CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Selpercatinib (Retevmo)

Indication: For the treatment of RET-mutant medullary thyroid cancer in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease.

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that selpercatinib be reimbursed for the treatment of rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC) in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease who have progressed on or are intolerant to first line therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, multicenter, multi-cohort, open-label, phase 1/2, single arm clinical study (LIBRETTO-001) demonstrated anti-tumour activity based on the response rates observed with selpercatinib in patients with advanced RET-mutant MTC [e.g., objective response rate (ORR): 69.1% (95%CI: 55.2-80.9) for primary analysis set (PAS: the first 55 patients with prior cabozantinib or vandetanib experience)]. Further, results suggest that the majority of patients experienced either improvement in quality of life or their quality of life remained stable, although definitive conclusions on health-related quality of life (HRQoL) outcomes could not be drawn due to the exploratory nature and potential for bias in the open-label single-arm study. Selpercatinib treatment was associated with a manageable toxicity profile. Selpercatinib addresses a therapeutic need for this rare and incurable disease as there are currently no funded therapies available for patients with RET-mutant MTC who progressed on or are intolerant to first line therapy.

Patients and clinicians expressed a need for effective treatments (and can be given orally) that improve survival and quality of life with fewer treatment-related harmful adverse effects. Given the totality of the evidence, pERC concluded that selpercatinib likely met some of these needs identified by patients and clinicians in terms of an additional oral treatment option, potential improvement in quality of life and fewer treatment-related adverse effects The cost-effectiveness of selpercatinib relative to vandetanib or best supportive care (BSC) is unknown owing to the lack of comparative clinical effectiveness information, as well as limitations with the pharmacoeconomic model submitted by the sponsor. As such, a base-case cost-effectiveness estimate was unable to be determined in patients with RET-mutant MTC.

The committee considered exploratory analyses conducted by CADTH and determined that the incremental cost-effectiveness ratio (ICER) was likely close to $350,341 per quality adjusted life year (QALY) compared with vandetanib and $347,785 per QALY compared with BSC; therefore, selpercatinib is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold. A price reduction of at least 87% is required for selpercatinib to be cost-effective at this threshold compared to BSC.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Treatment with selpercatinib should be reimbursed in patients 12 years of age and older with advanced or metastatic RET mutant medullary thyroid cancer who have progressed on or are intolerant to first line therapy.	The LIBRETTO-001 trial demonstrated anti-tumour activity based on the response rates observed with selpercatinib in patients with advanced RET-mutant MTC who were previously treated with cabozantinib or vandetanib. The Health Canada approved indication includes patients 12 years of age and older.	
2. Patients must have good performance status.	Patients enrolled in the LIBRETTO-001 study had an ECOG performance status of 0, 1, or 2.	pERC acknowledged that clinicians may consider using selpercatinib for patients with an ECOG performance status >2 at their discretion.
Renewal		
3. Selpercatinib should be renewed for patients who exhibit a response to treatment as per physician discretion and for whom treatment is tolerable.	Based on clinical expert opinion, different measures of response are evaluated based on clinical grounds and radiological examination such as the RECIST criteria, CEA, calcitonin, general symptoms, and HRQoL.	—
4. Patients should be assessed for treatment response every 3 to 6 months or as per physician discretion.	Based on clinical expert opinion, response to treatment in practice is usually assessed every 3 to 6 months.	—
5. ECG monitoring as clinically indicated.	As per Health Canada product monograph: QTc interval prolongation was reported in patients receiving selpercatinib in clinical trials and is listed among the serious warnings and precautions.	—
Prescribing		
6. Selpercatinib should be prescribed by clinicians with expertise in the management of thyroid cancer.	To ensure that selpercatinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
7. Selpercatinib should not be reimbursed if given in combination with other systemic anti-cancer drugs.	Selpercatinib was administered as monotherapy in LIBRETTO-001 and has a Health Canada indication only as monotherapy.	—
Pricing		
8. A reduction in price	The cost-effectiveness of selpercatinib compared to vandetanib or BSC is unknown.	—

Reimbursement Condition	Reason	Implementation Guidance
	Based on CADTH exploratory analyses, price reductions of at least 78% and 87% would be required to achieve an ICER of $50,000 per QALY relative to vandetanib and BSC, respectively. Due to the high degree of uncertainty in the evidence, additional price reductions may be necessary.	
Feasibility of Adoption		
9. The feasibility of adoption of Selpercatinib must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—
10. Access to RET testing	RET testing is needed to identify patients with RET-mutant medullary thyroid cancer, however, this may not be equally accessible across all jurisdictions	pERC agreed it would be desirable for jurisdictions to have RET testing available across Canada in order to identify the eligible patient population prior to treatment with selpercatinib.

BSC = best supportive care; CEA =carcinoembryonic antigen; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; MTC = mutant medullary thyroid cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumours; QALY = quality adjusted life year; RET = rearranged during transfection

Discussion Points

- While pERC acknowledged that selpercatinib produced anti-tumour activity based on the response rates observed in the LIBRETTO-001 trial in the Primary Analysis Set (PAS - first 55 patients with prior cabozantinib or vandetanib experience) and Integrated Analysis Set (IAS- all patients with prior cabozantinib or vandetanib experience), and SAS1 (treatment naïve to cabozantinib and vandetanib) subgroups, there remains uncertainty in overall survival (OS) and progression-free survival (PFS) data due to the limitations associated with the open-label, single-arm study design, lack of control group, and lack of statistical testing. pERC also acknowledged this was a rare and incurable disease with a high unmet need in the second line setting.
- While pERC acknowledged there is no currently funded treatment for MTC among patients aged less than 18 years, pERC did not recommend reimbursement of selpercatinib for patients 12 years and older in the first line setting because pERC felt there was insufficient evidence to recommend reimbursement for selpercatinib for the treatment of RET-mutant MTC in patients 12 years and older for the first line setting. pERC noted the small number of adolescent patients enrolled in LIBRETTO-001 and the uncertainty associated with an open-label, single-arm study design, lack of control group, and lack of statistical testing. pERC also noted that while the Health Canada approved indication of selpercatinib is for adolescents (age 12 years and above), the efficacy of selpercatinib in LIBRETTO-001 is mainly derived from adult patients, as only 3 adolescents were enrolled in the trial. pERC acknowledged that the results of the LIBRETTO-531 trial (multi-center, randomized, open-label phase 3 trial comparing selpercatinib to physicians' choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor naïve, RET-mutant medullary thyroid cancer) will address the evidence gap in the first line setting for patients 12 years and older. These results are expected after November 2026.
- pERC discussed that reimbursement of selpercatinib in patients less than 12 years of age is out of scope of the Health Canada indication, and concluded that at this time, there is insufficient evidence to recommended reimbursement for selpercatinib for the treatment of RET-mutant MTC in patients less than 12 years of age.
- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor: an unanchored matching adjusted indirect comparison (MAIC) of selpercatinib relative to BSC (placebo), followed by a naïve comparison of vandetanib to

BSC. pERC noted that while a statistically significant improvement in PFS and OS for selpercatinib versus placebo was reported, the results of the ITCs stem from highly uncertain evidence due to limitations that impact the internal and external validity despite the various adjustments.

- While the majority of patients experienced either improvement in quality of life or their quality of life remained stable, pERC acknowledged that a proportion of patients did experience a deterioration in quality of life. pERC also discussed the presence of diarrhea and impact of selpercatinib on diarrhea. pERC noted that while many patients presented with diarrhea upon baseline in the LIBRETTO-001 trial (61.5%), the presence of diarrhea while on selpercatinib was reduced (as 31.8% at any point) and patients reported little impact of diarrhea on quality life during the study treatment with selpercatinib.
- pERC noted that the estimated budget impact was highly sensitive to assumptions about the proportion of overall thyroid cancer patients who had MTC. In the CADTH base case, a value of 2% was used; however, clinical experts suggested that the true value may be closer to 10%. A larger eligible patient population would produce a notably higher budget impact.

Background

Thyroid cancer is one of the most common diagnosed cancers in Canada and the world. In 2020, the incidence of thyroid cancer in Canada is estimated to be 23 per 100,000 or about 8,600 new cases. MTC originates from the parafollicular neuroendocrine cells of the thyroid (c cells) and comprises 1% to 5% of all thyroid cancers. Metastases to cervical lymph nodes is a common initial presentation. Of all MTC cases, approximately 75% are sporadic and 25% are hereditary. Of the sporadic cases, 50% will present somatic mutations in the rearranged during transfection (RET) proto-oncogene. Of the hereditary cases, almost all (98%) will present a germline RET mutation. RET genetic analysis is recommended when the diagnosis of MTC has been established because it allows defining the sporadic or hereditary nature of MTC, as it can guide future diagnostic and therapeutic options and strategies. The prognosis of MTC is unfavorable, with a 10-year survival rate of approximately 50%, with a 5-year survival rate varying from 62% to 87% according to different epidemiological studies series. Early diagnosis and total thyroidectomy with resection of local and regional metastases is the basis for initial treatment and subsequent hormone replacement with L-thyroxine. The treatment goals in patients with MTC are aimed at improving survival, delaying disease progression, and improving health-related quality of life. For patients with unresectable/metastatic RET-mutant MTC – a condition with a very low cure rate – several targeted therapies have been used as first line treatments, such as cabozantinib and vandetanib of which only vandetanib is approved and funded in Canada. After first line treatments, patients can only continue using best supportive care (BSC) and, optionally, enter clinical trials.

Selpercatinib (Retevmo or LOXO-292), 40 mg, and 80 mg oral capsules, is a new, highly selective inhibitor of the RET receptor tyrosine kinase, approved by Health Canada (Notice of Compliance with condition) as monotherapy for the treatment of RET-mutant medullary thyroid cancer in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease. The product monograph (PM) recommends confirming the presence of a RET gene mutation before starting treatment, and a recommended dosage based on body weight, as 120 mg orally twice daily for patients less than 50 kg or 160 mg orally twice daily for patients equal to or greater than 50 kg. Selpercatinib received a Notice of Compliance with condition (NOC/c) on June 15th, 2021. Several warnings in the PM include QTc interval prolongation in the electrocardiogram (ECG), hypertension, hypersensitivity, hepatotoxicity, hemorrhage, and embryo-fetal toxicity. These situations warrant caution and recommend adjusting dosages for these adverse events.

Sources of Information Used by the Committee

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

- A review of one single-arm, open label clinical study in patients with MTC.
- Patients' perspectives gathered by 2 patient groups, the CanCertainty group, and a joint submission by the Canadian Cancer Society and Thyroid Cancer Canada group.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Two clinical specialists with expertise diagnosing and treating patients with thyroid cancer.
- Input from 2 clinician groups, including the Pediatric Oncology Group of Ontario (POGO) and Ontario Health (Cancer Care Ontario) Head and Neck and Thyroid Cancer Drug Advisory Committee.

- Other Relevant Evidence: ongoing trials
- A review of the pharmacoeconomic model and report and ITCs submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input was obtained from two patient groups: CanCertainty coalition and Canadian Cancer Society (CCS) with Thyroid Cancer Canada.

The CanCertainty coalition is composed of more than 30 Canadian patient groups, caregiver organizations, charities, as well as oncologists and cancer care professionals, and strives to improve the accessibility of cancer treatment. The group used the thyroid cancer incidence from Statistics Canada to estimate the number of RET-mutated thyroid cancer cases (both medullary and papillary) each year by age and province, i.e., the estimated number of Canadian residents who will become eligible for selpercatinib each year and provided input on estimates of financial hardships for cancer patients from their database of surveys of 1,600 Nova Scotians. The group states that a cancer diagnosis could lead to financial hardships, especially when they do not have private health insurance. Even though multiple programs support individuals with high drug costs, there are administrative barriers in many provinces and territories. Patients often face weeks of delay in starting cancer treatments.

The CCS does research and provides advocacy and support to patients living with cancer. CCS's patient panels and networks provided survey results from patients with thyroid cancer. In addition, Thyroid Cancer Canada patient networks submitted survey results and 2 testimonials from its staff/board members who have had thyroid cancer. A total of 17 survey responses were collected across Canada between October 22 and November 10, 2021. None of the respondents had direct or indirect experiences with selpercatinib. Patients living with MTC referred to issues associated with daily work and life, such as fatigue, brain fog, mental health, body image, cognitive ability, concerns about cancer returning, and dose regulation of thyroid medications. Overall, 71% reported a financial barrier related to treatments, especially blood tests and drug costs. Patients responded that they would like to see improvements in new treatments regarding cost, access, and support to improve their quality of life.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts consulted by CADTH agreed that there is an unmet need for drugs that are better tolerated and with better safety profiles that can be used in patients with RET-mutant, advanced/metastatic MTC who have very few options after surgery. Treatment goals are improving OS, PFS, and health-related quality of life by controlling symptoms such as diarrhea, flushing, minimizing adverse effects of treatments, and increasing work/life productivity. The experts considered that selpercatinib would be an appropriate therapy for RET-driven thyroid malignancies, including using it as first-line therapy. At this stage, there is only one approved and funded therapy (vandetanib) in Canada, and the experts consider that selpercatinib is expected to cause a shift in the current treatment paradigm.

The clinical experts considered that patients with RET-driven MTC that cannot be managed or cured by locoregional interventions (surgical interventions) and experiencing symptomatic disease progression or expected to experience symptomatic disease progression within the near future are the most likely to benefit from the use of selpercatinib. The experts did not find specific baseline characteristics or variables of prognostic value and consider that patients' response will not differ based on any disease characteristics, e.g., presence or absence of certain symptoms, stage of disease, etc. They suggested that patients with progressive metastatic MTC need to be screened for RET mutations and rearrangements with locally available comprehensive molecular tests, which should be available in institutions treating patients with progressive metastatic MTC.

Patients should be assessed to measure evidence of response or stabilization of the disease, based on clinical grounds and radiological examination such as the RECIST criteria, number/severity of symptoms, PFS, serum calcitonin, and CEA. All these measurements are mostly aligned with clinical trial endpoints. Improvement in survival, PFS, reduction in frequency and severity of symptoms (e.g., diarrhea) will be used to measure an adequate response, approximately every 3 to 6 months. Deterioration of

symptoms, functional status, radiological evidence of disease progression (together with other clinical criteria), and unacceptable toxicity from treatment are among the issues that could be used to decide to discontinue treatment on a case-by-case basis.

The experts concluded that patients should only receive selpercatinib from clinicians with experience in the treatment of thyroid cancer in a specialty outpatient clinic setting. Targeted therapies can have significant toxicity and related harms.

Clinician group input

Two clinician group summaries were received: Pediatric Oncology Group of Ontario (POGO) and Ontario Health – Cancer Care Ontario (OH-CCO) Head and Neck and Thyroid Cancer Drug Advisory Committee (DAC), gathering input from a total of 5 clinicians.

Overall, the clinician groups agreed with the view from the input provided by the clinical experts consulted by CADTH.

These groups explained that for RET-mutant MTC, the only currently approved and funded option is vandetanib, for which it is required to have special training and monitoring (e.g., QTc prolongation). Hence, an important goal of an ideal treatment would be reducing treatment-related toxicities. Once patients have progressed on currently available therapies, there is no other option.

In the treatment-naïve adult setting, OH-CCO noted that some clinicians may want to use selpercatinib in the first-line setting. Although selpercatinib appears to be more active and less toxic, there is a phase 3 trial (LIBRETTO-531 comparing selpercatinib to physician's choice of cabozantinib or vandetanib) in the first line setting that is still ongoing. Given the broader receptor profile of vandetanib, OH-CCO also expressed that clinicians would also like to be able to use vandetanib in patients progressing on (or intolerant of) selpercatinib. OH-CCO highlighted that some clinicians may reserve selpercatinib for RET-mutant MTC patients who are intolerant or unsuitable for vandetanib. In the previously treated population, OH-CCO expressed that selpercatinib offers a treatment option to those patients who have exhausted currently available treatments

In the pediatric setting, POGO highlighted that for children with MTC, the best chance of cure is comprehensive initial surgery and that POGO continues to advocate comprehensive initial surgery as first-line therapy. For the rare child with residual disease, however, existing therapies (cabozantinib and vandetanib) are associated with inferior response rates and higher toxicities, thus POGO would advocate selpercatinib as the initial second-line therapy. POGO also highlighted that a rare subset of pediatric patients with unresectable tumours may be considered for first-line therapy with selpercatinib in a neoadjuvant context to facilitate eventual surgical control.

The groups state that to identify eligible patients, RET testing is available in Ontario as part of reflex testing on all metastatic thyroid cancer. Patients without a RET-mutation or those with a performance status that would not allow selpercatinib treatment would be the least suitable population.

Response to selpercatinib would be primarily measured by response rates while addressing other key outcomes such as PFS and toxicity. Clinically meaningful response to treatment can be determined by reduction in tumor burden based on clinical assessment and/or imaging, cancer-related symptoms, and tumor marker levels. Treatment with selpercatinib should be re-assessed every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to16 weeks thereafter, especially in patients who had initial responses, feel well, and have reduced CEA and/or calcitonin levels. However, specific intervals should not be mandated. In case of a lack of response and/or treatment-related toxicities emerge, selpercatinib should be discontinued. As an oral, take-home cancer drug, selpercatinib is suitable for treatment in a community setting.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
The LIBRETTO-001 trial was an open-label, non-randomized, non-comparative Phase 1/2 trial evaluating selpercatinib in patients with RET-mutant medullary thyroid cancer (MTC) with or without prior vandetanib or cabozantinib treatment. The relevant funded comparator for first-line treatment would be vandetanib (for adult patients). In the second-line setting, the relevant comparator is best supportive care or clinical trial. Patients between 12 to 17 years of age currently do not have a funded comparator.	pERC acknowledged the availability of current treatment options for the adult and pediatric population in the first-line and beyond setting.
Considerations for Initiation of Therapy	
In the LIBRETTO-001 trial, there were only 3 adolescent patients with advanced/metastatic RET-mutant medullary thyroid cancer (patient ages: 15,16,17). The requested indication is for patients 12 and older. Vandetanib, the currently funded comparator for medullary thyroid cancer and is only funded for adult patients. *What is the relative safety/efficacy of selpercatinib for patients between 12-17 years old with RET-mutant medullary thyroid cancer?* *Patients of childbearing potential will require additional counselling/support due to potential impact of selpercatinib on reproduction/fertility.*	pERC noted the small number of adolescent patients enrolled in LIBRETTO-001, and also discussed data from a conference abstract for the LIBRETTO-121 study (pediatric patients) where 12 patients were enrolled (median age = 14 years), with 8 patients diagnosed with RET-mutant MTC, and 7 out of 8 patients still on treatment at the time of analysis. ORR of 50% (95%CI; 16 to 84%). pERC acknowledged the input from the clinical experts that little evidence exists regarding pediatric patients with RET-mutant MTC and that the balance between the benefits and harms should always be considered since this is a rare disease with poor prognosis. pERC noted that the Health Canada approved indication of selpercatinib is for pediatric patients 12 years and above and that selpercatinib is not indicated for patients under 12 years of age.
Is the efficacy of selpercatinib expected to be similar across the various RET mutations? *Is the efficacy of selpercatinib expected to be similar in patients with sporadic MTC vs hereditary MTC?*	pERC agreed with the clinical experts, they do not expect to see variations in response based on any of these subgroups or population's characteristics.
Considerations for continuation or renewal of therapy	
The LIBRETTO-001 trial evaluated patients via radiologic assessments every 8 weeks for 1 year and then every 12 weeks thereafter. Calcitonin and carcinoembryonic antigen (CEA) levels were measured. *In clinical practice, how will treatment response to selpercatinib be assessed?*	pERC noted that according to clinical experts, patients are assessed approximately every 3 to 6 months during follow-up visits, and clinicians (besides OS and PFS) will evaluate different measures of response such as the RECIST criteria, CEA, calcitonin, general symptoms, and HRQoL.
Considerations for discontinuation of therapy	
In the LIBRETTO-001 trial, patients with documented disease progression could continue selpercatinib if they were deriving clinical benefit. *What are the discontinuation criteria for selpercatinib?*	pERC noted that clinical experts stated that deterioration of symptoms, functional status, radiological evidence of disease progression (together with other clinical criteria), and unacceptable toxicity from treatment are among the issues commonly used in clinical practice to decide to discontinue treatment on a case-by-case basis.
Considerations for prescribing of therapy	
Selpercatinib dose is based on weight and is available as 40 mg and 80 mg capsules: Under 50 kg: 120 mg orally twice daily	pERC acknowledged the recommended dosage as per the Health Canada product monograph and agreed with proceeding with the recommended dosage.

Implementation Issues	Response
50 kg or greater: 160 mg orally twice daily Administered at home by patient or caregiver.	
Generalizability	
Patients with an ECOG of greater than 2 were excluded from the trial. *Can patients with and ECOG > 2 be considered eligible for treatment?* Only patients 12 years and older were eligible for the trial. *Can the results of the trial be applied to children under 12 years of age with unresectable or metastatic RET-mutant medullary thyroid cancer?*	pERC noted the input from the clinical experts. For both questions/situations, the clinical experts recognize that the evidence is very uncertain and scarce, and considering this, the clinical expert input is that selpercatinib could be offered in the pediatric population on a case-by-case basis. The same would apply to patients with an ECOG status above 2. pERC acknowledged that clinicians may consider using selpercatinib for patients with an ECOG performance status greater than 2 at their discretion. pERC noted that the Health Canada approved indication of selpercatinib is for pediatric patients 12 years and above and that selpercatinib is not indicated for patients under 12 years of age.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs. Drug may change place in therapy of drugs reimbursed in subsequent lines.	pERC acknowledged the drug plan statement. pERC noted that there are currently no targeted therapies available for RET-mutant MTC. pERC agreed with the clinical experts that selpercatinib will have an impact in the treatment paradigm of patients with RET-mutant MTC.
Is the efficacy of selpercatinib impacted by the line of therapy in which it is used?	pERC felt that there is no clear evidence of any difference in activity based on prior treatments.
Is there evidence to support the use of vandetanib after progression on selpercatinib?	pERC noted that no evidence available from the LIBRETTO-001 study looked at vandetanib after selpercatinib.
Care provision issues	
Selpercatinib is supplied as 40 mg capsules (60 capsules per bottle) and 80 mg capsules (60, or 120 capsules per bottle). There are multiple dosing schedules and potential for dose adjustments with selpercatinib. Current manufacturer packaging/storage requirements allow for flexible dispensing options (e.g., blister packaging of doses, using capsules from one bottle for multiple prescriptions, if necessary).	pERC acknowledged the recommended dosage as per the Health Canada product monograph and noted the care provisions highlighted by the Drug Plans.
RET testing needs to be in place to identify eligible patients.	pERC discussed access to RET testing across Canada and agreed with the drug plan statement.
System and economic issues	
There is confidential pricing for vandetanib.	pERC acknowledged that vandetanib is a funded treatment option for adult patients.

CEA =carcinoembryonic antigen; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; IAS = integrated analysis set; MTC = mutant medullary thyroid cancer; OS = overall survival; PAS = primary analysis set; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; RET = rearranged during transfection SAS 1 = supplemental analysis set 1

Clinical Evidence

Description of studies

One clinical study, LIBRETTO-001, is included in this report. This is an ongoing, multicenter, open-label, phase 1/2, single arm study of oral selpercatinib (LOXO-292) in patients with advanced solid tumors, including RET fusion-positive solid tumors, MTC, and other tumors with RET activation. The focus of this CADTH report is on the MTC population. The sponsor has used different cutoff dates; first, the 17 June 2019 cut-off date was used for Food and Drug Administration (FDA) / European Medicine Agency (EMA) initial submissions. Then the 16 December 2019 data cut-off served as the basis of the Summary of Clinical Efficacy in LIBRETTO-001, which was used in the submissions to the FDA, Health Canada, and the EMA. The pre-planned analysis at the 16 December 2019

data cut-off was conducted to support the submission of the "Day 60 Efficacy and Safety Update" for the Food and Drug Administration (FDA), which provided at least 6 months of follow-up information for all patients enrolled as of the initial data cut-off of June 17, 2019. Furthermore, data for a cut-off of 30 March 2020 submitted by the sponsor is described in this report. The main analyses of efficacy are presented in this report with a data cutoff date of 16 December 2019 where the pre-planned primary analysis set is described

There were two main phases in the LIBRETTO-001 study. Phase 1 or dose escalation phase, and phase 2 or dose expansion phase. In both phases, patients were planned to be enrolled to one of five Phase 2 cohorts to characterize the safety and efficacy of selpercatinib in specific RET abnormalities. Cohort 1 includes patients with RET fusion-positive solid tumor progressed on or intolerant to ≥ 1 prior standard first-line therapy, Cohort 2 includes patients with RET fusion-positive solid tumor without prior standard first-line therapy, Cohort 3 included patients with RET-mutant MTC who progressed on or were intolerant to ≥ 1 prior standard first-line cabozantinib and/or vandetanib, Cohort 4 with RET-mutant MTC without prior standard first-line cabozantinib or vandetanib or other kinase inhibitors(s) with anti-RET activity, and Cohort 5 included patients in Cohorts 1 through 4 without measurable disease, MTC not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), or poorly differentiated thyroid cancers with other RET alteration/activation, and cfDNA positive for a RET gene alteration not known to be present in a tumor sample. This CADTH review focuses on the MTC population that was included in Cohort 3 and Cohort 4.

For phase 1, the primary objective of the study was to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of selpercatinib. Secondary objectives for Phase 1 included determination of the safety and tolerability of selpercatinib, characterization of the pharmacokinetic (PK) properties, and assessment of the anti-tumor activity of selpercatinib. For phase 2, the primary objective was to assess, for each expansion cohort, the anti-tumor activity of selpercatinib by determining objective response rate (ORR) using Response Evaluation in Solid Tumors version 1.1 (RECIST 1.1) or Response Assessment in Neuro- Oncology (RANO), as appropriate to tumor type. Secondary objectives for Phase 2 included other efficacy parameters including best change in tumor size from baseline, duration of response (DOR), central nervous system (CNS) ORR, CNS DOR, time to any and best response, clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and determination of the safety and tolerability of selpercatinib, and characterization of the PK properties. Exploratory objectives were PK and collection of patient-reported outcomes (PROs) data to explore disease-related symptoms and health-related quality of life (HRQoL). After MTD was defined, a dose expansion assessment was conducted to obtain the recommended RP2D of 160 mg orally twice a day, selected by the Safety Review Committee (SRC).

ORR was calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of CR or PR) with 95%CIs. DOR was defined as the number of months from the start date of CR or PR and using Kaplan Meier estimates for the median, right censoring patients with subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression, patients who died or experienced documented disease progression after missing 2 or more consecutively scheduled disease assessment visits, and those alive and without documented disease progression on or before the data cutoff date. OS and PFS were similarly assessed with methods used for DOR. All efficacy results presented were evaluated by IRC.

For December 16, 2019, data cut-off (n=226), the mean age of patients with RET-mutant MTC was 56.1 years with only 3 patients being less than 18 years of age, and two-thirds between 45 and 75 years of age. Of note, in terms of distribution by sex, 65.5% were of the male sex group. Most patients were ECOG PS status of 0 or 1, with only 12 (5.3%) presenting an ECOG of 2, with an average of 95 months since diagnosis. All but two patients had a history of metastatic disease. Most patients presented with diarrhea at baseline (61.5%).

Efficacy Results

In the population of patients with RET-mutant MTC from LIBRETTO-001 (cut-off date 16 December 2019), for OS, with a median duration of follow up of [redacted]. The rate of survival [redacted]. For the cut-off date of 30-March-2020, the group of

patients in the PAS (n=55) reached a median OS of 33.2 months (range 1.1+ to 33.3+) with similar values in the IAS group. The SAS group did not reach the median of survival.

For PFS (cut-off date 16 December 2019) with a median duration of follow-up of 16.7 months (IQR 14.8 to 22.1), the median for PFS for the PAS population was not reached and the range went from 0 to 29.4 months. The rate of PFS at 12 months or more was 82.3% of the population. For the cut-off date of 30-March-2020, none among the groups evaluated (PAS, IAS, SAS) reached a median for PFS (range 0.0+ to 32.2+).

The percentage of patients reaching an ORR (cut-off date 16 December 2019) was 69.1% (95%CI 55.2 to 80.9) and it was similar across the different sets. For the cut-off date of 30 March-2020, results on the ORR were similar (69.1% for the PAS and similar across other sets).

With a median follow-up of 14.06 months (IQR 10 to 17.5), the median DOR (cut-off date 16 December 2019) was not reached in any analysis set, except for the SAS1 (of 21.9 months, range 1.8 to 22). For the cut-off date of 30 March 2020, the results were similar, except for SAS 1 group, where the duration of response reached a median of 21.9 months (range 1.5 to 24.1), but with a median follow-up of 9.2 months. The percentage of patients with an observed DOR of 12 months or greater (cut-off date 16 December 2019) was 55.2% in the PAS. For the cut-off date of 30 March 2020, the percentage of patients with an observed DOR of 12 months or greater was 68.4% in the PAS group.

HRQoL published data from the 16 December 2019 cut-off date was obtained from one sponsor publication, including patients at the cut-off date 16-December-2019 (n=226), of which 88 (41.5%) patients were treatment-naïve and 124 (58.5%) had previously received MKIs at study entry. Of all patients evaluated, 18.7% (36/193) met the criteria for a definite improvement and 13.0% (25/193) met the criteria for definite worsening in physical function in the QLQ-C30. Among the treatment-naïve and previously treated subgroups, respectively, 10.5% and 22.5% met the criteria for definite improvement and 14.5% and 11.3% met the criteria for definite worsening in physical function in QLQ-C30. Most patients improved or remained stable on the global health status/QoL subscale at each cycle (cycles of 28 days) during study treatment with selpercatinib. Of all patients, 29.0% (56/193) met the criteria for a definite improvement in global health status/QoL and 13.0% (25/193) met the criteria for definite worsening in global health status/QoL. Among the treatment naïve and previous treatment subgroups, respectively, 26.3% and 31.3% met the criteria for definite improvement and 17.1% and 12.5% met the criteria for definite worsening in global health status/QoL. Most patients' diarrhea improved or remained stable at each cycle during study treatment with selpercatinib. Of all patients, 43.5% (84/193) met the criteria for definite improvement in diarrhea and 9.8% (19/193) met the criteria for definite worsening in diarrhea.

Harms Results

Adverse events were reported in all but 2 patients taking selpercatinib. Among the 299 patients with RET-mutant MTC included in the safety population, 297 (99.3%) presented at least one AE, with 56.2% and 2% with grade 3/4 and grade 5 AEs respectively. A total of 11 patients (3.7%) had AEs and discontinued the drug. The most commonly reported AEs (>20% of patients with at least one of these) included hypertension, diarrhea, constipation, fatigue, headache, peripheral edema, nausea, and abdominal pain.

Serious AEs occurred in 89 (29.8%) of the 299 patients in the safety population, with 16 (5.4%) categorized as being related to selpercatinib. Among these, 6 (2%) patients had a fatal AE. The most common serious AEs were pneumonia, hypocalcemia, and hypertension, which were present in 2.3%, 2.0%, and 2% of patients respectively.

Among the 299 patients in the safety population with RET-mutant MTC, 7 (2.3%) deaths occurred within 28 days of the last dose of selpercatinib (2 due to disease progression, 5 due to adverse events), and 13 (4.3%) occurred more than 28 days after the last dose, of which 11 (3.7%) were due to disease progression, none were due to adverse events, and two were due to other events unrelated.

For harms of special interest, liver enzymes elevations occurred frequently, with 78 (26.1%) and 82 (27.4%) patients with ALT and AST elevations respectively, although most were of low grades (see Table 13). Hypertension was reported (reported as AE by preferred term) in 113 (37.8%) of patients. Diarrhea was present in 95 (31.8%) of patients at any point, and hypersensitivity was rare (3 patients). A common concern among clinicians was the QTc prolongation, which was reported in 181 (60.7%) of patients with values increased >30 msec from baseline, and 36 patients (12.1%) with values >60 msec.

For the cut-off date of 30 March 2020, harm events were similar to the ones presented in the cut-off of 16 December 2019, with 313 (99.4%) of total adverse events, and 97 patients (30.8%) with at least one serious AE. At this cut-off, 28/315 (8.9%) deaths occurred within 28 days of the last dose of selpercatinib (18 due to disease progression, 8 due to adverse events, and 2 due to other), and no deaths occurred more than 28 days after the last dose. The most common adverse effects (>5%) included dry mouth (39%), diarrhea (35%), hypertension (38%), fatigue (36%), constipation (32%), increased AST (28%), increase ALT (28%), peripheral edema (27%), nausea (25%), increased blood creatinine level (24%), abdominal pain (24%), QT interval prolonged on electrocardiograph (19%), arthralgia (19%), cough (16%), and rash (16%).

Critical Appraisal

The LIBRETTO-001 study is a single-arm, open-label, phase 1 and phase 2 design study. As such, the study is descriptive in nature as it did not evaluate the primary or secondary endpoints, e.g., ORR, DOR, OS, PFS, formally with adjustment for multiple comparisons. These limitations stem from the single-arm design and lack of comparator groups and constrain the estimation of relative effects of treatment with selpercatinib. The open-label design may also increase uncertainty in patient reported outcomes such as HRQoL, introducing bias due to inherent subjectivity of the outcome in an unblinded assessor. This bias would be less likely in more objective outcomes such as ORR, OS, or PFS if evaluated against a properly a priori set hypothesis. Furthermore, HRQoL outcomes were evaluated as exploratory endpoints with adjustments for multiplicity.

At the cut-off date of 16-December-2019, 17.7% of patients discontinued the study drug and 12.4% discontinued from the study within the efficacy population, mostly due to disease progression and death respectively. At the 30 March 2020 cut-off date, the discontinuation rates remained consistent (17.1% of patients discontinued treatment and 12.7% discontinued from the study with 7.9% and 4.4% of patients who discontinued treatment due to progressive disease and adverse events, respectively). The sponsor evaluated all 226 patients in the efficacy population and 299 patients in the safety population for primary and secondary endpoints.

There were fewer concerns about the generalizability of the population included on the effects on survival and response. According to the clinical experts consulted by CADTH, except for the variable of female sex proportion, the baseline characteristics of the population included in the LIBRETTO-001 study were overall representative of the population of patients with RET-mutant MTC seen in Canadian clinical practice. The inverse ratio of female to male patients is lower than expected as noted by the clinical experts, although they did not consider it to be a concern for applicability. Most patients had good baseline performance status (e.g., low number of patients with ECOG of 2 or higher) suggesting that the included population might be healthier when compared to the Canadian clinical practice, however, clinical experts did not consider it highly different from what is expected. All outcomes measured in the LIBRETTO001 study are of clinical relevance and, according to the clinical experts, important for patients and well known and used by clinicians in Canada. A main concern was the limitation of the follow-up, that it might be considered short for assessing longer periods of observations in those patients continuing the study and for assessing overall survival.

Indirect Comparisons

The sponsor-submitted ITC conducted a systematic review and used an unanchored matching-adjusted indirect comparison to evaluate the relative clinical efficacy of selpercatinib to cabozantinib, vandetanib, lenvatinib, sorafenib and placebo for the treatment of advanced RET-mutation positive medullary thyroid cancer (MTC). Of these comparators, cabozantinib, vandetanib, and placebo are considered relevant for this review. Three outcomes were analyzed, including overall survival, progression-free survival, and objective response rate. As part of the MAIC that compares selpercatinib and cabozantinib, weights were generated by propensity score matching methods with logistic regression. The same weights were reused for the comparison of selpercatinib with placebo.

The sponsor-submitted ITC reported that after weighting, there was a statistically significant improvement in PFS for selpercatinib versus placebo [redacted] and a statistically significant improvement in OS for selpercatinib versus placebo [redacted]. Sources of heterogeneity between the studies include differences in patient characteristics such as age, ECOG performance status, and RET M918T mutation status and differences in trial design (single- vs. multi-arm trials). The variables included in the weighting model were [redacted].

The sponsor-submitted ITC had several limitations including the lack of inclusion of all prognostic factors and effect modifiers in the MAIC weighting process ,which leads to a high risk of residual confounding, use of MAIC weights calculated for one comparison for

another comparison that involves a different patient population, heterogeneity between patient populations used in different components of the ITC, and lack of consideration and inclusion of outcomes from the CADTH systematic review protocol including DOR, HRQoL, and safety outcomes. Given these limitations, there is uncertainty around the relative treatment effect estimates estimated by the MAIC, which undermines the internal and external validity of the ITC.

Other Relevant Evidence

CADTH identified three ongoing studies relevant to this submission. LIBRETTO-531 (Phase 3 RCT of selpercatinib vs cabozantinib or vandetanib), LIBRETTO-321 (phase 2 trial conducted in China), and LIBRETTO-121 (Phase 1/2 trial in a pediatric population), none of which have peer-reviewed published data available at this time (except for LIBRETTO –121, which has results presented from a conference abstract) and are expected to be completed by 2026, 2025, and 2024, respectively.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target populations	Patients aged 12 years and older with RET-mutant medullary thyroid cancer (MTC), including treatment-naïve RET-mutant MTC (i.e., first-line treatment) and previously treated RET-mutant MTC (i.e., second- and later-line treatment).
Treatment	Selpercatinib
Submitted Price	$66.50 per 40 mg capsule; $133.00 per 80 mg capsule
Treatment Cost	$11,172 to $14,896 per 28 days
Comparators	• Vandetanib • Best supportive care (BSC; consisting of monitoring and palliative care)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	• Selpercatinib: single-arm non-randomized ”basket trial” (LIBRETTO) – analysis of data limited to RET-mutant MTC patients – treatment-naïve (n = 124); treatment-experienced (n = 88) • Unanchored matching adjusted indirect comparison (MAIC) comparing selpercatinib to BSC • Naïve comparison of BSC to vandetanib
Key limitations	• The comparative efficacy of selpercatinib on PFS and OS is unknown due to lack of head-to-head evidence for selpercatinib to vandetanib or BSC, as well as unresolvable uncertainty in the sponsor’s unanchored MAIC comparing selpercatinib to BSC and naïve comparison to vandetanib. • The pharmacoeconomic model was informed by pooled OS and PFS data for treatment-naïve and treatment-experienced patients. As such, the sponsor’s results, as well as CADTH exploratory reanalyses results, reflect the use of selpercatinib in any line of therapy, and the cost-effectiveness of selpercatinib specifically in the first- or second-line setting is unknown. • The choice of a PSM to evaluate the cost-effectiveness of selpercatinib is inappropriate given the high level of uncertainty associated with the PFS and OS data from the LIBRETTO trial. The sponsor’s model assumes that patients are at risk of death only after disease progression, which is not supported by data from LIBRETTO. • Adjustment of drug acquisition costs by dose intensity observed in the LIBRETTO trial biased the ICER in favor of selpercatinib.

Component	Description
	• A lack of clinical data means that the cost-effectiveness of selpercatinib among patients aged 12 to 17 years was not considered in the sponsor's submission. Findings among adult patients were assumed to apply to adolescents, which may be inappropriate. • The model lacks transparency and is inefficiently programmed. Numerous errors were identified in the analysis, and CADTH could not ensure the model results were accurately calculated.
CADTH reanalysis results	• Due to the identified limitations regarding the lack of comparative clinical effectiveness information, as well as issues with the submitted model (including poor modelling practices and structural limitations), the comparative clinical effectiveness and, as a result, the cost-effectiveness of selpercatinib relative to vandetanib or BSC is unknown. • CADTH conducted exploratory analysis, which included adjusting for pre-progression mortality and adopting appropriate estimates of drug acquisition costs. CADTH was unable to explore the cost-effectiveness of selpercatinib in the first- or second-line setting owing to a lack of clinical data. • In CADTH exploratory reanalyses, the ICER for selpercatinib is $350,341 per QALY ($350,703 per QALY including RET mutation testing) compared to vandetanib and $347,785 per QALY ($348,105 per QALY including RET mutation testing) compared to BSC in any line of therapy. Price reductions of 78% and 87% would be required for selpercatinib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY threshold compared to vandetanib and BSC, respectively. The results of these reanalyses should be viewed only as exploratory given the limitations highlighted above

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; MAIC = matching adjusted indirect comparison; PFS = progression-free survival; PSM = partitioned survival model; QALY= quality-adjusted life-year

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for selpercatinib is uncertain; the drug cost of selpercatinib was underestimated; and the sponsor's base case included a drug cost for BSC, which conflicts with BSC costing in the cost-utility analysis.

CADTH reanalysis included: adopting alternative assumptions about the proportion of MTC patients with a RET mutation and assuming a dose intensity of 100% for all drugs. In the CADTH base case, the budget impact of reimbursing selpercatinib is expected to be $532,786 in year 1, $1,028,241 in year 2, and $1,436,958 in year 3, with a three-year total of $2,997,985 in the second-line setting.

The estimated budget impact is highly sensitive to the estimated proportion of thyroid cancer patients with MTC.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: April 12, 2022

Regrets

3 expert committee members did not attend.

Conflicts of Interest

None