CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

larotrectinib (Vitrakvi)

(Bayer Inc.)

Indication: For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.

December 4, 2020

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**Larotrectinib (Vitrakvi®)**
Indication	**Larotrectinib (Vitrakvi®) for the treatment of adult and pediatric cancer patients with solid tumours harboring NTRK gene fusions 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.**
Name of the Clinician Group	**Advanced Thyroid Cancer Joint Clinician Input:** **Dr. Nicole Chau (lead author) and:** • **Dr. Sebastien Hotte** • **Dr. Shereen Ezzat** • **Dr. Cheryl Ho**
Author of the Submission	**Dr. Nicole Chau**
Contact information	[redacted]

1. About Your Clinician Group

Clinician input was not obtained through a clinician group. Instead, this submission represents the collective perspectives of four thyroid clinicians who collaborated to produce a thoughtful and compelling submission on the therapy under review (larotrectinib). The goal is to help inform the expert committee's deliberative process for a disease site (thyroid cancer) in need of an additional therapeutic for the advanced thyroid cancer patient population.

The clinicians who collaborated to provide meaningful and critically important input are as follows:

- **Dr. Nicole Chau (lead author), Medical Oncologist, BC Cancer Agency**
- **Dr. Sebastien Hotte, Medical Oncologist, Juravinski Cancer Centre**
- **Dr. Shereen Ezzat, Head, Endocrine Oncology, UHN**
- **Dr. Cheryl Ho, Medical Oncologist, BC Cancer Agency**

2. Information Gathering

To ensure the valuable thyroid clinician perspective was captured and provided for the therapy under review, Colorectal Cancer Resource & Action Network (CCRAN) assisted with the coordination of the joint thyroid clinician input submission. It reached out to the various clinicians who were prepared to complete the clinician template and have it

circulated for review and additional input. Outreach to various clinicians began on November 9, 2020 and the outreach continued for approximately 14 days. Dr. Chau kindly agreed to lead the submission while Drs. Hotte, Ezzat and Ho agreed to review and provide additional input. This submission represents the highly valued collective input of the four clinicians.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Response:

Patients with radioactive iodine refractory advanced differentiated thyroid cancer have limited therapeutic options. The current available treatment in Canada for individuals with advanced radioactive iodine refractory differentiated thyroid cancer is the tyrosine kinase inhibitor lenvatinib or sorafenib. Lenvatinib is an oral multi-kinase inhibitor (inhibits VEGFR 1-3, FGFR1-4, PDGFR alpha, RET and KIT) associated with a 65% objective response rate in advanced radioactive iodine refractory differentiated thyroid cancer patients (in the phase 3 SELECT trial), however there are significant toxicities (76% of patients develop grade 3 or higher treatment-related adverse effects) and side effects include hypertension (69%), diarrhea (60%), fatigue (59%), arterial and venous thromboembolic events (5%), gastrointestinal fistula (2%) and renal failure (4%). Adverse effects to lenvatinib result in 82% of patients requiring dose holds, 68% of patients requiring dose reduction, permanent lenvatinib discontinuation in 14% of patients, and treatment-related adverse events result in death in 2.3% of patients. All patients invariably develop resistance to lenvatinib, and the median progression free survival is 18 months with no overall survival benefit compared to placebo. Sorafenib is an oral multi-kinase inhibitor associated with an only 12% objective response rate in advanced radioactive iodine refractory differentiated thyroid cancer patients (in the phase 3 DECISION trial), however there are significant toxicities (60% of patients develop grade 3 or higher treatment-related adverse effects) and side effects include hypertension (10% grade 3), hand foot rash (20%), diarrhea, alopecia, fatigue, weight loss, hypocalcemia. Lenvatinib is considered the preferred agent as first line therapy. Importantly, only lenvatinib has been approved for reimbursement in Canada and, therefore, is the only de-facto available option for this group of patients. In addition, pCODR Expert Review Committee did not recommend funding for sorafenib in part due to concerns with toxicity.

Patients with radioactive iodine refractory advanced differentiated thyroid cancer who develop resistance to lenvatinib or sorafenib or who do not tolerate lenvatinib or sorafenib and have no other treatment options funded in Canada. The efficacy of lenvatinib or sorafenib in patients with brain metastases has not been established. Traditional cytotoxic chemotherapy has minimal efficacy in patients and is associated with an extremely low response rate (3%).

Patients with anaplastic thyroid cancer have even worse outcomes and limited treatment options with a disease-specific mortality approaching 100%. Median survival from diagnosis is approximately 5 months (3 months if disease extends beyond the neck). Traditional cytotoxic chemotherapy has minimal efficacy. No other treatment options are funded in Canada for anaplastic thyroid cancer patients.

TRK inhibitors offer more efficacious therapeutic options with less toxicity for patients with radioactive iodine refractory differentiated thyroid cancer or anaplastic thyroid cancer harboring an NTRK gene fusion. The NCCN recommends TRK inhibitors for thyroid cancer patients with NTRK gene fusion-positive tumors.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Response:

The most important goals would be to prolong life, delay cancer progression, delay or prevent cancer related symptoms (e.g. address or prevent development of brain metastases, and skeletal-related events), improve quality of life, maintain independence, while reducing burden on caregivers.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

The majority of goals are not met by lenvatinib, the only currently available treatment in Canada. No treatments are available that have demonstrated significant improvement on survival. In a subset of patients older than 65 years of age, lenvatinib was associated with an overall survival benefit compared to placebo, but this was as part of a post-hoc, subgroup analysis. Furthermore, older patients had increased toxicity, greater dose reductions and lower objective responses.

Notably, the only available systemic therapy treatments in Canada, lenvatinib and sorafenib, are associated with significant treatment related toxicities which negatively impacts quality of life and in some cases can be life threatening. Lenvatinib and sorafenib are associated with limited efficacy as all patients invariably develop resistance (median progression free survival of 18 months for lenvatinib and median progression free survival of 10.8 months for sorafenib). Less toxic and more effective therapies are desperately needed.

A debilitating and life threatening complication of thyroid cancer is CNS metastases. Lenvatinib and sorafenib do not have established efficacy in addressing or delaying brain metastases. Systemic therapies that can address or prevent the development of brain metastases are also desperately needed.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

Patients with thyroid cancer harboring a NTRK gene fusion are a genomically defined subset of thyroid cancer patients who are in need of more effective and less toxic therapies. NTRK gene fusions are found in 6-26% of thyroid cancers and tend to be mutually exclusive of other oncogenic driver events.

Larotrectinib, an only orally available selective TRK inhibitor, provides these patients with the highest chance of progression free survival and quality of life. Larotrectinib appears to have high efficacy and less toxicity compared to published reports on the impact of the other available agents, lenvatinib and sorafenib, in patients with advanced differentiated thyroid cancer.

Larotrectinib has demonstrated efficacy in patients with CNS metastases which is a critical complication of advanced thyroid cancer and an area of current unmet need.

Patients with anaplastic thyroid cancer are in desperate need of therapeutic options and larotrectinib would be the first targeted systemic therapy available for patients with anaplastic thyroid cancer harboring TRK gene fusion.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Response:

Larotrectinib should be available and considered as a first line or subsequent line therapy for patients with NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer.

NTRK gene fusions are oncogenic driver events that are typically mutually exclusive. For patients with advanced radioactive iodine refractory NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer, immediate inhibition of this oncogenic fusion driver with the first TRK specific inhibitor, larotrectinib may provide these patients with their best chance of response, durable disease control and quality of life.

Larotrectinib has demonstrated superior efficacy profile in patients who are systemic therapy naïve and those who have received multiple prior lines of therapy.

The response rate to larotrectinib in patients with NTRK gene fusion positive differentiated thyroid cancer is 90%, whereas the response rate to lenvatinib is 65% and sorafenib is 12% in advanced differentiated thyroid cancer.

The median progression free survival on larotrectinib has not yet been reached in differentiated thyroid cancer patients with PFS proportion at 18 months of 86%. This compares favorably to the median progression free survival of 18 months observed with lenvatinib, or of 10.8 months with sorafenib.

Patients with anaplastic thyroid cancer have an extremely poor prognosis and there are no targeted systemic therapies options in Canada and no effective palliative systemic therapies. The response rate to larotrectinib in patients with NTRK gene fusion positive anaplastic thyroid cancer is 29%.

Regarding toxicities, clinical trials describe a treatment discontinuation rate of 14% for lenvatinib but only 2% for larotrectinib. Grade 3 or higher Larotrectinib-related adverse events were reported in 14% of patients and include increased AST or ALT (3%), anemia (2%) and decreased neutrophil count (2%).

Therefore larotrectinib represents a more favorable therapeutic option in the first or subsequent line of therapy for patients with NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer and is associated with the highest response rate, longest duration of response and best tolerance.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

Larotrectinib should be considered the optimal first line agent in patients with NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer, but in

patients who have received prior tyrosine kinase inhibitor therapy (lenvatinib and/or sorafenib), larotrectinib's unique mechanism of action and favorable toxicity profile warrants its use in any line of treatment. Larotrectinib is indicated for NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer patients with progressive or symptomatic metastatic or unresectable disease or disease for which there are no other management options including surgical interventions.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

Larotrectinib has demonstrated clinical efficacy in patients who are systemic therapy naïve and those who have received multiple prior lines of therapy. Therefore larotrectinib should be made available in the first line setting or subsequent lines of therapy for patients who may have already received prior systemic therapies.

If larotrectinib fails, the subsequent therapies would include second generation TRK inhibitors which are currently being evaluated in clinical trials (e.g. NCT03215511) as these agents have been developed specifically to overcome the known resistance mutations that can develop with first generation TRK inhibitors. Lenvatinib could also be employed following failure of larotrectinib (lenvatinib demonstrated activity in patients who were systemic therapy naïve and those who received one prior line of tyrosine kinase inhibitor therapy in the phase 3 SELECT trial).

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

Only patients with tumors harboring NTRK gene fusions will have sensitivity to larotrectinib. Patients with advanced radioactive iodine refractory NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer, with performance status ECOG 0-2 and 0 or more lines of therapy have achieved clinical responses to larotrectinib. Patients with CNS metastases have also demonstrated treatment responses. The safety profile in patients 65 years and older was generally consistent with that seen in adult patients under 65 years of age.

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

Patients will be identified by clinical judgement and tumor testing for NTRK gene fusion.

Clinical judgement will be required to identify patients who are symptomatic or have advanced radiographic unresectable progressive disease requiring systemic therapy. Patients with radioactive iodine refractory differentiated thyroid cancer who do not have symptoms but have significant radiographic progression (tumor growth 20% or more over 6-12 months) or tumors near critical structures (airway, spinal cord) should be considered for palliative systemic therapy. Clinical judgement is necessary to ensure appropriate performance status, and management and tolerance of treatment related toxicities.

NTRK testing is available without cost to patients through Bayer's FastTRK Testing Program to determine the presence or absence of tumor NTRK gene fusions. The turn around time is approximately 2-4 business days for the initial pan-TRK IHC test, and 7-14 business days for confirmatory NTRK gene

fusion by NGS. This can be performed on existing archival tumor tissue and almost all patients should have sufficient archival tumor tissue from their initial thyroidectomy specimen or other diagnostic biopsy of recurrence or metastases. NTRK gene fusion testing is also available through many other commercial vendors.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients who have tumors that do not harbor a NTRK gene fusion should not be offered larotrectinib.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

Response:

Yes. NTRK testing is available cross Canada without cost through Bayer's FAST-TRK program to determine the presence or absence of tumor NTRK gene fusion as described above.

Larotrectinib has demonstrated benefit in NTRK positive patients across varying degrees of pre-treatment or performance status, and response rates were highest in patients who were treatment naïve or with an ECOG performance status of 0.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

The outcomes used in clinical practice are aligned with the outcomes typically used in clinical trials for this cancer. These include overall survival, progression free survival, blood work and toxicity assessment, imaging (CT, MRI or PET), tumor markers (thyroglobulin in differentiated thyroid cancers), quality of life and clinical assessment of treatment tolerance.

6.9. What would be considered a clinically meaningful response to treatment?

Response:

Clinically meaningful response to treatment includes improvement in survival, delay in disease progression, reduction in disease burden, reduction in disease related symptoms (e.g. pain, dyspnea, fatigue, weight loss etc.), ability to perform activities of daily living, improvement or maintenance of quality of life and performance status. These are fairly standard assessments for physicians who treat patients with thyroid cancer.

6.10. How often should treatment response be assessed?

Response:

Tumor response assessments with radiographic imaging should be assessed ideally every 3-4 months initially and can subsequently be adjusted depending on response and stability of disease. Clinical response assessments can be performed more frequently as dictated by the patient's status and pace of disease progression.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

Numerous factors are considered when deciding to discontinue treatment and include but are not limited to clinically significant symptomatic disease progression, significant radiographic disease progression and patient specific preferences. Adverse events including grade 3 or higher elevated liver enzymes (2%), grade 3 or higher neurologic adverse events (delirium, dysarthria, dizziness, gait disturbance, paresthesia) require dose interruption and consideration of dosage reduction or discontinuation.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Oncology outpatient clinic in either community or academic setting.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

N/A

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

NTRK gene fusions are present in a subset of patients with advanced thyroid cancer patients (approximately 6-26% of thyroid cancer patients) and therefore it is not feasible to perform a large randomized phase 3 trial.

For patients with advanced radioactive iodine refractory NTRK gene fusion positive differentiated thyroid cancer or advanced NTRK gene fusion positive anaplastic thyroid cancer, direct inhibition of this oncogenic fusion driver with the first TRK specific inhibitor, larotrectinib may provide these patients with their best chance of response, durable disease control and quality of life based on recent data from phase 2 and phase 1 studies leading to FDA approval of larotrectinib.

Patients with advanced NTRK gene fusion thyroid cancer who received larotrectinib on the phase 2 basket trial (NAVIGATE NCT02576431) (n=24) and adult phase 1 trial (NCT02122913) (n=4) were analyzed for best overall response, duration of response and PFS, OS and safety (Cabinallas ME et al ESMO 2020 1916P). The median age of this cohort of NTRK gene fusion thyroid cancer patients was 61.5 years, 14% CNS metastases, 43% had no prior systemic therapy, 25% had one prior line, 25% had 2 prior lines and 7% had 3 or more prior lines of therapy. The objective response rate was 90% (10% CR, 81% PR, 10% SD) in patients with differentiated thyroid cancer, and 29% (0% CR, 29% PR, 14% SD) in patients with anaplastic thyroid cancer. In the total cohort the objective response rate was 75% (95% CI 55, 89), median time to response was 1.9 months and the duration of treatment was ongoing in 19 patients (68%) at data cut off. In the total cohort of thyroid cancer patients, the duration of response rate at 12 months was 95%, PFS rate at 12 months was 81%, OS rate at 12 months was 92%. Larotrectinib related adverse events were mainly grade 1 or 2 and the most common treatment related AEs were fatigue (36%), constipation (32%), dizziness (29%), elevated liver enzymes (29%), peripheral

edema (29%). Grade 3 treatment related AEs occurred in 2 patients (7%) and included anemia and decreased lymphocyte count. Two patients (7%) had dose reductions due to an AE. No patients experienced AEs leading to permanent treatment discontinuation.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Please state full name **Dr. Nicole Chau, MD, FRCPC***
Position	*Please state currently held position Medical Oncologist*
Date	*Please add the date form was completed (25-11-2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Please state full name:* ***Sebastien J. Hotte, MD, FRCPC***
Position	*Please state currently held position Medical Oncologist, Member of CCO HN and GU DACs*
Date	*Please add the date form was completed (25-11-2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☐	☒	☐	☐
Eisai	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Please state full name:* ***Shereen Ezzat, MD, FRCP(C) FACP***
Position	*Please state currently held position Professor of Medicine*
Date	*Please add the date form was completed (25-11-2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Please state full name* ***Cheryl Ho, MD, FRCPC***
Position	*Please state currently held position Medical oncologist, BC Cancer*
Date	*Please add the date form was completed (DD-MM-YYYY) 29-11-2020*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Eisai	☐	☒	☐	☐
Roche	☐	☐	☒	☐

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0221-000
Generic Drug Name (Brand Name)	Larotrectinib (Vitrakvi)
Indication	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.
Name of the Clinician Group	Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada, and other GI cancer-treating Clinicians.
Author of the Submission	Lead author: Dr. Eric Chen*Medical Oncologist, Princess Margaret Cancer Centre, Toronto. Disease site specialty: gastrointestinal cancers Co-Authors Dr. Howard Lim*, Medical Oncologist, BC Cancer Agency, Vancouver. Disease site specialty: gastrointestinal cancers. Dr. Brandon Meyers*, Medical Oncologist, Juravinski Cancer Centre, Hamilton, Disease site specialty(s): gastrointestinal cancers, head & neck cancers. Dr. Vincent Tam*, Medical Oncologist, Tom Baker Cancer Centre, Calgary. Disease site specialty: Gastrointestinal cancers, particular focus on hepatobiliary cancers. Dr. Yoo-Joung Ko*, Medical Oncologist, St. Michael's Hospital/Unity Health, Toronto, Toronto. Disease site specialty: gastrointestinal cancers. Dr. Petr Kavan*, Medical Oncologist, McGill University Health Centre. Disease site specialty: gastrointestinal (GI) cancers and neuroendocrine tumors (NETs). Dr. Ravi Ramjeesingh*, Medical Oncologist, Dalhousie University, Halifax. Disease site Specialty: Gastrointestinal cancers, particular focus on hepatobiliary cancers Dr. Brandon Sheffield, Anatomic Pathologist, William Osler Health System, Brampton. Specialty: biomarker testing Dr. Shahid Ahmed, Medical Oncologist, Saskatchewan Cancer Agency, Saskatoon. Specialty: Breast and gastrointestinal cancers

	Dr. Stephanie Snow, Medical Oncologist, QEII Hospital, Halifax. Specialty: Head and neck, thoracic and GI malignancies Dr. Michael Sawyer, Medical Oncologist/Hematologist, Cross Cancer Institute, Edmonton. Speciality: Gastrointestinal Malignancies, Neuroendocrine Tumors Dr. Kimberly Hagel, Medical Oncologist, Saskatchewan Cancer Agency, Regina. Dr. Rachel Goodwin, Medical Oncologist, The Ottawa Hospital Cancer Center, Ottawa. Specialty: Gastrointestinal & Neuroendocrine cancers Dr. Shaqil Kassam, Medical Oncologist, Southlake Regional Health Centre, Newmarket. Dr. Mark Vincent, Medical Oncologist, London Regional Cancer Program. Specialty: Lung and gastrointestinal cancer. Dr. Ron Burkes, Medical Oncologist, Mount Sinai Hospital/Princess Margaret Cancer Centre/UHN. Specialty: Colorectal and gastric cancers. Dr. Patricia Tang, Medical Oncologist, Tom Baker Cancer Centre, Calgary. Specialty: GI malignancies and breast cancer. Dr. Jennifer Spratlin, Medical Oncologist, Cross Cancer Institute, Edmonton. Specialty: GI malignancies. Dr. Mahmoud Abdelsalam, Medical Oncologist, The Moncton City Hospital, Moncton. *members of Canadian GI Oncology Evidence Network (CGOEN)
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The Canadian GI Oncology Evidence Network (CGOEN) is a recently formed virtual and inclusive network of Canadian GI Oncology clinicians who contribute to the knowledge of GI cancer and its treatments, including participating in clinical trials, conducting observational research, and involvement in local/provincial and national clinical guideline developments and health technology assessment. The Medical Advisory Board of Colorectal Cancer Canada works alongside the patient group to ensure our activities and health information are relevant and useful for patients and caregivers. The main responsibilities of this Advisory Board are to provide oversight of health related information; identify treatment and access issues; and provide a link to the Canadian medical community. Link:

https://www.colorectalcancercanada.com/about/staff-board-medical-advisory/

2. Information Gathering

Information is gathered through literature review, personal experience in treating patients with NTRK fusion, and virtual discussion among experts. While these clinical experts strongly support tumor agnostic funding for larotrectinib, our comments focus solely on larotrectinib use in GI cancers.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Response:

At the present time, there is no treatment option targeting NTRK fusions for this group of patients in Canada. All of these patients would have progressed on standard of care treatments, and would be cared for by healthcare providers with expertise in supportive/palliative care. Examples of standard of care treatments these patients might have received include 5-FU, oxaliplatin, irinotecan, bevacizumab, anti-EGFR antibodies (if RAS wild type), regorafenib/TAS-102 (through private insurance/funding) for colorectal cancers; cisplatin, gemcitabine, capecitabine, paclitaxel for cholangiocarcinoma patients; 5-FU, oxaliplatin, irinotecan, gemcitabine, nab-paclitaxel for pancreatic cancer patients; and sorafenib, levantinib, regorafenib or cabozantinib for hepatocellular carcinoma.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Response:

GI cancer patients with NTRK fusions all have advanced incurable disease and limited life expectancy. These patients may have symptoms from disease, such as pain, fatigue, loss of appetite and ascites. Therefore, the most important goals of any treatment will be to improve their overall survival, and quality of life by controlling their disease progression. As a result, patients will be able to maintain independence and the caregiver burden will be reduced.

With our improved understanding of tumor biology, more oncogenic driver mutations/fusions, such as NTRK fusions, will be identified. Although the number of patients with each oncogenic driver mutation/fusion is small and patients might have different tumor histologies, drugs targeting these mutations/fusions such as larotrectinib will be more effective with much higher response rates than in unselected patient populations and with favorable toxicity profiles. The availability of these drugs is resulting in changes cancer treatment paradigm.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

As mentioned previously, GI cancer patients with NTRK fusions all have advanced disease, and would have progressed on all currently available therapies. There are no therapeutic options currently for these patients. There is an urgent and unmet need for these patients.

Therefore, we concur with the findings of the pCODR Clinical Guidance Panel *Final Clinical Guidance Report: Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours (October 31, 2019)* in its general assessment of how Larotrectinib fills unmet needs in cancer treatments:

…the CGP believes there is an unmet need for better therapies in adult and pediatric patients with NTRK-gene fusion advanced solid cancers that either have no satisfactory alternative therapies or have exhausted currently available standard therapies.

And we concur specifically with the assessment of the Clinical Guidance Panel with respect to Gastrointestinal Cancers:

For patients with advanced colorectal cancer (CRC), there is an unmet need for better therapies in patients with chemorefractory disease (i.e. have progressed on two or more prior lines of therapy). … For patients with non-colorectal GI cancers, particularly pancreatic cancer and cholangiocarcinoma, there is a significant unmet need for better therapies.

And we concur with the assessment of the Clinical Guidance Panel with respect to pediatric patients:

In pediatric advanced solid cancers with an NTRK fusion, the CGP believes there is a significant unmet need for efficacious therapies.

Expert clinicians in Canada and worldwide recognize that the tumor-agnostic therapy, as demonstrated through the efficacy of larotrectinib in patients with TRK fusion cancers, is an extremely important advancement in the treatment of cancers based on their tumor genomics, rather than the tissue of origin.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

NTRK fusions are rare and found at low frequencies (commonly <1%) in a range of common tumour types and at higher frequencies in rare cancer types, so patients with TRK fusion cancers are a niche population. In these patients, NTRK fusion is the dominant genomic driver for cancer development and progression, targeting NTRK fusions result in high and rapid responses in patients, resulting in improvement in their quality of life and overall survival.

Since these patients will have no other treatment options, larotrectinib addresses an urgent and significant unmet need for these patients.

Peitrantonio et al, 2017[1] reported the extremely poor prognosis of patients with this rare subtype of mCRC -- where the Hazard Ratio for death was 2.17 among the NTRK fusion patients with a median overall survival (OS) of just 15.6 months vs 33.7 months in those without a NTRK fusion. This difference was persistent even after controlling for the subgroups that were microsatellite instability–high (MSI-high) vs microsatellite-stable (MSS). The extremely poor prognosis for patients with mCRC (that harbour a fusion, including NTRK fusions), is independent of the correlation with MSI-high in many cases, and further highlights the unmet need for treatment for this population.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Response:

In contrast to conventional chemotherapy, drugs like larotrectinib address the underlying molecular determinants of cancer and this is why these drugs are effective across a variety of cancer histologies.

For GI cancer patients with NTRK fusions, larotrectinib will be last possible treatment option after these patients have progressed on all currently available and funded therapies. It will be administered alone, not in combination with other drugs.

The development and availability of drugs like larotrectinib represent a paradigm shift in cancer therapy in that these drugs targeting the oncogenic driver mutation/fusion in a small number of patients with different tumor histologies. As a matter of fact, larotrectinib is the only 2nd drug approved by the Food and Drug Administration across a variety of tumor types as long as NTRK fusion is present. The 1st tumor agnostic drug is pembrolizumab in patients with microsatellite unstable tumors.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

Larotrectinib will only be used for patients with NTRK fusions. These patients would have progressed on all currently available treatments and there would be no other therapeutic options for them other than symptomatic support. It would be inappropriate and unethical to recommend that patients with NTRK fusions to try other treatments.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

Since intended patients have progressed on all other available/funded therapies, treating these patients with larotrectinib will not affect the sequencing of therapies.

In addition, these patients will have guarded prognosis, their survival will be less than 6 months if not treated. It is likely that they will not be alive or well enough for larotrectinib in a subsequent line of therapy.

[1] Filippo Pietrantonio, Federica Di Nicolantonio, Alexa B Schrock, et al ALK, ROS1, and NTRK Rearrangements in Metastatic Colorectal Cancer, JNCI: Journal of the National Cancer Institute, 2017; 109(12), https://doi.org/10.1093/jnci/djx089

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

Larotrectinib is indicated for GI cancer patients with NTRK fusions who have progressed on all currently available/funded therapies. Since this indication is based on the presence of a dominant cancer driver mutation, larotrectinib produces a much higher response rate and cancer control than conventional therapies.

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

Patients will be identified through genomic screening. While we recognize that there will be challenges in identifying patients with NTRK fusions, clinicians are familiar and comfortable with genomic testing for various mutations/fusions, such as RAS, Her-2, EGFR, ALK etc. There are existing a variety of provincial / local genomic testing programs, such as **O**ntario-wide **C**ancer **TA**rgeted **N**ucleic **A**cid **E**valuation (OCTANE), in which NTRK fusions are included. We believe that patients can be identified appropriately. We believe that the substantial effect on survival demonstrated with larotrectinib in patients with NTRK fusions constitutes a major breakthrough in precision oncology, necessitating its use in Canadian patients.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients without NTRK fusions should not be treated with larotrectinib. Based on our current knowledge, only patients with NTRK mutations should be treated with larotrectinib.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Cocco et al. have suggested a diagnostic framework to improve the selection of patients eligible for gene fusion testing. The frequency of NTRK fusion is higher in BRAF/RAS wild-type, MSI-H colorectal carcinoma[2]. If testing for MLH1 promoter hypermethylation is also available, the testing population can be further enriched to get as high as ~40% incidence of NTRK fusions. These tests are already being routinely performed across Canadian centres, and thus could lead to “smart use” of testing resources.

[2] Emiliano Cocco, Jamal Benhamida, Sumit Middha, et al, Colorectal Carcinomas Containing Hypermethylated MLH1 Promoter and Wild-Type BRAF/KRAS Are Enriched for Targetable Kinase Fusions, Cancer Res 2019; 79(6):1047-1053;

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

Patients will be assessed for side effects, changes in their clinical status, laboratory investigations and imaging such as CTs. These measures are similar to those used in clinical trials.

6.9. What would be considered a clinically meaningful response to treatment?

Response:

Patients will be considered to have meaningful responses when they experience less pain with reduction in the use of pain medications, improved sense of well-being, being more active clinically and able to carry out more activities of daily living.

Additional endpoints to consider include time to deterioration of symptoms due to progressive disease, and longer survival, which can be inferred from the non-randomized data from the considerable Duration of Response (DOR) and Overall Survival (OS) seen in these trials that exceeds what we would see with Best Supportive Care (BSC only).

6.10. How often should treatment response be assessed?

Response:

Patients are seen and assessed clinically every 2-4 weeks or more frequently if needed while they are on treatment with larotrectinib. Imaging is usually performed every 2-3 months.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

Patients with clear evidence of disease progression, such as deterioration in clinical status, objective progression on imaging should be discontinued from larotrectinib treatment.

6.12. What settings are appropriate for treatment with the drug under review?

Response:

Patients will be assessed and prescribed larotrectinib at cancer centers, with the medication administered at home as an outpatient as it is an oral medication and does not require a medical setting for administration.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Response:

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

One of us, Dr. Eric Chen, a medical oncologist at the Princess Margaret Cancer Center, has personal experience in treating a NTRK positive colorectal cancer patient with larotrectinib. The patient has consented for her case to be discussed without disclosing any identifying information. The patient is a 55-year old woman who was diagnosed of metastatic colon cancer in Feb 2017. Her tumor genomic screening at the time showed MLH1/PMS2 loss, RAS/RAF wild type. She was treated with FOLFOX initially, followed by FOLFIRI and pembrolizumab. She was discovered to brain metastases in Feb 2018 and had surgical resection and radiation. She also received radiation on 3 occasions to a left chest wall lesion. By March 2020, the chest wall lesion became ulcerated and caused significant pain and discomfort, severely impacting her quality of life. She was found to be have a LMNA-NTRK1 fusion through the FastTRK program, and was started on larotrectinib 100 mg BID in April 2020. Within 2 weeks, her pain improved and the requirement for analgesics reduced. The chest wall lesion started to heal, and it completed closed by June 2020. As of the date of this submission, she is tolerating larotrectinib and continues to do well clinically.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

Not to my knowledge

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

Not to my knowledge

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Eric Chen*
Position	*Staff Physician, Department of Medical Oncology and Hematology, Princess Margaret Cancer Center*
Date	*03-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Shahid Ahmed*
Position	*Medical oncologist, Professor, and Medical Director of Academic in Saskatchewan Cancer Agency, Saskatoon, University of Saskatchewan*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
MERCK Canada	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Stephanie Snow*
Position	*Medical Oncologist*
Date	*12-11-2020*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☐	☒	☐	☐
Merck	☐	☐	☒	☐
Pfizer	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Ronald Burkes*
Position	*Medical Oncologist*
Date	*12/11/2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name Merck	☒	☐	☐	☐
Add company name Bayer	☒	☐	☐	☐
Add or remove rows as required Pfizer	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Brandon Sheffield*
Position	*Pathologist, William Osler Health System*
Date	*12/11/2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Eli Lilly	☐	☐	☐	☒
Pfizer	☐	☐	☐	☒

Roche	☐	☐	☐	☒

Declaration for Clinician 6

Clinician Information	
Name	*Shaqil Kassam MD. MSc. FRCPC*
Position	*Medical Oncologist*
Date	*13/11/2020*
✓ ☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	x☐	☐	☐	☐
Merck	x☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Michael Sawyer*
Position	*Senior Medical Oncologist Cross Cancer Institute, Professor University of Alberta*
Date	*15-Nov-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Merck	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Mylan	☐	☒	☐	☐
Ipsen			☒	
Eisai	☒			
Celgene	☒			
Leo	☒			

Declaration for Clinician 8

Clinician Information	
Name	*Jennifer Spratlin*
Position	*Medical Oncologist, Cross Cancer Institute*
Date	*20-11-2020*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Patricia Tang*
Position	*Medical Oncologist, Tom Baker Cancer Centre*
Date	*21-11-2020*
X	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	x	☐	☐	☐
Novartis	x	☐	☐	☐
Eisai	x			
AMGEN	x			
ASTRAZENECA	x			
ROCHE	x			
Merck	x	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*Mahmoud Abdelsalam*
Position	*Medical Oncologist*
Date	*25-11-2020*

X	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Roche	X			
EMD Serono	X			
Astellas	X			
Melanoma meeting	X			
Novartis			x	
Sanofi Genzyme		x		
J and J Janssen		x		
Merck			x	
Pfizer		x		
Astra Zeneca		x		
Ipsen		x		
Odonate	x			
Takeda	x			
GPO Oncology Health Day	x			
BMS		x		
Genomic Health	x			
Taiho		x		
Exactis	x			
IO Symposium		x		

Declaration for Clinician 11

Clinician Information	
Name	*Mark David Vincent MD FRCPC*
Position	*Consultant Medical Oncologist, London Regional Cancer Program*
Date	*27-11-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐

Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 12

Clinician Information	
Name	*Dr. Rachel Goodwin*
Position	*Medical Oncology*
Date	*December 1, 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Ipsen (research grant)	☐	☐	☐	☒
Bayer (consultant + speaker)	☒	☐	☐	☐
Eisai (consultant)	☒	☐	☐	☐
Ipsen (consultant money)	☒	☐	☐	☒
AAA (consultant)	☒	☐	☐	☐
Pfizer (consultant)	☒	☐	☐	☐
Roche (consultant)	☒	☐	☐	☐
Merck (consultant)	☒	☐	☐	☐

Declaration for Clinician 13

Clinician Information	
Name	*Howard Lim*
Position	*Medical Oncology*
Date	*December 3, 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Roche	☐	☐	☒	☐
BMS	☐	☒	☐	☐
Ipsen	☒	☐	☐	☐

Declaration for Clinician 14

Clinician Information	
Name	*Ravi Ramjeesingh*
Position	*Medical Oncologist, Division of Medical Oncology, Dalhousie University*
Date	*03-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 15

Clinician Information	
Name	*Yoo-Joung Ko*
Position	*Medical Oncologist, St. Michael's Hospital/Unity Health, Toronto*
Date	*04-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 16

Clinician Information	
Name	*Dr. Vincent Tam*
Position	*Medical Oncology*
Date	*December 1, 2020*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer (Research/education grant)	☐	☒	☐	☐
BMS (Advisory board)	☒	☐	☐	☐
Eisai (Advisory board)	☐	☒	☐	☐
Eisai (Research/education grant)	☐	☐	☒	☐
Ipsen (Advisory board)	☐	☒	☐	☐
Ipsen (Research/education grant)	☒	☐	☒	☐
Roche (Advisory board)	☐	☒	☐	☐
Roche (Research/education grant)	☐	☐	☒	☐

Declaration for Clinician 17

Clinician Information	
Name	*Kimberly Hagel*
Position	*Medical Oncologist, Allan Blair Cancer Centre*
Date	*04-DEC-2020*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☒	☐	☐	☐
Leo	☒	☐	☐	☐
Astra Zeneca	☒	☐	☐	☐
Pfizer	X			
Sanofi	X			

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**larotrectinib (Vitrakvi)**
Indication	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee**
Author of the Submission	**Dr. Erin Kennedy, Dr. Jim Biagi, Dr. Christine Brezden, Dr. Tim Asmis**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information based on larotrectinib's publications and clinician experience.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Currently, there are no publicly funded targeted treatments for GI cancers.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

In a heavily pretreated population, response rate, duration of response, disease control, progression free time period, minimize adverse effects and improve health-related quality of life

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

In a pretreated population (e.g., colon patients were heavily pretreated):

- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients with NTRK marker fusion protein

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

NTRK is a pathogenic driver mutation. Larotrectinib is a novel agent and the current data support use in later line of treatment. Larotrectinib is expected to be used sequentially after current available treatment.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Yes. These are previously treated patients.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

After current standard of care treatments

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with good performance status and have the NTRK fusion protein are most likely to respond

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Companion diagnostic for NTRK mutation will be needed

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients with poor performance status and does not have NTRK mutation

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Via companion diagnostic (e.g., NGS)

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Imaging, tumour markers, clinical improvement, performance status

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

All of the above (except 2nd bullet point)

6.10. How often should treatment response be assessed?

Response:

Tumour markers – every 4 weeks; Radiologically every 8-12 weeks; bloodwork and physical exam every 4 weeks

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression and certain adverse events

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Larotrectinib is an oral cancer drug and will be used in outpatient/community setting

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** Not applicable

7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: Real world evidence will likely identify better efficacy and tolerability with larotrectinib when used in an earlier line. Consideration of reflexive tumour agnostic testing program as part of companion diagnostic, e.g., as part of NGS panel testing, may be more cost effective.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the DAC in completing this input.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each</u>**

clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Erin Kennedy*
Position	*Surgeon*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Jim Biagi*
Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Christine Brezden*

Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Tim Asmis*
Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**larotrectinib (Vitrakvi)**
Indication	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Head, Neck and Thyroid Cancer Drug Advisory Committee**
Author of the Submission	**Dr. John Kim** **Dr. Martin Smoragiewicz** **Dr. Sebastien Hotte (*for salivary gland portion of the clinician input)**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information based on larotrectinib's publication and clinician experience.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

For thyroid tumours – radioactive iodine refractory population, differentiated thyroid cancer – papillary, follicular – sorafenib and lenvatinib are approved but only lenvatinib is funded

Salivary gland – currently there is no standard of care (SOC); chemotherapy provides minor responses and usually short-lived

Mammary analogue secretory carcinoma of salivary glands – NTRK fusion mutation is pathognomonic for this disease – currently there is no treatment option

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Delay disease progression, prolong life, disease control in a majority of patients

Toxicity profile of larotrectinib compares favourably to lenvatinib

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*

- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Thyroid cancer – limited treatment options with TKI; NTRK fusion mutation is usually not found with other driver mutations

Salivary gland tumours – no treatment options

Mammary analogue secretory carcinoma of salivary glands – NTRK fusion mutation is pathognomonic for this disease – currently there is no treatment option

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Greatest unmet need – patients with salivary gland tumours

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Salivary gland – larotrectinib can potential be used first line due to no treatment options

Thyroid tumour – larotrectinib may be used in TKI naïve or TKI-treated population

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

For diseases with no/limited treatment options or treatment options with limited benefits, e.g., salivary gland tumours, larotrectinib has high response rate and would be preferred over current available treatment

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Salivary gland – larotrectinib can become standard of care

Thyroid cancer – larotrectinib may be used sequentially with TKI

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients who are NTRK+

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Companion diagnostics; NGS would be the optimal way to test

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Non NTRK+ population

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Yes. Through companion diagnostics.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Imaging and clinical assessment

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Improvement in symptoms

6.10. How often should treatment response be assessed?

Response:

Every 3 to 4 months

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression and unacceptable toxicities

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response: Community setting – larotrectinib is a take home cancer drug
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** NA
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: Mammary analogue secretory carcinoma (MASC) of salivary glands – NTRK fusion mutation is pathognomonic for this disease and larotrectinib will have a positive impact. Any NTRK+ patients will have a high likelihood of positive impact with larotrectinib.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

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2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each</u>**

clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Clinician Information	
Name	*Dr. John Kim*
Position	*Radiologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	Dr. Sebastien J Hotte, MD, FRCPC
Position	Medical oncologist; Associate Professor. Member of GU and HN Drug Advisory Committees (DAC)s.
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
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Bayer	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	Dr. Martin Smoragiewicz

Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
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Add or remove rows as required	☐	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**larotrectinib (Vitrakvi)**
Indication	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancer Drug Advisory Committee**
Author of the Submission	**Dr. Gail Darling, Dr. Andrew Robinson, Dr. Natasha Leighl, Dr. Peter Ellis**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information based on larotrectinib's updated analysis (Hong 2020) and clinician experience.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Currently, NTRK-fusion positive NSCLC is treated as standard therapy for non-driver mutation lung cancer. Platinum doublet chemotherapy and PD-1 immunotherapy are given either in combination first line therapy, or in sequence. After failure of immunotherapy and doublet chemotherapy, a subset of patients will go on to receive docetaxel therapy depending on performance status and patient preferences. When chemotherapy and immunotherapy fail, some of these patients may receive erlotinib therapy for non-EGFR mutation lung cancer as third or fourth line therapy.

For the patient population requested ("have no satisfactory treatment options"), a number of patients find docetaxel 'unsatisfactory", while some also find immunotherapy "unsatisfactory" (due to contraindications).

For "patients with no satisfactory treatment options" - i.e. no further systemic therapy that is tolerable or useful, the treatment options are palliative care.

The ASCO guidelines on stage IV NSCLC with driver mutations, that will be released in the near future, recommend larotrectinib and entrectinib as first line therapy in patients with TRK fusion

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Prolonging life and improving quality of life/preventing deterioration in quality of life are always important. For driver mutation positive non-small cell lung cancer, delaying disease progression and causing tumour shrinkage are expected to achieve these goals.

Molecularly targeted therapies with high response rates like larotrectinib, in general result in longer periods of disease control, fewer AEs and better QoL.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Almost all patients who have systemic therapy for stage IV/advanced NSCLC will have their therapy stop working. The goal of patients (prolong life/prolong quality of life) continues even in the post-initial progression setting. The goals/needs of prolonging QOL and length of life are only partially met for a modest proportion of patients.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients with NTRK fusion positive cancer is a niche population of patients. The availability of molecularly targeted therapy for this rare group of patients would meet an unmet need.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

For many patients, the treatment would be used in lung cancer after chemotherapy and immunotherapy. In some patients, it would be used instead of chemotherapy/immunotherapy. Often driver mutation therapies in lung cancer are used as first line therapy in the metastatic setting, particularly when response rates are in the 60-80% range. The data from the larotrectinib studies showing a 75% response rate and a similar drug (entrectinib) showing a 70% response rate, suggest that for the very small number of NTRK positive NSCLC, first line larotrectinib may be an option.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

I think it's inappropriate to recommend this as no one knows the answer, and it's inappropriate to make recommendations without data. You could say "chemotherapy/immunotherapy may be considered"

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

After larotrectinib is failed, most likely the next line of therapy would be platinum doublet chemotherapy with pemetrexed, and then immunotherapy at progression.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with an NTRK fusion positive metastatic NSCLC would be most likely to respond. They are also in most need of an intervention.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Currently challenged by testing availability. We are doing IHC followed by NGS, although in reality these fusions are on current NGS panels (the same panels we should/will be using for k-ras, b-raf, RET, ROS, MET, EGFR..)

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients without NTRK fusions.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Yes, test for NTRK.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Yes

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:
Stabilization, no deterioration of symptoms, improvement in symptoms, reduction in frequency or severity of pain/SOB/cough/anorexia/cachexia.

6.10. How often should treatment response be assessed?

Response:

Clinical assessment every 4-8 wks, CT scans every 3-6 months.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:
- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Systemic disease progression (i.e. progression in more than areas that can be treated easily with local therapies).

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Outpatient clinic, community oncology, occasionally hospitalized patients.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

No

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

No

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the Lung DAC in completing this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Gail Darling*
Position	*Surgeon*
Date	*03-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Andrew Robinson*
Position	*Medical Oncologist*
Date	*03-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Natasha Leighl*
Position	*Medical Oncologist*
Date	*17-Nov-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Peter Ellis*
Position	*Medical Oncologist*
Date	*03-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

Clinician Input Template for CADTH pan-Canadian Oncology Drug Review Program

Before completing this template, be sure to register with the pCODR program. Please visit www.cadth.ca/pcodr/registration for information about the registration process.

1. About the Registered Clinician

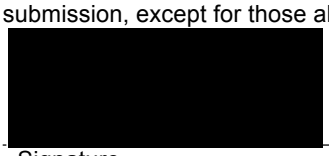
Name of Registered Clinician	**Paul Wheatley-Price**
Title	**Associate Professor, University of Ottawa. Medical Oncologist, The Ottawa Hospital**
Disease Specialty (if applicable)	**Medical Oncology**
Province	**Ontario**
Organization Membership (if applicable, national or provincial)	**President of Lung Cancer Canada**
Email	[redacted]
Telephone Number	[redacted]

If this is a joint clinician input submission, please indicate the organization this submission is on behalf of, as well as list the names of the other clinicians and disease site specialty (if applicable). Please note that all clinicians listed must also register with CADTH and complete conflict of interest declaration forms.

Dr Barbara Melosky
Dr Randeep Sangha
Dr Ronald Burkes
Dr Geoffrey Liu
Dr Donna Maziak
Dr Quincy Chu
Dr Kevin Jao
Dr Jeffrey Rothenstein
Dr Rosalyn Juergens
Dr Callista Phillips
Dr David Dawe
Dr Catherine Labbé
Dr Nicole Bouchard
Dr Normand Blais
Dr Cheryl Ho
Dr Sunil Yadav
Dr Parneet Cheema
Dr Stephanie Snow

Confirmation of Authorship

I declare that I am the author of this submission and I confirm that no other parties have written or participated in the writing of the submission, except for those above named in this joint submission (if applicable).



Signature

2020/11/17

Date (YYYY/MM/DD)

CADTH

2. About the Drug and Indication Under Review

CADTH pCODR Project Number	**pCODR 10221**
Generic Drug Name (Brand Name)	**Larotectinib (Vitraki)**
Indication	**Larotrectinib (Vitraki) for the treatment of adult and pediatric patients with solid tumors that:** **• have a Neurotrophic Tyrosine Receptor Kinase (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.**
Funding Request	**Same as indication**
Trial(s) Being Submitted to pCODR[a]	**NCT02122913, SCOUT (NCT02637687), and NAVIGATE (NCT02576431)**
Health Canada Status	**Approved (7-10-2019)**
FDA	**Approved (11-26-2018)** **For adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.**
European Medicines Agency Status	**Approved (9-19-2019)**
Practice Guidelines[a]	**NCCN Guidelines for: Colon, Head and Neck, Melanoma, NSCLC, Thyroid, Sarcoma, Breast, Pancreatic, and Hepatobiliary** **ASCO Guidelines for: Breast Cancer, Colorectal Cancer, Lung Cancer, Pancreatic Cancer** **ESMO Guidelines for: Soft Tissue and Visceral Sarcomas, Gastrointestinal Stromal Tumours, Thyroid Cancer, Cutaneous Melanoma, Colorectal Cancer, NSCLC, Cancer of the Pancreas, Biliary Cancer, and Breast Cancer**
Provincial Funding of Current Treatments or Funding Algorithm	**PAG identified that there is no standard of care for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harboring a NTRK gene fusion. Treatment is dependent on the specific type of solid tumour, clinical trials may be offered to patients harboring a NTRK gene fusion. For patients who have experienced disease progression on all available treatment options, best supportive care would be available. PAG concluded that the relevant comparator for this drug submission would be best supportive care. Since the latter is meant to alleviate patient discomfort, PAG would appreciate demonstration that larotrectinib improves quality of life or other outcomes meaningful to patients, relative to usual care.**

[a] Please note that access to some online publications require subscription.

3. Key Questions for Clinician Input

3.1 Current Treatment(s) for the Indication Under Review:

- If this is different than what is listed in the Provincial Funding of Current Treatments or Funding Algorithm on the previous page, identify the treatment(s) you would use.
- If more than one treatment is funded in your province, identify the treatment(s) that would be the most appropriate comparator for the drug under review.

NTRK cancers, across a broad range of malignancies, represent a new paradigm in oncology. The concept of a 'tumor agnostic' driver mutation has not previously been so readily identifiable until NTRK.
As a result, the current treatment is diverse depending on the standard of care treatment options in each known cancer.
That being said, there are no approved therapies for NTRK cancer until now.
Specifically in lung cancer, treatment options include chemotherapy (platinum doublet chemotherapy) and immunotherapy (either monotherapy or in combination with chemotherapy), and then best supportive care.
Larotrectinib would therefore represent an additional line of therapy, and for patients who would have not been eligible for standard treatments because of comorbidities or performance status, larotrectinib represents the only line of care (as it is extremely well tolerated), and will be discussed in this document.

3.2 Eligible Patient Population

Describe the patients for whom you would use the new treatment. Examples can include, but are not limited to, the following questions:

- Does the patient population in the reimbursement request align with the need identified in your clinical practice? Is there an unmet need?
- Can the inclusion and exclusion criteria of the clinical trial be applied in clinical practice?
- Is there a subgroup of patients beyond the study population that you would like to use the new treatment in? Is there a subgroup of patients within the study population that the new treatment should be limited to?

NTRK cancers are not common, and in the lung cancer population represents only 0.23% of cases, but of course they are present in a wide range of pediatric and adult malignancies.

Due to the extremely impressive efficacy and tolerability date, the larotrectinib eligible population is likely all patients with a cancer that has been demonstrated to harbor an NTRK fusion driver mutation.

Regarding eligibility, the trials included in the submitted analysis pleasingly did include patients with ECOG PS 0-3, and with a wide range of numbers of prior treatments. The efficacy was seen across NTRK fusion types, cancer types, ages, prior treatments or the presence of brain metastases. This means that the trial population hopefully largely is reflective of a real world practice.

In terms of subgroups, because the efficacy was seen across the aforementioned groupings and across cancer types, it is our hope that pCODR will not single out subgroups for approval, but rather approve this for all NTRK fusion cancers, regardless of other factors such as cancer type, line of therapy, age or functional status.

In the 2019 pCODR submission the pERC panel 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, inability to interpret variation in outcomes by tumour type, lack of evidence as to whether or not the*

NTRK gene fusion is an oncogenic driver in all tumour types, and lack of historical evidence on outcomes with available therapies in patients with the gene fusion'. By the nature of the scarcity of this cancer, the risk of this conclusion is that it can never a priori be satisfactorily challenged. However the expanded cohort of data now submitted (approximately triple the initial submission) does address many of these concerns, with efficacy confirmed at the very high rate across tumour types, longer follow up demonstrating the durability of effectiveness, and increasing evidence that NTRK itself is not independently prognostic for favourable outcomes.

3.3 Relevance to Clinical Practice

Do you have experience with using the treatment (through clinical trials, manufacturer's access program, private drug insurance) under review?

☒Yes ☐No

- How or when would you use the new treatment? Is there any population/subpopulation where you particularly want to use this drug?
- How is the new treatment different than currently available treatments with respect to efficacy, safety, and tolerability?
- Are there contraindications to using the new treatment? Are there contraindications to current treatments that would make the new treatment favourable?

Please note: Scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission and a rigorous, independent literature search.

Date from the European Society of Medical Oncology (ESMO) 2020 meeting (Italiano et al) describes the Growth Modulation Index, which is a method to compare progression free survival on larotrectinib with the previous line of therapy in the same patient. This demonstrates the significantly higher efficacy in terms of important time points compared to standard of care. Further, the Hong et al manuscript (Lancet Oncology 2020) confirms high response rates (79%) and durable responses with a median duration of response of 35.2 months.

Specifically in the lung cancer subgroup, NTRK fusions are typically identified at a younger age than most lung cancers (median 47 years, compared to about 70 in lung cancer overall). In the lung cancer group, the partial response rate to prior therapies (such as chemotherapy or immunotherapy) was only 14%, but when treated with larotrectinib the response rate was 71% (Drilon et al, ESMO 2020). Of note, 50% of this lung cancer group also had brain metastases, with partial response (57%) or stable disease (29%) meaning a clinical benefit rate of 86%.

Therefore for lung cancer patients with an NTRK fusion it is likely that clinicians would use this as the 1st line of therapy after the NTRK fusion has been identified. For patients with NGS analysis at diagnosis this would be 1st line treatment. As this should be available to all NTRK patients there are no specific subgroups to be highlighted, although in the lung cancer population one can foresee that the CNS benefits would also mean patients can be spared the potential toxicities of CNS radiotherapy, as has been seen in other oncogene driven lung cancer subtypes with pCODR approved targeted therapies (osimertinib in EGFR+ NSCLC and alectinib in ALK+NSCLC).

While there can never be randomized data because of the rarity of this disease, it is clearly and unequivocally superior to standard therapies.

Standard treatments for lung cancer would be chemotherapy or immunotherapy, that are widely used and the toxicity profiles well understood in terms of emesis, neutropenia, alopecia and immune-related toxicities etc.

For larotrectinib there is now expanded safety data in the Hong et al paper, where among 260 patients evaluated for safety, grade 3 or 4 treatment-related adverse events were extremely uncommon (<3%). Relative to toxicities from standard non-targeted systemic therapy this is obviously has high clinically relevance.

There are few contraindications to larotrectinib, but patient age and performance status or comorbidities are more

frequently a contraindication (relative or absolute) to current standard of care options.

In conclusion to this question, in 2019 in the pERC final recommendation the committee stated that they were '*uncertain that there is a net clinical benefit of larotrectinib treatment compared with available treatment options or best supportive care'*. In this new submission with mature and more granular data, it is clear that larotrectinib has a major and clear benefit compared to available options.

3.4 Sequencing and Priority of Treatments

- Please describe how the new treatment could be sequenced with current treatment(s), if appropriate.
- In your opinion, in the event that the drug under review becomes available for funding in your jurisdiction, would the new treatment be a replacement of current treatment(s) or another option?

This would be an additional option for patients, but would automatically become the standard of care based on factors discussed (high response rate, including CNS response; long duration of response; low adverse event rate).
In lung cancer, this would become the first option when disease progression occurs after the NTRK fusion has been discovered. Therefore depending on the timing of NTRK testing, the line of therapy would vary, which is in line with the published clinical data where efficacy was independent of line of therapy.

3.5 Companion Diagnostic Testing

- If companion diagnostic testing is required for the new drug, is the test available in your jurisdiction? Is it funded by your jurisdiction? What concerns, if any, do you have on the test and turnaround time for test results? Are there specific considerations to a testing algorithm that you think would be important to share with the pCODR Expert Review Committee?

NTRK gene fusions can be detected either through next generation sequencing (NGS), optimally using DNA and RNA platforms. It can also be detected as a stand alone test, which is a 2 part process of IHC, which if positive then leads onto a confirmatory NGS panel.
For lung cancer, currently many centres do perform NGS panels, and this will only increase with time as multiple molecular subtypes of lung cancer will required identification (for example, EGFR, ALK, ROS1, BRAF, KRAS G12C, Her2, c-Met exon14, ret fusion and NTRK fusions).
For centres who offer a more limited panel at present, NTRK testing can be reserved for those who are already pan-negative from the initial molecular panel, as NTRK is not reported to co-exist with other driver mutations.

IMPLEMENTATION QUESTIONS

- **With respect to NTRK gene fusion testing, how are patients currently being tested?**

Across all tumour types, this is difficult to answer, but hopefully high testing rates in cancers like infantile fibrosarcoma and secretory breast cancer where NTRK fusion is present in >90% cases. In those malignancies where NTRK fusions are rare, like lung cancer, testing varies from institution to institution and numbers are not available.
However it is reasonable to assume in general, and specifically in lung cancer, that as NGS testing generally increases more of these cases will be identified.
It is important to note that NTRK testing will almost certainly NOT lead to increased testing costs to the healthcare system, as currently and in the future it is overwhelmingly going to be part of an NGS panel that will also be reporting all the other known and approved molecular driver mutations (such as EGFR).

- **Should all adult and pediatric patients with locally advanced or metastatic solid tumors be tested, or specific types of solid tumors?**

We believe NTRK gene fusions are tumour agnostic, therefore testing policies should correspondingly be broad. There are two primary processes that could be followed, illustrated by the situation with lung cancer. All advanced non-small cell lung cancer cases should have NTRK testing, either as part of an initial NGS panel, or as a follow up test if all routinely tested oncogenic driver mutations are absent.

- **Should testing be available at all cancer centres?**

Lung Cancer Canada has called for timely molecular testing to be available to all patients diagnosed with lung cancer, regardless of location. With newer NGS technologies that is becoming more feasible.
Therefore if local NGS testing is available, that should be the first choice. If not available, then secondary NTRK testing after common mutations have been excluded is a reasonable option.

- **When should testing be completed (i.e., at diagnosis or at time of relapse)?**

As many patients may not have other treatment options, or have contraindications to other treatment options, testing ideally will be completed at diagnosis.
For lung cancer this can be at diagnosis of advanced disease, but it should be noted that in other tumor types with an NTRK gene fusion identified, the use of the larotrectinib in advanced disease was efficacious to the extent of subsequently allowing surgical resection of disease.

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Paul Wheatley-Price**
Name of drug and indication under review:	**Larotrectinib for metastatic NTRK gene fusion positive solid tumors**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

1. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

   ☒ Yes
   ☐ No

   If no, please go to Section B.

2. What form of payment did you receive? (Check all that apply.)

   ☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
   ☐ Conference attendance
   ☐ Royalties
   ☐ Gifts
   ☐ Honoraria
   ☐ Program or Operating Funding (e.g., website)
   ☐ Research/educational grants
   ☐ Travel grants
   ☐ Sponsorship of events
   ☐ Other, please specify: _____

3. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	Advisory Role	☐	☒	☐	☐
Bayer	Advisory Role	☒	☐	☐	☐
Boehringer Ingeihelm	Advisory Role	☒	☐	☐	☐

Bristol-Myers Squibb	Advisory Role	☒	☐	☐	☐
Merck	Advisory Role	☐	☒	☐	☐
Norvatis	Advisory Role	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17, 2020 — Date

Paul Wheatley-Price — Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Barbara Melosky**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

4. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

   ☒ Yes
   ☐ No

   If no, please go to Section B.

5. What form of payment did you receive? (Check all that apply.)

   ☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
   ☐ Conference attendance
   ☐ Royalties
   ☐ Gifts
   ☐ Honoraria
   ☐ Program or Operating Funding (e.g., website)
   ☐ Research/educational grants
   ☐ Travel grants
   ☐ Sponsorship of events
   ☐ Other, please specify: _____

6. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis	Advisory Board	☒	☐	☐	☐
Roche	Advisory Board	☒	☐	☐	☐
Merck	Advisory Board	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No, I do not have holdings or other interests in organizations that may have a direct or indirect interest in the drug under review.

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No, I do not have personal or commercial relationships either with a drug or health technology manufacturer or other interest groups.

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Barbara Melosky
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Randeep Sangha**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

7. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

   ☐ Yes
   ☒ No

   If no, please go to Section B.

8. What form of payment did you receive? (Check all that apply.)

   ☐ Advisory role (e.g., advisory boards, health technology assessment submission advice)
   ☐ Conference attendance
   ☐ Royalties
   ☐ Gifts
   ☐ Honoraria
   ☐ Program or Operating Funding (e.g., website)
   ☐ Research/educational grants
   ☐ Travel grants
   ☐ Sponsorship of events
   ☐ Other, please specify: _____

9. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
		☐	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

Dec 3, 2020 — Date

Randeep Sangha — Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Ronald Burkes**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

10. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

    ☐ Yes
    ☒ No

    If no, please go to Section B.

11. What form of payment did you receive? (Check all that apply.)

    ☐ Advisory role (e.g., advisory boards, health technology assessment submission advice)
    ☐ Conference attendance
    ☐ Royalties
    ☐ Gifts
    ☐ Honoraria
    ☐ Program or Operating Funding (e.g., website)
    ☐ Research/educational grants
    ☐ Travel grants
    ☐ Sponsorship of events
    ☐ Other, please specify: _____

12. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Ronald Burkes
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Geoffrey Liu**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

13. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

    ☒ Yes
    ☐ No

    If no, please go to Section B.

14. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)	☐ Program or Operating Funding (e.g., website)
☐ Conference attendance	☒ Research/educational grants
☐ Royalties	☐ Travel grants
☐ Gifts	☐ Sponsorship of events
☐ Honoraria	☐ Other, please specify: _____

15. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Takeda Canada	Advisory Board, Health Technology Assessment Submission Advice, Speaker's Bureau, past 10 years	☐	☐	☒	☐
Takeda Canada	(To institution, not individual) Observational Study funding, past 10 years	☐	☐	☐	☒
Hoffman La Roche	Advisory Board, Health Technology Assessment Submission Advice, past 10 years	☐	☐	☒	☐
Pfizer	Advisory Board, Health Technology Assessment Submission Advice, part 10 years	☐	☐	☒	☐
AstraZeneca	Advisory Board, Health Technology Assessment Submission Advice, Speaker's Bureau, past 10 years,	☐	☐	☒	☐
AstraZeneca	(To institution, not individual) Observational Study funding, past 10 years	☐	☐	☐	☒
Bristol Myers Squibb	Advisory Board	☒	☐	☐	☐
Boehringer Ingerheim	(To institution, not individual) Observational Study funding, past 10 years	☐	☐	☒	☐
Abbvie	Advisory Board, past 10 years	☐	☒	☐	☐
Merck	Advisory Board, Health Technology Assessment Submission Advice, past 10 years	☐	☒	☐	☐
EMD Serono	Speaker's Bureau, past 10 years	☒	☐	☐	☐
Novartis	Advisory Board,past 10 years	☐	☐	☒	☐
Glaxo Smith Kline	Advisory Board, past 10 years	☐	☒	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

17 November, 2020
Date

Geoffrey Liu
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Donna Maziak**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

16. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☐ Yes
☒ No

If no, please go to Section B.

17. What form of payment did you receive? (Check all that apply.)

☐ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☐ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

18. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Donna Maziak
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Quincy Chu**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

19. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

20. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria
☐ Program or Operating Funding (e.g., website)
☒ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

21. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

CADTH

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie	Advisory Board and Honoraria	☒	☐	☐	☐
Amgen	Advisory Board and Honoraria	☒	☐	☐	☐
Astra Zeneca	Advisory Board and Honoraria	☐	☐	☒	☐
Boehringer Ingeiheim	Advisory Board and Honoraria	☐	☒	☐	☐
Bristol-Myers Squibb	Advisory Board and Honoraria	☐	☒	☐	☐
Eisai	Advisory Board and Honoraria	☒	☐	☐	☐
Merck	Advisory Board and Honoraria	☐	☐	☒	☐
Novartis	Advisory Board and Honoraria	☐	☒	☐	☐
Pfizer	Advisory Board and Honoraria	☐	☒	☐	☐
Roche	Advisory Board and Honoraria	☐	☒	☐	☐
Astra Zeneca	Research Funding	☐	☐	☐	☒
Bristol-Myers Squibb	Educational Grant	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Quincy Chu
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Kevin Jao**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

22. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

23. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☐ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

24. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol-Myers Squibb	Advisory Role	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Kevin Jao
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Jeffrey Rothenstein**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

25. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

26. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)	☐ Program or Operating Funding (e.g., website)
☐ Conference attendance	☐ Research/educational grants
☐ Royalties	☐ Travel grants
☐ Gifts	☐ Sponsorship of events
☒ Honoraria	☐ Other, please specify: _____

27. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Roche	Advisory Role and Honoraria	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Jeffrey Rothenstein
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Rosalyn Juergens**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

28. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

29. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

30. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol-Myers Squibb	Advisory role and honoraria	☒	☐	☐	☐
Astra Zeneca	Advisory role and honoraria	☐	☒	☐	☐
Merck Sharp and Dohme	Advisory role and honoraria	☒	☐	☐	☐
Roche	Advisory role and honoraria	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 17th 2020
Date

Rosalyn Juergens, MD PhD
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Callista Phillips**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

31. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

    ☒ Yes
    ☐ No

    If no, please go to Section B.

32. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)	☐ Program or Operating Funding (e.g., website)
☐ Conference attendance	☐ Research/educational grants
☐ Royalties	☐ Travel grants
☐ Gifts	☐ Sponsorship of events
☒ Honoraria	☐ Other, please specify: _____

33. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	Advisory Board Stage 3 NSCLC	☒	☐	☐	☐
Bayer	National Consultancy Meeting and Train the Trainer- Larotrectinib in NTRK fusion positive cancers	☒	☐	☐	☐
Roche	Lung Regional Consultancy Meeting	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box. N/A

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box. N/A

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 25th 2020
Date

Callista Phillips
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr David Dawe**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

34. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

35. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria
☐ Program or Operating Funding (e.g., website)
☒ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

36. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Name of Organization	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	Advisory boards	☒	☐	☐	☐
Merck	Advisory Boards	☒	☐	☐	☐
AstraZeneca	Research Grant	☐	☐	☒	☐
Boehringer-Ingelheim	Honoraria	☒	☐	☐	☐
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November, 17th 2020
Date

David Dawe
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Catherine Labbé**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

37. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

38. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria
☐ Program or Operating Funding (e.g., website)
☒ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

39. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Name of Organization	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BMS	Advisory boards and Clinical trials	☐	☒	☐	☐
Astra Zeneca	Advisory Boards, clinical trials and honoraria for conferences	☐	☒	☐	☐
Merck	Advisory Board and honoraria for conferences	☒	☐	☐	☐
Pfizer	Advisory Board and honoraria for conferences	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November, 18th 2020 — Date

Catherine Labbé — Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Nicole Bouchard**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

40. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

41. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)	☐ Program or Operating Funding (e.g., website)
☒ Conference attendance	☒ Research/educational grants
☐ Royalties	☐ Travel grants
☐ Gifts	☐ Sponsorship of events
☐ Honoraria	☐ Other, please specify: _____

42. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	Advisory Role/Conference	☒	☐	☐	☐
Bristol-Myers Squibb	Advisory Role/Research	☒	☐	☐	☐
Merck	Advisory Role /Research/Conference	☒	☐	☐	☐
Bayer	Advisory Role	☒	☐	☐	☐
Pfizer	Conference/Research	☒	☐	☐	☐
Roche	Advisory Role	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

Expert for INESSS (diagnosis and treatment for Lung Cancer in Quebec)

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 18th 2020
Date

Nicole Bouchard
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Normand Blais**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

43. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

44. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☐ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

45. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis	Medical advisor	☒	☐	☐	☐
		☐	☐	☐	☐
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

N/A

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

N/A

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

Nov 19 2020 — Date

Normand Blais — Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Cheryl Ho**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

46. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

47. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☐ Honoraria
☐ Program or Operating Funding (e.g., website)
☒ Research/educational grants
☒ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

48. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	Advisory role	☒	☐	☐	☐
Roche	Advisory role, travel, research grants	☐	☐	☐	☒
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

Nov 20 2020 — Date

Cheryl Ho — Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Sunil Yadav**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

49. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

50. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria (Speaking)
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

51. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol-Myers Squibb	Advisory Board	☒	☐	☐	☐
Astra Zeneca	Advisory Board and Speaking	☒	☐	☐	☐
Merck	Advisory Board and Speaking	☐	☐	☒	☐
Roche	Advisory Board and Speaking	☐	☒	☐	☐
Takeda	Advisory Board and Speaking	☒	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 21st 2020
Date

Sunil Yadav
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Stephanie Snow**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

52. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

53. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☐ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

54. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen	Advisory Role	☒	☐	☐	☐
Astra Zeneca	Advisory Role	☐	☐	☒	☐
Bayer	Advisory Role	☐	☒	☐	☐
Boehringer Ingeiheim	Advisory Role	☒	☐	☐	☐
Bristol-Myers Squibb	Advisory Role	☐	☐	☒	☐
Eisai	Advisory Role	☒	☐	☐	☐
Merck	Advisory Role	☐	☐	☒	☐
Novartis	Advisory Role	☒	☐	☐	☐
Pfizer	Advisory Role	☒	☐	☐	☐
Purdue	Advisory Role	☒	☐	☐	☐
Roche	Advisory Role	☐	☐	☒	☐
Taiho	Advisory Role	☒	☐	☐	☐
Takeda	Advisory Role	☐	☒	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

No

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

No

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 23th 2020
Date

Stephanie Snow
Name

CADTH

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician:	**Dr Parneet Cheema**
Name of drug and indication under review:	**Larotrectinib (Vitrakvi)** **For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

55. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

☒ Yes
☐ No

If no, please go to Section B.

56. What form of payment did you receive? (Check all that apply.)

☒ Advisory role (e.g., advisory boards, health technology assessment submission advice)
☐ Conference attendance
☐ Royalties
☐ Gifts
☒ Honoraria
☐ Program or Operating Funding (e.g., website)
☐ Research/educational grants
☐ Travel grants
☐ Sponsorship of events
☐ Other, please specify: _____

57. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

Company	Nature or description of activities or interests	Check Appropriate Dollar Range

		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol Myers Squibb	Advisory board/Honoraria	☒	☐	☐	☐
Merck	Advisory board/Honoraria	☒	☐	☐	☐
Astrazeneca	Advisory board/Honoraria	☒	☐	☐	☐
Roche	Advisory board/Honoraria	☒	☐	☐	☐
Novartis	Advisory board/Honoraria	☒	☐	☐	☐
		☐	☐	☐	☐

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than $10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

NO

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

NO

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge. ☒

November 21, 2020 — Date

Parneet Cheema — Name

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**Larotrectinib (Vitrakvi)**
Indication	**For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.**
Name of the Clinician Group	**Pediatric Oncology Group of Ontario**
Author of the Submission	**Dr. Paul Gibson**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

POGO is a collaboration of Ontario's 5 specialized childhood cancer centres and the official advisor to the Ministry of Health and Long-Term Care on pediatric cancer care and control. This submission represents a collaboration of pediatric cancer clinicians from across the province with membership informed by POGO's Therapeutic and Technology Advisory Committee (TAC). For more information on POGO, please visit www.pogo.ca

2. Information Gathering

POGO previously sought clinician input and feedback on the use of larotrectinib from Ontario pediatric oncologists in conjunction with the previous submission. This feedback served as a starting point. Next, there was a call for interested parties via the POGO TAC. The drafted submission was then shared with all interested parties for feedback and contribution.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

NTRK gene fusions are found across a wide variety of histologies in pediatric cancer. Importantly, these tend to be all rare tumours. The potential therefore for large scale clinical trials in these populations is extremely low.

High Frequency TRK Fusion Harboring Pathologies

- These include Infantile Fibrosarcoma (IFS), Congenital mesoblastic nephroma (CMN), secretory breast cancer (SBC) and Mammary analog secretory carcinoma of the salivary gland (MASC)
- The upfront therapy of choice for these patients remains surgical resection, however for many it is not feasible without significant morbidity
- At present, patients are considered candidates for larotrectinib (via special access or compassionate supply) if low intensity/low toxicity traditional cytotoxic therapy (such as vincristine and dactinomycin) are not sufficient to control disease and allow resection. Larotrectinib is prioritized over traditional cytotoxic agents with higher potential late effects such as anthracyclines or alkylators.

Lower Frequency TRK Fusion Harboring Pathologies

- Significant subsets of poor prognosis diagnoses (i.e. high grade gliomas, metastatic sarcoma, metastatic papillary thyroid cancer) harbour NTRK gene fusions. There are no curative therapies and traditional cytotoxic therapy provides only palliation of the disease and symptoms. For patients that respond, such as those with infantile gliomas, larotrectinib is a life-changing, offering survival where no other options exist. Patients whose malignancies are shown to harbour NTRK fusions are offered larotrectinib early in therapy via compassionate access. Patients achieving stable disease or significant responses in the absence of intolerable toxicities continue therapy until either a complete response is achieved, or they show evidence of progressive disease.

In all cases, we believe larotrectinib targets the underlying genetic drivers of malignancy. Reduction in tumour mass generally reduces symptom burden. It may also convert a tumour not amendable to low morbidity surgical resection to one that is resectable with minimal morbidity.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

For many histologies, the goal of therapy is to provide cure with minimal long-term toxicity. For malignancies with good prognosis such as infantile fibrosarcoma, for example, surgical resection following traditional cytotoxic therapy may still carry significant long term sequalae. These patients are in need of new therapies to minimize the lifelong impact of surgical intervention.

In high-risk malignancies such as metastatic tumours and intracranial gliomas, the goal of therapy is to prolong life while simultaneously providing optimal quality of life. While many of these diagnoses may have transient responses to traditional cytotoxic therapy and or radiation therapy, that therapy is often accompanied by significant toxicity, including myelosuppression, infectious complications, nausea and vomiting and mucositis.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

- Infants, children and adolescents with metastatic tumours such as sarcomas and thyroid malignancies have minimal options to provide even transient disease response. These patients have an unmet need for effective and low toxicity therapy to minimize their symptoms and prolong their lives
- Patients with intracranial high-grade gliomas at present receive palliative chemotherapy and radiation therapy. The unmet need in these patients is effective therapy that can lead to a sustained response (stable or reduced disease burden) for longer survival
- Patients with favourable prognosis malignancies that fail to respond to traditional front-line therapies have an unmet need for second line therapies that minimize long term toxicities

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

The proposed criteria represent a very heterogenous population. Many malignancies with a high frequency of NTRK fusions have existing front line therapies with excellent prognosis. In this group, only those who fail to adequately respond to front therapy would be considered for therapy. Classically, these are infants with infantile fibrosarcoma who do not respond to traditional cytotoxic therapy sufficiently to allow a low morbidity resection.

Unlike those favourable prognosis diagnoses, patients with metastatic tumours or high-grade intracranial gliomas lack therapeutic options that will provide long term survival with quality of life. While only a small proportion of this population will harbour NTRK fusions, they have the potential to be profoundly benefited in both survival and quality of life.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

At present, the data is insufficient to suggest larotrectinib be used in combination with other therapies. Instead, it should be administered as monotherapy. As mentioned above, we suggest it be used as second line in good prognosis diseases and be considered as a front-line option in poorer prognosis diagnoses.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

As previously described, for diagnoses with known therapies associated with favourable outcomes and minimal long-term morbidity, we suggest those therapies be offered first. We suggest this primarily because of the known long term late effects in children of these traditional cytotoxic agents. In poorer prognosis situations however, we feel the unclear long term late effect risk is acceptable given the known dismal outcomes.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

There is insufficient data at present to suggest larotrectinib in combination with other therapies. While we suggest larotrectinib should be used as an early line therapy in poor prognosis patients whose tumour

harbours an NTRK fusion, we do not expect failure or progression to alter the limited therapeutic options open to these patients in subsequent line therapies.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

We suggest this therapy be used in patients with recognized NTRK alterations only. Those harbouring the fusion are all expected to have a high rate of response regardless of histology. Those with the highest disease or symptom burden are expected to be most in need of intervention.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Potential patients belong to 2 groups. The first is the group of histologies where NTRK alterations are common and are examined as part of routine pathologic diagnosis. These include Infantile Fibrosarcoma (IFS), Cellular congenital mesoblastic nephroma (CMN), secretory breast cancer (SBC) and Mammary analog secretory carcinoma of the salivary gland (MASC).

The second group is those diagnoses with a low frequency of NTRK alterations. (i.e. high grade gliomas, metastatic sarcoma, metastatic papillary thyroid cancer). This group will normally require extra assessment at the request of treating clinicians. In this group, detection of NTRK alterations may be detected as part of broader tumour sequencing efforts or by targeted assessment by immunohistochemistry or genetic assessment. Of note, the manufacturer currently provides access to this testing via a private laboratory.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Given the lack of long-term late effect data in children, patients with an alternative low morbidity curative option may be least suitable for front line therapy with larotrectinib.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

At present, the existing data does not allow for accurate prediction of which patients are most likely to respond outside of the characterization of an NTRK fusion. While we do not feel this should be a barrier to access, we do think that continued collection of data, particularly in rare histologies is key to better direct therapy in the future.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Given the variety of histologies and presentations, it is difficult to suggest universal strategies for measuring response. Generally speaking, cross sectional imaging, via CT or MRI will inform disease status. A combination of radiologic response and patient reported quality of life should be used to determine efficacy.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Given the variety of histologies and presentations in the potential patient population, clinically meaningful response will be variable. For example, in patients with infantile fibrosarcoma, clinically meaningful response would include the facilitation of a low morbidity resection. In a high-grade glioma, a clinically meaningful response may be stable disease and/or improvement of existing neurologic deficits.

6.10. How often should treatment response be assessed?

Response:

The frequency of assessment will depend on the clinical presentation. We favour early assessment (i.e. 2-3 months) in patients initiating therapy. Patients showing sustained responses may require assessment less frequently, particularly if there are challenges such as sedation requirements around radiologic assessment.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression on therapy should be considered an indication to halt therapy. Decisions in regard to stopping therapy in patients with clinical response should be made in conjunction with patients and their families considering both the clinical impact of therapy and the acceptability of associated toxicities.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

We feel pediatric patients should receive larotrectinib on an outpatient basis under the supervision of a specialized pediatric cancer program.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

N/A

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

We recognize that the total patients with very rare histologies harbouring NTRK fusions treated with larotrectinib is low. We also feel it is neither feasible nor ethical, however, to delay access while awaiting further trial data. We suggest instead that data collection of real-world experience be used to evaluate outcomes in these patients with potential reassessment in the future.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

This group of clinicians has received no direct funding to prepare this submission. POGO has received educational grants to support our annual symposium from Amgen, Servier and Jazz Pharmaceuticals. Bayer has previously provided educational support for the POGO symposium, but not in the past 2 years.

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Paul Gibson*
Position	*Pediatric Oncologist, POGO Associate Medical Diretor*
Date	*Please add the date form was completed (30-11-2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer Advisory Board	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Carol Portwine*
Position	*Pediatric Oncology, Division Head, Pediatric Hematology/Oncology, McMaster Children's Hospital*
Date	*02-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None				

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Meredith Irwin*
Position	*Pediatric Oncologist, Paediatrician-in-Chief, The Hospital for Sick Children*
Date	*03-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000`**
None	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Adam Fleming*
Position	*Pediatric Neuro-oncologist; Associate Professor of Pediatrics, McMaster Children's Hospital*
Date	*03-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer Advisory Board	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Donna Johnston*
Position	*Pediatric Oncologist, Division Head, Pediatric Hematology/Oncology, Children's Hospital of Eastern Ontario*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr. Alexandra Zorzi*
Position	*Pediatric Oncologist, Division Head, Pediatric Hematology/Oncology, Children's Hospital, London Health Sciences Centre*
Date	*04-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer Ad Board	☒	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Dr. Laura Wheaton*
Position	*Pediatric Oncologist, Kingston General Hospital*
Date	*04-12-202*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Dr. Eric Bouffet*
Position	*Pediatric Neurooncologist, Director, Brain Tumour Program, The Hospital for Sick Children*
Date	*04-12-202*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer Ad Board	☒	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0221-000
Generic Drug Name (Brand Name)	**Larotrectinib (VITRAKVI**
Indication	**Adult and pediatric patients with solid tumours with NTRK gene fusions without a known acquired resistance mutation, whose disease is metastatic, or where surgery would result in severe morbidity, and who have no satisfactory alternate treatment options**
Name of the Clinician Group	**Pediatric oncology group**
Author of the Submission	**Sébastien Perreault, Daniel Morgenstern, MagimairajanIssai Vanan**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are Canadian clinicians and researchers involved in various fields of pediatric oncology including solid tumors and central nervous system tumors. We are currently practicing in different institutions (Dr Morgenstern SickKids, Toronto, Dr Vanan Winnipeg Children's Hospital, Winnipeg, Dr Perreault CHU Sainte-Justine, Montreal). We are all members of the C17 oncology group www.c17.ca

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information presented in this submission were gathered through review of the literature (articles and abstract presentations), Canadian oncology group meetings and based on clinical experiences. This document was reviewed and validated by all authors.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Larotrectinib is a highly selective TRK inhibitor studied in a tumor agnostic approach. Pediatric patients with various solid tumors were included in clinical trials. The most frequent tumors harboring a NTRK gene fusion in the pediatric population are: Infantile fibrosarcomas, soft tissue sarcomas, thyroid carcinomas and brain tumors (glioma). Current available treatments vary between tumor types and age. For this submission, we focused on these four main tumor types but we expect similar benefits in all tumors with NTRK gene fusions.

*Of note, since larotrectinib is only efficacious for patients with NTRK gene fusions, all tumors discussed in this submission are assumed to harbor this molecular arrangement (see section on identification of patients for more details)

Infantile fibrosarcoma (IFS) usually occurs in young infants. When possible, surgery is the treatment of choice but 39% will require chemotherapy (vincristine, actinomycin-D, and cyclophosphamide (VAC)) and 9% will require disfiguring amputations. Response rate to chemotherapy is 75%.

Soft tissue sarcomas (STS) are a heterogeneous group of tumors. Standard treatment for STS includes doxorubicin and ifosfamide or cisplatin followed by surgery. Despite standard treatment, STS have the second poorest 5-year survival of childhood cancers at 71%, with a 20.4% 5-year relapse rate despite standard treatment.

Thyroid carcinoma is the most common form of cancer in adolescents and young adults. Surgery is the primary treatment modality with a sub-group of individuals meeting indications for radio-nuclide therapy (systemic therapy). A small subset of patients (7%) will be refractory to systemic therapy.

Gliomas are the most frequent brain tumor in children. High-grade gliomas are usually treated with surgery followed by radiation therapy and alkylating agents (temozolomide and CCNU). Responses are transitory with a poor overall survival below 5% at 5 years. Low-grade gliomas are treated with weekly chemotherapy (vincristine/carboplatin or vinblastine). Response rate is below 35% and progression free survival with this current approach is less than 50% at 5 years.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The most important goals in pediatric oncology are to improve overall survival, decrease recurrences while maintaining a good quality of life with few short and long term side effects.

-

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Treatment gaps differ between tumor subtypes.

For infantile fibrosarcoma: surgery in these young infants can lead to significant morbidity including amputation in tumors of the limbs. Furthermore, 25% will be refractory to standard systemic treatment. There is a need to decrease morbidity associated with surgery and improve outcome in refractory patients.

For soft tissue sarcoma there is a high relapse and mortality rate despite standard treatment. Salvage therapies are usually not efficacious. There is a need to improve response and decrease relapse rate.

A subset of thyroid carcinoma is refractory to standard systemic therapy. These patients would benefit from a different approach in order to improve the outcome.

Outcome for patients with a pediatric high-grade glioma is extremely poor and treatments including radiation therapy are associated with long term morbidity including neurocognitive sequelae and strokes. There is a need to improve outcome and decrease long term sequelae.

For low-grade glioma, weekly IV infusions are administered over a 70 weeks period with a disappointing progression free survival at 5 years. There is a need to improve response and improve quality of life during treatment.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients with a NTRK gene fusion cancer are likely to benefit from treatment with larotrectinib.

Morbid surgery could be avoided for patients with infantile fibrosarcoma.

Relapse/refractory sarcoma with NTRK fusion could be salvaged with larotrectinib

Relapse/refractory thyroid carcinoma with NTRK fusion could be salvaged with larotrectinib

In patient with high-grade glioma with NTRK fusion, radiation therapy could be avoided or postponed with the use of larotrectinib. In low-grade glioma, progression free survival can be improved. Furthermore, quality of life can be improved since the medication is administered in form of tablets or liquid solution.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Larotrectinib is a highly selective TRK inhibitor used in monotherapy for patients with a known NTRK gene fusion.

The place of larotrectinib in the treatment algorithm depends on the tumor types, extend of disease, age and comorbidities.

For infantile fibrosarcoma, larotrectinib would be used for patients expected to have unresectable tumors or recurrence despite standard therapy approach.

For sarcoma with NTRK fusion, larotrectinib would be used for complex and refractory cases despite standard treatment.

For thyroid carcinoma, larotrectinib would be used for cases refractory to standard systemic therapy

For high-glioma, larotrectinib would be used when radiotherapy is not possible due to age or when high morbidity is expected. For low-grade glioma, larotrectinib would be used for patients refractory to standard chemotherapy.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

It is appropriate to recommend standard treatment before initiating larotrectinib in tumors with a good outcome with current standard treatment. This is the case for thyroid carcinoma. Depending on tumor location, extent of resection, age and expected side effects, standard chemotherapy can be considered as an initial treatment for infantile fibrosarcoma, soft tissue sarcoma and low-grade glioma with NTRK fusion.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Given the high response rate and good safety profile, patients with NTRK fusion tumors that have failed standard treatment or when there are no available therapies are likely to benefit from larotrectinib. Larotrectinib would be used as a second line treatment when there is an efficacious first line therapy. In accordance with Health Canada approval, larotrectinib would be used when there are no satisfactory alternate treatment options.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Only patients with NTRK gene fusion cancers are likely to respond to treatment. So far, pooled data from different studies suggest an overall response rate of 80% regardless of tumors subtypes in non-CNS tumors. Data suggest that patients can respond regardless of stage and extent of disease. In the SCOUT trial, some patients heavily pretreated and in palliative care had an excellent and durable response with larotrectinib

Seven pediatric patients are currently treated and followed in our institutions.

Infantile fibrosarcoma appears to have a particularly excellent outcome with rapid response and long durable disease.

For sarcoma with NTRK gene fusion, a good response is also expected. In our experience, one patient

with a metastatic disease and severe pain had a partial response with improved pain control and quality of life. One lesion progressed despite treatment due to acquire resistance in the context of a TP53 germline mutation.

In CNS tumors, the ORR is 36% but tumor shrinkage is seen in most patients. Giving the nature of these tumors, this level of response is clinically significant. Furthermore, in our Canadian experience with larotrectinib, two patients with a high-grade glioma have reached complete response within two cycles. Both patients have now been treated for more than 2 years without progressive disease.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Patients with NTRK gene fusion can be identified through different approaches depending on tumor type.

NTRK fusion is pathognomonic of infantile fibrosarcoma. The classic ETV6-NTRK3 fusion can be easily identified with FISH.

For soft tissue sarcoma, infantile fibrosarcoma without the classic fusion, thyroid carcinoma, CNS tumors and all other tumor types, NTRK gene fusion can be identified with next generation sequencing (usually RNA based). While these approaches are not available everywhere in Canada, there are different platforms and initiatives that can be used. Pediatric patients may have access to molecular testing through national or institutional research projects such as the pan-Canadian Terry Fox PROFYLE research project (for patients aged 0-29 who have high risk cancers with <30% 5 year survival and no other treatment options), the SickKids Cancer Sequencing Program (KiCS), the Personalized Oncogenomics (POG) program in Quebec, and the SIGNATURE project in Quebec. In addition, the ongoing CANTRK Ring Study aims to establish concordance at 17 sites across Canada for IHC and NGS testing for NTRK gene fusions. Finally, NTRK gene fusion testing is available through Bayer's complimentary FastTRK clinical testing program (fasttrk.ca) and privately through companies such as Foundation Medicine (foundationmedicine.ca).

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients without a NTRK gene fusion or a known resistance to larotrectinib are not expected to benefit from larotrectinib

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment

with the drug under review?

If so, how would these patients be identified?

Response:

As mentioned, a good response rate is expected in all tumor types regardless of the extend of the disease if they have a NTRK fusion and no resistance to larotrectinib.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Tumor response with imaging (assess by MRI or CT scan) allows to evaluate if the patient is responding to treatment. Other parameters can also be followed depending on tumor location and associated symptoms such as pain control, improve level of functioning and improve quality of life.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Tumor shrinkage and progression free survival are considered clinically meaningful in most patients with pediatric cancer. Improvement in pain control, level of functioning and quality of life are also clinically significant changes.

6.10. How often should treatment response be assessed?

Response:

Tumor response by imaging should be evaluated at least every three months and clinical status/tolerance every month during clinical visit.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Discontinuation of larotrectinib should be considered when there is a tumor progression despite optimal treatment or severe side effects related to treatment. Discontinuation can be considered in patients with a complete response for more than two years depending on tumor type but more data is needed to

determine the best time to stop treatment. Discontinuation may also be considered for patients who achieve remission following surgical resection (especially in infantile fibrosarcoma), although there are limited data available on the optimal approach.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Patients with NTRK gene fusion cancer treated with larotrectinib should be followed in a pediatric oncology outpatient clinic (hospital).

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

Click here to enter response.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

NTRK gene fusion cancers are relatively rare, but for these patients larotrectinib offers an unprecedented opportunity. Based on available data and in our experience, larotrectinib is an efficacious targeted therapy with few short-term side effects. We believe that larotrectinib can salvage patients with progressive disease, decrease side effects associated with other available treatments and improve quality of life.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	Sébastien Perreault
Position	MD neuro-oncology CHU Sainte Justine Hospital
Date	18-Nov-2020
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer-advisory board/conference	☐	☒	☐	☐
Eisai conference	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	Daniel Morgenstern
Position	Staff Oncologist, Hospital for Sick Children
Date	19-NOV-2020
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Roche	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Boehringer-Ingelheim	☒	☐	☐	☐
ymAbs Therapeutics	☒	☐	☐	☐
EUSA Pharma	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	Magimairajan Issai Vanan
Position	Pediatric Neuro-Oncologist, CCMB
Date	22/11/2020
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0221-000**
Generic Drug Name (Brand Name)	**larotrectinib (Vitrakvi)**
Indication	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (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.
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee**
Author of the Submission	**Dr. Frances Wright, Dr. Teresa Petrella, Dr. Tara Baetz, Dr. Marcus Butler, Dr. Xinni Song, Dr. Elaine McWhirter**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information based on larotrectinib's updated analysis (Hong 2020) and clinician experience.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Larotrectinib shows very high response rates in patients with a NTRK mutation and would help symptoms.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Given its high response rates it would help with symptoms and improve QOL and reduce the severity of symptoms and hopefully improve ability to maintain employment and reduce burden on caregivers.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Not all patients respond to available treatments and Patients become refractory to current treatment options

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Sub population of melanoma patients with NTRK mutation.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Current data is as a single agent and is used as a single agent

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Most patients would receive immunotherapy first but would be good to have access to Larotrectinib for patients where immunotherapy is contraindicated

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

As above usually post immunotherapy. Patients have limited options and hence may not have other treatments available to them post Larotrectinib

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Those with TRK mutation are most likely to respond

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Would need to test for NTRK mutation and test would need to be available

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Those without the mutation

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Click here to enter response.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Yes usually clinical assessment and imaging and bloodwork are used.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

All of the above as well as reduction in tumour burden and improvement in survival

6.10. How often should treatment response be assessed?

Response:

Usually every 3 to 6 months

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

All of the above

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

It is oral therapy therefore can be treated in community as well as outpatient clinic
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** N/A. It's an oncology drug.
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: Larotrectinib has great response rate for a very small subgroup of melanoma patients with limited options for therapy

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the DAC in completing this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Frances Wright*
Position	*Surgeon – Sunnybrook Health Sciences Centre*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Teresa Petrella*
Position	*Medical Oncologist*
Date	*27-11-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Tara Baetz*
Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Marcus Butler*
Position	*Medical oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Xinni Song*
Position	*Medical Oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr. Elaine McWhirter*
Position	*Medical Oncologist*
Date	*04-Dec-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐