a CR and PR, respectively.
- pERC discussed the results of 3 additional analyses provided by the sponsor in response to concerns raised in pERC's 2019 recommendation regarding the inherent heterogeneity across tumour types, as well as the heterogeneity of patients included in the aforementioned trials, and the lack of a comparator group. These analyses included a Bayesian hierarchical model, a permutation analysis, and an intra-person growth modulation index (GMI) analysis. Results from the intra-patient GMI analysis mitigated concerns over between-patient heterogeneity because of the lack of controls. However, none of the alternative analyses supported uniform effectiveness of larotrectinib across all tumour types.
- pERC also reviewed the results from 4 real-world evidence studies with large sample sizes that supported the oncogenicity and mutual exclusivity of *NTRK* fusion in certain cancers but showed no increase or reduction in progression-free or overall survival (OS) among *NTRK*-positive cancer patients.
- Patient group input to CADTH identified an unmet need in the treatment of adult and pediatric patients with *NTRK* gene fusion–positive tumours who have no satisfactory options and who are debilitated by current treatments (surgery, radiation, or chemotherapy). These patients would benefit from a less toxic, less invasive treatment. pERC agreed that larotrectinib aligns with patient values, as it improves symptom control, provides better disease control, has a manageable toxicity profile, and provides patients with ease of administration as an oral therapy.
- pERC discussed what a tumour-agnostic approach would entail from a health technology assessment point of view and noted that the available evidence supports antitumour activity but with varying degrees of response across all tumour types. pERC also noted that some tumour types were underrepresented in the pooled analysis population because of the rare nature of the *NTRK*-positive solid tumours, resulting in wide confidence intervals and larger uncertainty around the magnitude of benefit from larotrectinib across all tumour sites. However, pERC agreed that the subgroup analysis by tumour type was exploratory and hence non-inferential.

- pERC agreed that the submitted pooled overall response rates were high in non-CNS *NTRK*-positive solid tumours, while the OS and progression-free survival (PFS) results were difficult to interpret given the methodological limitations of pooling patient populations with varying survival distributions and immature survival data. pERC noted that, as ORR is not a validated surrogate for OS and PFS in most tumour types, the longer-term effects of larotrectinib remain uncertain.
- pERC deliberated on ethical considerations arising from differences between different tumour types relevant to the equity consideration. These included variations in the frequency of *NTRK* gene fusions across tumour types, line of therapy for which larotrectinib is used, levels of unmet need (e.g., pediatric cancers, avoiding debilitating surgeries), and cost-effectiveness. pERC agreed that these differences should be taken into account by decision-makers to address accessibility, heath disparities, and promoting individual and public health. pERC further discussed ethical and social implications of grounding a decision for public funding on limited evidence from ongoing trials that focus on a biomarker as an oncogenic driver and the methodological issues surrounding the submitted evidence.
- pERC weighed various considerations related to disease rarity, patient values, and unmet need expressed by patient and clinician groups, and uncertainties around the available evidence, and agreed that the reimbursement recommendation should be made for all patients with solid tumours harbouring a *NTRK* gene fusion.
- pERC agreed that *NTRK* gene fusion status is required before initiating treatment with larotrectinib. The Committee noted that it would be ideal for jurisdictions to have the *NTRK* mutation testing at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation for larotrectinib. Testing is a rapidly evolving field; the clinical experts suggested the development of a testing algorithm that is being updated on a regular basis. pERC noted that, upon implementation of the larotrectinib funding, the jurisdictions may need to consider a common approach to define their *NTRK* testing strategies through an additional health technology review of companion diagnostics and testing algorithms to ensure timely and equitable access to testing and treatment.
- pERC noted the considerable heterogeneity of cost-effectiveness across tumour sites because of differences in comparators, clinical effects, and the prevalence of an *NTRK* mutation. Because of the rarity of the NTRK mutation in some cancers, there would be considerable cost in simply identifying eligible patients. Cost-effectiveness could be improved and the budget impact reduced if larotrectinib was restricted to certain patient populations.

Background

This resubmission for larotrectinib has a Health Canada indication for the treatment of adult and pediatric patients with solid tumours that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options. Larotrectinib is an oral selective inhibitor of *NTRK 1*, *2* and *3* genes. It is available in 25 mg and 100 mg capsules (as larotrectinib sulphate) and in a 20 mg/mL oral solution (as larotrectinib sulphate); the recommended dose is 100 mg twice daily in adults or 100 mg/m^2 twice daily, with a maximum of 100 mg per dose in pediatric patients aged 1 month to 18 years, taken

orally until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Submission History

The original CADTH systematic review of larotrectinib included a pooled analysis of 3 open-label, single-arm trials of larotrectinib (LOXO-TRK-14001, a phase I adult dose escalation and expansion trial; SCOUT, a phase I/II pediatric trial; and NAVIGATE, a phase II basket trial in adults and adolescents) in adult and pediatric patients with advanced or metastatic solid tumours. A total of 122 patients were included in the original CADTH submission, which had a data cut-off of July 30, 2018. Based on the evidence, pERC did not recommend the reimbursement of larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring an *NTRK* gene fusion. pERC made this recommendation because:

- The Committee was uncertain that there was a net clinical benefit of larotrectinib treatment compared with available treatment options or best supportive care. While pERC noted that larotrectinib treatment appeared to be associated with antitumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of larotrectinib given the heterogeneity of the patients in the included trials and pooled analysis, the inability to interpret variation in outcomes by tumour type, the lack of evidence as to whether or not the *NTRK* gene fusion is an oncogenic driver in all tumour types (tumour-agnostic driver), and because of a lack of historical evidence on outcomes with available therapies in patients with the gene fusion. pERC noted that the evidence available for outcomes important to decision-making, such as OS and PFS, were uninterpretable given the heterogeneity of the tumours among the included patient population. pERC concluded that larotrectinib aligned with patient values based on its antitumour activity, manageable toxicity profile, and ease of administration as an oral therapy.
- The Committee could not draw any definitive conclusions regarding the cost-effectiveness of larotrectinib compared with available drugs given the heterogeneity of the patients included in the pooled analysis, which created considerable uncertainty in the magnitude of clinical benefit.

This resubmission is based on the latest larotrectinib clinical trial data, the extended primary analysis set 4 and 5 (ePAS4 and ePAS5, with164 and 192 patients included, respectively), and the primary CNS tumour analysis set (SAS3, N = 24 and SAS3 New, N = 33), which provides more mature data with greater patient enrolment and longer follow-up (July 15, 2019 for ePAS4 and SAS3, and July 2020 for ePAS5 and SAS3 New). Three additional analyses were submitted to address CADTH's concern of heterogeneity of patients in the clinical trials. Finally, several real-world studies were submitted that were used as supportive evidence to address uncertainties associated with the oncogenicity and natural history of larotrectinib in the original submission.

Summary of Evidence

To make their recommendation, the Committee considered the following information:

- a review of the pooled analysis of 3 open-label, single-arm clinical studies in adult and pediatric patients with advanced or metastatic solid tumours
- patient perspectives gathered by patient groups Lung Cancer Canada, Canadian Breast Cancer Network, Colorectal Cancer Canada, Sarcoma Cancer Foundation of Canada, and the Canadian Cancer Survivor Network (which provided a collective submission with Advocacy for Canadian Childhood Oncology Research Network [Ac2orn], Colorectal Cancer Resource and Action Network [CCRAN], and GIST Sarcoma Life Raft Group Canada [LRGC])
- input from 5 clinical specialists with expertise diagnosing and treating patients with advanced or metastatic solid tumours
- input from 9 clinician groups, including Advanced Thyroid Cancer; Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada and other gastrointestinal cancer-treating clinicians; Ontario Health/Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee; Ontario Health/Cancer Care Ontario Head, Neck, and Thyroid Cancer Drug Advisory Committee; Lung Cancer Canada; Ontario Health/Cancer Care Ontario Lung and Thoracic Cancer Drug Advisory Committee; Pediatric Oncology Group of Ontario; Pediatric Oncology Group; and Ontario Health Cancer/Care Ontario Skin Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Summary of Patient Input

A total of 5 patient groups provided input for this submission, including Lung Cancer Canada, Canadian Breast Cancer Network, Colorectal Cancer Canada, Sarcoma Cancer Foundation of Canada, and the Canadian Cancer Survivor Network (which provided a collective submission with Advocacy for Ac2orn, CCRAN, and GIST Sarcoma LRGC). Patient perspectives were obtained from surveys, interviews, literature reviews, and various patient engagement events. The following is a summary of key input from the perspective of the patient group(s):

- Tumours with *NTRK* fusion generally have a poor prognosis, as most patients are diagnosed at an advanced stage or have an aggressive or rare form of cancer. There is an unmet need for targeted therapies aimed at the *NTRK* fusion with a better safety and efficacy profile than conventional therapy.
- Most patients had suboptimal success with conventional therapies, which are associated with significant side effects and are not targeted at the *NTRK* fusion.
- Patients expect a new treatment to result in disease control, extension of life, improvement in quality of life, and minimal and tolerable toxicity. Patients also noted that a treatment that specifically targets the underlying *NTRK* mutation and that could minimize the non-specific targeting of other tissues and organs is highly desired.

Clinical Trials

The CADTH resubmission of larotrectinib was based on a pooled analysis of 3 ongoing, multi-centre, open-label, single-arm trials of larotrectinib in adult and pediatric patients with advanced or metastatic solid tumours: LOXO-TRK-14001 (phase I), LOXO-TRK-15003/SCOUT (phase I/II), and LOXO-TRK-15002/NAVIGATE (phase II basket trial). The pooled analysis is updated periodically with revised data, larger sample sizes, and longer follow-up at each

update. The current resubmission was based on the following pooled datasets, with a data cut-off on July 15, 2019: ePAS4 (n = 164 patients with *NTRK* gene fusion and non-CNS primary tumour), SAS3 (n = 24 patients with *NTRK*-positive primary CNS tumours), patients included in the health-related quality of life (HRQoL) analyses (n = 126 patients with non-CNS primary solid tumours, with an *NTRK* gene fusion; 74 adults, 24 children aged 2 years and older, and 28 infants younger than 2 years of age) for efficacy; and *TRK* fusion cancer labelled dose safety analysis set (n = 196 patients with *TRK* fusion cancer) and overall labelled dose safety analysis set (n = 238 patients with or without *TRK* fusion cancer).[22] In addition, a new data cut-off at July 2020 was used to create 4 updated datasets: ePAS5 (n = 192 patients, the most updated dataset with the highest number of patients and follow-up data, which was an update of the ePAS4 dataset), SAS3 new (n = 33, an update of the previous data cut-off point), *NTRK* fusion cancer safety set (n = 260, an update of the *TRK* fusion cancer labelled dose safety analysis set), and overall safety set (n = 331, an update of the overall labelled dose safety analysis set).

Most patients in the pooled analysis were treated with larotrectinib 100 mg orally twice daily in individuals with a body surface area (BSA) of 1 m^2 or greater, or 100 mg/m^2 orally twice daily for children with a BSA of less than 1 m^2. Data for patient disposition was available for the ePAS4 dataset, only, where 74 out of the 164 patients discontinued treatment (45.1%) primarily because of disease progression (23.8%). The trials were single-arm; therefore, the pooled analysis had no active comparator, nor any active comparator trials met the review criteria, although the rarity of the *NTRK* fusion creates practical and ethical challenges to conduct a randomized controlled trial with an established standard of care. A major uncertainty around the pooled analysis results was due to a mixed population of various tumour histologies being combined; however, some of the tumour types were underrepresented. Therefore, the generalizability of findings of the pooled population remains uncertain for the different tumour types.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the Committee discussed the following: ORR, time to response (TTR), duration of response (DOR), PFS, OS, and HRQoL assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ C-30) and Pediatric Quality of Life (PedsQL) version 4.0 Generic Core Scale. The primary outcome in all 3 trials and the pooled analysis was ORR, defined as the proportion of patients with a best overall response of either complete response or partial response (CR and PR, respectively), according to the RECIST for solid tumours or Response Assessment in Neuro-Oncology for CNS tumours criteria.

Efficacy

ORR: In the ePAS4 dataset, ORR assessed by an IRC was 73% (95% CI, 65% to 79%); 19% of patients achieved a CR, 5% achieved a pathological CR, and 49% achieved a PR. Consistent in the ePAS5 analysis, the ORR was 72% (95% CI, 65% to 79%); 23% and 7% patients achieved CR and pathological CR, respectively.

Among patients with a CNS tumour, the ORR by investigator assessment was 21% (95% CI, 7% to 42%) in the SAS3 dataset; 8% of patients achieved a CR, 13% achieved a confirmed PR, and the disease control rate was 63%. In the New SAS3 dataset, the ORR was 24% (95% CI, 11% to 42%); 9% and 15% of patients achieved a CR and PR, respectively.

The range of ORR across the different subgroups varied widely, although the subgroup analyses were non-inferential and presented descriptively. Notably across various tumour types, the ORR ranged from 0% (95% CI, not estimated) for appendix, pancreas, cholangiosarcoma (each with 2 patients or fewer) to 100% (95% CI, 40% to 100%) for gastrointestinal stromal tumour (with 4 patients). Although non-inferential, the wide range of ORR, as well as the associated 95% CI across the different tumour types, limit the interpretability of the ORR for the individual tumour types.

TTR: In the ePAS4 dataset, the median TTR was 1.84 months (minimum 0.92 months; maximum 14.55 months). The percentage of patients experiencing a TTR of 2 months or less was 81% (96/119). In the SAS3 dataset, the median TTR was 1.82 months (range: 0.99 to 3.75); 67% of patients experienced a response in under 2 months.

DOR: In the ePAS4 dataset, the median DOR was not estimable (NE) (95% CI, 27.6 months to NE) after a median follow-up of 15.7 months (Q1 to Q3: 6.6 months to 24.8 months). In the ePAS5 dataset, however, the DOR was 34.5 months (95% CI, 27.6 to 54.7) with a median follow-up of 20.3 months (Q1 to Q3: data NA). In the SAS3 dataset, the median DOR had not been reached (95% CI, 3.8 months to NE) after a median follow-up duration of 5.3 months (Q1 to Q3: 3.6 to 10.1 months).

PFS: In the ePAS4 dataset, the median PFS was 33.4 months (95% CI, 19.3 months to NE) after a median follow-up of 14.0 months (Q1 to Q3: 7.9 months to 26.6 months). In the ePAS5 dataset, after a median follow-up of 22.1 months (Q1 to Q3: data NA), the median PFS was 33.4 months (95% CI, 22.5 to 43.5). In the SAS3 dataset, the median PFS was 11.0 months (95% CI, 5.4 to NE), with a median duration of follow-up of 5.6 months (Q1 to Q3: 3.6 to 13.1). In the New SAS3 dataset, the median PFS was 18.3 months (95% CI, 6.7 to NE) after a median follow-up of 16.5 months.

OS: In the ePAS4 dataset, the median OS was NE (95% CI, 44.4 months to NE) and 85% of patients were alive after a median follow-up of 15.8 months (Q1 to Q3: 9.3 months to 28.8 months). In the SAS3 dataset, the median OS was NE (95% CI, 9.4 months to NE), with a median duration follow-up of 6 months. With the new data cut-off, the OS was still NE for ePAS5 and New SAS3.

HRQoL: HRQoL outcomes were only measured in the SCOUT and NAVIGATE trials. For adults and pediatric patients, the proportions of patients with above-normal/normal and below-normal HRQoL scores were determined at baseline and at best response using the EORTC QLQ-C30 Global Health Scale (GHS) and PedsQL total score. The mean EORTC QLQ-C30 GHS for the US general population (63.9) minus 10 points (the estimated minimum important difference, or MID) was used to construct the normal/above-normal (53.9 or greater) and below-norm (less than 53.9) score categories for adults. The average score for the combined self and proxy-reported PedsQL questionnaire for US healthy children (85.0) minus 4.5 points (the estimated MID) was used to construct the normal/above-normal (80.5 or greater) and below-normal (less than 80.5) score categories for children 2 years of age or older. The sponsor-identified MID for PedsQL total score for children younger than 2 years of age was 7.2 points.

Of the 52 adult patients with EORTC QLQ-C30 GHS at normal/above-normal at baseline, 98% remained in this category at the best response and of the 22 patients at below-normal at baseline, 9% remained in this category and 91% improved to normal/above-normal. Of the 9 pediatric patients aged 2 years of age or greater with PedsQL total score at normal/

above-normal at baseline, 100% remained in this category at the best response and of the 15 patients at below-normal at baseline, 33% remained in this category and 67% improved to normal/above-normal. Data were not available for pediatric patients younger than 2 years of age.

When compared with baseline, the mean of best change in total score (standard deviation) was 17.5 (20.0), 20.7 (17.2), and 12.0 (13.8) for adults, children 2 years of age and older, and younger than 2 years of age, respectively. The changes exceeded the sponsor-identified (and literature-supported) MIDs for the respective instruments; 10 points for EORTC QLQ-C30 GHS in adults, 4.5 points and 7.2 points for PedsQL total score in pediatric patients older and younger than 2 years of age, respectively. Among patients (or parents and caregivers) who completed the respective questionnaires (74 adult, 24 children 2 years of age and older, and 28 children younger than 2 years), 59% of adult patients, 79% of children 2 years of age and older, and 57% of children younger than 2 years of age had improvements in the best post-baseline score at or above the estimated MIDs. Of the patients evaluable for a sustained improvement (i.e., with baseline and 2 or more post-baseline assessments, magnitude not defined), the improvement was sustained for 2 or more consecutive cycles for 47% of adult patients, 75% of children 2 years of age and older, and 43% of children younger than 2 years of age; and the improvement was sustained until the end of assessments in 30%, 50%, and 29%, respectively.

Harms (Safety)

The majority of the reported adverse events (AEs) in the pooled analysis were Grade 1 or 2, most commonly reported as increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), cough, constipation, dizziness, fatigue, nausea, vomiting, pyrexia, and anemia. Treatment-related Grade 3 or 4 AEs occurred in 15% or less of patients, most commonly anemia, increase in liver enzyme (ALT and AST) levels, and decreased neutrophil count. Larotrectinib treatment interruptions or dosage modifications attributable to treatment occurred in 19% of patients in the *TRK* fusion cancer labelled dose safety set (n = 196) and in 21% of patients in the overall labelled dose safety set (n = 238), while permanent discontinuation of larotrectinib for treatment-emergent adverse events, regardless of attribution, occurred in 5% and 8% of patients, respectively, in the 2 safety sets. Results were consistent in the newly submitted overall *NTRK* fusion cancers safety set (N = 260) and the overall safety set (N = 331).

Overall, the clinical experts consulted by CADTH agreed that the safety and tolerability of larotrectinib was acceptable and that larotrectinib resulted in minimal significant toxicity. Additionally, the availability of an oral treatment was valued considering that most treatment alternatives involve invasive surgery or IV therapy. In addition, patients valued having both a tablet and liquid formulation that facilitates dosing in young children, as well as in adults, who have difficulty swallowing due to the nature of their tumours or the impact of prior treatments.

Indirect Evidence (If Applicable)

An indirect treatment comparison (ITC) was not submitted by the sponsor, nor was a relevant ITC found from the literature.

Other Relevant Evidence

Three analyses were submitted by the sponsor to address sources of heterogeneity using the available data. The submitted analyses include: the Bayesian hierarchical model (BHM), the permutation analysis, and the intra-person GMI analysis. The first 2 attempt to quantify and account for the heterogeneity in ORR over tumour location and study, possibly also accounting for other differences in histology, while the third attempts to mitigate for the lack of control and therefore heterogeneity between participants due to histology, location, as well as many other factors, by using the individual's time to progression or time to treatment failure (TTPF) under previous treatment to compare to their PFS under their later treatment with larotrectinib.

The BHM analysis, although appropriately performed, is presented as a means of accounting for rather than investigating heterogeneity in ORR over tumour type. The BHM clearly identifies heterogeneity over the tumour types and no further analysis is presented to show that this heterogeneity can be explained by participant-level characteristics outside of tumour type; i.e., the subject-level characteristics that are controlled for in the GMI analysis. The BHM analysis does not provide evidence to support the combined analysis of the data for approval over all tumour types. The permutation analysis does not seem to add to the evidence to support or reject the pooling of all data in a single analysis, as the presented distribution over all subgroups may merely be an artifact of smaller groups having lower ORR and larger groups having higher ORR. Additionally, in both of these analyses, ORR and not PFS or OS is used as the outcome. Therefore, this may not answer the more relevant question of the effect on survival, as ORR may not be a reasonable surrogate for PFS or OS over all tumour types, participants, or treatments.

The intra-patient GMI analysis provides the most evidence that larotrectinib is effective over a number of patient types. If the assumptions underlying this analysis are believed to be valid, then it helps to mitigate concerns about patient heterogeneity due to the lack of controls. However, it is not clear if the needed assumptions hold and there is a lack of information about how the end point was calculated and the analysis performed that raises further questions about the results. Additionally, this analysis does not directly address concerns about heterogeneity over tumour type. This is particularly evident, as most tumour types with very low ORR are not included in the GMI analysis. None of the analyses provide strong evidence that larotrectinib is as active in these smaller groups defined by particular tumour types.

Cost and Cost-Effectiveness

Larotrectinib is available as a 100 mg tablet at a submitted price of $209.35. At a recommended adult dose of 100 mg twice per day and a pediatric dose of 100mg/m^2 twice per day (up to a maximum of the adult dose) in continuous 28-day cycles, the cost per 28-day cycle is $11,724 for adult patients and $8,207 for pediatric patients.

Relative to the sponsor's previous submission for larotrectinib, this resubmission provided stratified analyses by additional tumour types, the clinical data used to inform the pharmacoeconomic (PE) analysis was more mature, the cost of larotrectinib was 34.7% lower, and the clinical data used to inform the analysis included patients with additional tumour types.

The sponsor submitted a cost-utility analysis comparing larotrectinib to therapies that represented current best supportive care for each tumour site assessed. A 3-state partitioned

survival model was submitted. The 3 mutually exclusive states were "progression-free," "progressed disease," and "death." Time spent in each state was based on direct modelling of OS and PFS curves. PFS and OS curves for larotrectinib were based on data from the larotrectinib clinical trials. PFS and OS curves for the comparator arms were derived using estimates from the literature. In the sponsor's analysis, patients in the larotrectinib arm received treatment until disease progression. Aligned with the dosing schedule for larotrectinib, the model's cycle length was 7 days. The sponsor presented results by individual tumour site, as well as in a pooled analysis. For the pooled analysis, the sponsor considered a weighted combination of the discounted costs and discounted survival outcomes associated with best supportive care options across 11 cancer sites (NSCLC, CNS/glioma, adult non-GIST STS, adult GIST STS, pediatric STS, thyroid, colorectal, salivary gland, cholangiocarcinoma, melanoma, secretory breast, and pancreatic cancer) to create a single comparator arm. Weights were determined partially on the distribution of tumour types in the larotrectinib trial.

The following key limitations were identified:

- Pooled analysis masks the variability in the comparative effectiveness and cost-effectiveness of larotrectinib across tumour sites. Pooled analysis does not represent the heterogeneity in response, progression-free, or OS observed in the stratified Kaplan-Meier survival curves. Averaging across comparators that vary in their own costs and effectiveness masks the patient populations, settings, or conditions under which larotrectinib may be cost-effective or not cost-effective.
- Stratified analysis is presented for 7 adult cancer subtypes when reimbursement is sought for all adult cancer indications. For some tumour sites with 5 or fewer patients, the sponsor assumed incremental effectiveness and incremental cost-effectiveness were represented by other tumour types without clinical justification.
- There was an underestimation of the costs of identifying patients with *NTRK* fusion mutations. The sponsor assumed that patients would largely be identified using immunohistochemistry; however, CADTH clinical experts describe immunohistochemistry for the detection of *NTRK* fusion mutations as under development and not clinically validated with known test accuracy for all tumour types.
- The sponsor's analysis extrapolated PFS and OS survival curves without assuming any treatment waning, leading to analysis representing very little uncertainty about long-term outcomes substantially past the observation period of the clinical trial data.
- The sponsor's costs were not inflated to the level they claimed to be and likewise relevant health care costs related to non-cancer health care utilization were excluded.
- The sponsor did not adopt a lifetime time horizon contrary to recommendations from CADTH guidelines.

CADTH undertook reanalyses to address several key limitations of the sponsor's model. CADTH's reanalysis included a more plausible extrapolation for long-term PFS and OS; increased uncertainty in the PFS and OS consistent with the small sample sizes for each patient subtype; incorporated an assumption of no expected treatment benefit in patient subtypes, with observational data representing 5 or fewer patients (all of which were not modelled by the sponsor); and incorporated the incremental costs of testing using next-generation sequencing to identify eligible patients.

In the CADTH reanalysis, incorporating the costs of identifying treatment-eligible patients with *NTRK* fusion mutations resulted in an overall ICER for larotrectinib of $929,434 per QALY

gained compared to best supportive care across all tumour types (pooled analysis). However, the pooled analysis masks heterogeneity in the cost-effectiveness across each indication. Across tumour sites, the ICER of larotrectinib, when including patient identification costs, varied from $183,055 per QALY in adult patients with non-GIST soft tissue sarcomas and $203,383 per QALY in pediatric patients with infantile fibrosarcoma to $818,375 per QALY in patients with NSCLC. In some cancers, larotrectinib was both clinically and economically dominated, meaning that the alternative treatment costs less and provides, on average, greater clinical benefit than larotrectinib. In some tumour sites with small sample sizes, whether larotrectinib provides any net clinical benefit is unknown because of the lack of evidence. In some cancer types, such as melanoma, there is no price reduction that will make larotrectinib cost-effective because the major driver of outcomes is uncertainty in clinical benefit. In a setting where NGS testing is not routinely performed, the costs of patient identification dominate the costs of larotrectinib treatment, resulting in a situation where no reduction in drug cost will make larotrectinib cost-effective. Excluding the cost of testing reduced the pooled ICER to $426,077 per QALY where cost-effectiveness at a $50,000 per QALY threshold could only be achieved with a greater than 90% price reduction.

It is important to note that CADTH was unable to address limitations stemming from the excessive complexity of the sponsor's model. CADTH was therefore unable to validate calculations in the model and it is possible that further limitations exist beyond those identified, which may result in an underestimation of the true ICER for larotrectinib.

Initial meeting date: April 15, 2021

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Regrets: None

Conflicts of Interest: None

Reconsideration meeting date: August 11, 2021

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Regrets: Two pERC members did not attend.

Conflicts of Interest: None