CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

ELEXACAFTOR/TEZACAFTOR/IVACAFTOR AND IVACAFTOR (Trikafta)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Cystic fibrosis, F508del CFTR mutation

February 12, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0673-000**
Generic Drug Name (Brand Name)	**Elexacaftor/tezacaftor/ivacaftor and ivacaftor**
Indication	**People with a diagnosis of cystic fibrosis ages 12 and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene**
Name of the Clinician Group	**Canadian Cystic Fibrosis Clinic Directors**
Author of the Submission	[redacted]
Contact information	[redacted]

1. About Your Clinician Group

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

There are 42 cystic fibrosis clinics in Canada, delivering multi-disciplinary specialty care to people with cystic fibrosis. Each clinic has a physician who serves as the medical director of the clinic. Clinic directors have special training, expertise, and experience in delivering medical care and support to people with cystic fibrosis.

2. Information Gathering

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

1) Personal experience gained by working with and delivering medical services to people with cystic fibrosis.
2) Personal experience treating people with cystic fibrosis who received elexacaftor/tezacaftor/ivacaftor and ivacaftor, either during participation in clinical trials or the Health Canada Special Access Program.
3) Review of the medical and scientific literature, including clinical trial results.
4) The Cystic Fibrosis Canada Canadian Cystic Fibrosis Registry, a collection of patient data and other information regarding CF care and outcomes.

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:

Cystic fibrosis (CF) is a fatal, progressive genetic disease that affects approximately 4,300 Canadians, with an incidence of approximately 1/3,600 live births. In 2019 there were 116 new cases diagnosed in Canada, with 76 of those diagnosed through provincial newborn screening programs.[1] It is a lifelong, chronic, degenerative disease that affects multiple organ systems, most importantly the lungs and the digestive system.

People living with cystic fibrosis are prescribed a multitude of treatments, including high-calorie high fat high protein diets, medications, and airway clearance treatments. Because it has been shown that the physiological manifestations of CF start very early in life and in otherwise asymptomatic patients, many of these treatments start at the time of diagnosis and continue throughout life. There are several classes of medications, including acute and chronic antibiotic therapies, mucolytics, bronchodilators, pancreatic enzymes, fat soluble vitamin supplementation, insulin for people with cystic fibrosis related diabetes, ursodiol for liver disease, and more. Physiotherapy (airway clearance) treatments are prescribed once to several times a day. Most people with cystic fibrosis spend at least 1-2 hours a day on treatments, and this time commitment and treatment complexity increases as the severity of the disease increases.

In addition to these treatments, the recommendations for CF care include routine medical visits to the cystic fibrosis clinic every three months. Additional visits may be required due to illness or for closer follow up of progressing symptoms, severe disease, or pre- and post-transplant care. Hospitalizations and home intravenous treatments may be required for acute respiratory infections or other complications of cystic fibrosis, such as distal intestinal obstructive syndrome. According to the 2019 Cystic Fibrosis Registry report, Canadians with CF had over 18,900 clinic visits that year and logged 25,200 hospital days and 15,500 home IV treatment days.[1]

In addition to the direct medical costs for these clinic visits, hospitalizations, and treatments, there are indirect costs: lost days of work and school, travel costs, risk of employment insecurity and decreased lifetime earning potential, non-insured personal medical expenses, reduced participation in creative and leisure activities, and others.

The population of Canadians with CF has had a much better median age of survival than populations in other countries, due to multiple factors.[2] With the disparity in the availability of CFTR modulator therapies in the US and Europe, Canadian clinicians are concerned that our patients may fall behind.

Lung transplant is a treatment for end-stage CF pulmonary disease. It comes with risk factors and additional treatment burden and does not address CF disease in other organ systems. The median length

of survival after lung transplant reported in the 2019 Registry report was 10.6 years, so it is not a cure, and the direct cost of medical care involved in lung transplant is around $1,000,000. Lung transplantation is only offered at four centres in Canada, and relocating to one of these centres (Toronto, Montreal, Edmonton, or Vancouver) is required during parts of the transplant process

Most of the current CF treatments treat the symptoms, attempt to slow down the progression of the disease, and treat acute exacerbations such as acute pulmonary infections.

The first- and second-generation cystic fibrosis transmembrane regulator (CFTR) modulator medications ivacaftor, ivacaftor-lumacaftor, and ivacaftor-tezacaftor, were the first commercially available treatments to treat the underlying disease mechanism: a poorly produced and/or malfunctioning CFTR protein. They are currently available to only about 12% of Canadians with CF. Ivacaftor was recommended for provincial reimbursement and is generally available for qualifying patients, but access to the the other mildly effective CFTR modifier medications is limited to participation in clinical trials, private insurance coverage, or very limited special provincial programs.

References:

1. Cystic Fibrosis Canada. Canadian Cystic Fibrosis Registry, 2019.
2. Stephenson, AL, Sykes J, Stanojevic S, et al. Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States. A Population-Based Cohort Study. Ann Intern Med. 2017;166:537-546. doi: 10.7326/M16-0858

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:

An ideal treatment for CF would be one that decreased the daily burden of the disease incurred by people with CF, including decreasing treatment burden, decreasing symptoms, and improving the quality and duration of life. It would decrease disability and delay disease progression. It would eliminate or delay the need for double lung transplant.

It would not be excessively burdensome, and the risks of the treatment would be minor compared to the benefits.

An ideal treatment would decrease the burden on families of children with CF, as parents are the main caregivers providing the extra nutrition, physiotherapy, medication regimens, and medical visits needed, and would allow adults with CF to remain independent longer. By delaying the progression of the disease and the disability associated with moderate and severe lung disease, it would allow people with CF to remain in employment, pursue creative endeavours, and engage in other activities that benefit society. Education and work activities would not need to be as curtailed by symptoms, hospitalizations, and health care visits.

It would allow people with CF to plan more confidently for careers, relationships, and family life, and could decrease the factors associated with the disease that can negatively affect mental health.

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:

The current commonly available treatments only treat the symptoms and complications of CF and thus attempt to slow down the eventual fatal progression of the disease.

Development of progressive, non-reversible lung disease and antibiotic resistance in bacteria involved in acute and chronic lung infections due to repeated antibiotic exposure make treatment of infection more difficult with time.

Burden of care is high and increases with age and the severity of the disease. A recent study by the James Lind Alliance Priority Setting Partnership (JLA PSP) in cystic fibrosis surveyed people with CF, parents of children with CF, and health care workers to determine perceived priorities for CF research.[1] Important themes than emerged were that the lived experience of treatment burden in CF is high, that it extends beyond just the time taken to perform routine daily treatments, and that the impact on daily life varies. Adherence to the more burdensome treatments, such as nebulized antibiotics and airway clearance are often the first to be missed. Of the subset of people with CF who answered questions regarding work and education, “87% (202/233) felt that their treatments get in the way of their job or career and 77% (168/217) in the way of their education. Two thirds (67%; 207/311) reported that their treatments get in the way of family relationships, relationship with a partner (69%; 162/236), and relationships with friends (75%; 227/304). An impact of treatments on socialising and on sports and hobbies was reported by 81% (250/308) and 80% (231/289), respectively.”[1]

Other treatments to treat the molecular basis of the disease, such as gene therapy, have been under development for years but have not progressed beyond the research stage.

The CFTR modulators currently available have been shown to be effective for some patients. Ivacaftor can lead to an important improvement in lung function and various symptoms of CF, but it is only effective for a small number of people with CF (about 4% in Canada) with specific mutations. Ivacaftor-lumacaftor shows a modest effect on lung function and other parameters in clinical trials, but it was previously reviewed by CADTH and was not recommended for reimbursementcoverage due to high cost and the cost-benefit factors. Ivacaftor-tezacaftor has effects similar in scale to ivacaftor-lumacaftor.

The development of a highly effective CFTR modifier such as elexacaftor/tezacaftor/ivacaftor fills a niche in CF care that is not currently occupied by another equally effective treatment.

While elexa/teza/iva is currently available through the Special Access Program, it is only available to persons with advanced very severe lung disease. While it has improved the status of patients at this level

of disease, they remain with severe disease that may have been prevented or delayed by earlier treatment with a highly effective modulator.

There will remain approximately 10% of people with CF in Canada who have CFTR mutations that do not respond to any of the current CFTR modulator therapies. Research continues to find a treatment for this group.

In addition, the current application for elexa/teza/iva is for ages 12 and up. There are clinical trials in younger age groups underway, and if the results are positive, we hope that there will be another application for younger patients. Also, it has not yet been determined if CF patients with lung transplant will have non-pulmonary benefits from this medication.

References:

1. Davies G, Rowbotham NJ, Smith S, Elliot ZC, Gathercole K, Rayner O, et al. Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. J Cyst Fibros 2020;19(3):499–502.

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:

Elexacaftor/tezacaftor/ivacaftor (elexa/teza/iva) has the potential to treat the majority of Canadians with cystic fibrosis.

Currently, patients who are heterozygous for F508del and another non-gating CF mutation (so not eligible for ivacaftor) would not benefit from currently available CFTR modulator medications (ivacaftor-tezacaftor and ivacaftor-lumacaftor).

Although people who are homozygous for F508del (2 copies) are eligible for the currently approved CFTR modulators, the high cost and lack of payment coverage meansthat many patients do not have access to these medications. For example, in the Saskatoon Pediatric CF Clinic, only 1 out of 19 eligible patients has been able to have the medication reimbursed by private insurance.

The current Health Canada Special Access Program for elexa/teza/iva is currently limited to patients with severe lung disease. While they are in particular need of the medication to stave off death or transplant, the chronic organ damage has already been done. Treatment must also be available to people with CF in the early stages of the disease, to help prevent or delay the more severe manifestations that impose a high burden on the person with CF and the health care system. However, people with severe lung disease are benefiting clinically from the SAP, with transplant centres reporting delisting patients due to clinical improvement, so they should also be considered for this therapy if the SAP is discontinued once market approval is obtained.

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:

Currently, elexa/teza/iva is added on to existing therapies. There are studies underway, particularly in the US, where this medication is widely available and reimbursed, and is part of the regular treatment guidelines, to look at the effect decreasing the number or intensity of other CF treatments in people taking elexa/teza/iva.

While elexa/teza/iva is not the first CFTR modulator developed, it is so far the most effective for most persons with CF, and expands the number of people who will be eligible for treatment with a modulator,according to clinical trial results.

A Canadian group used a microsimulation transition model to estimate the effect of the introduction of elexa/teza/iva on the Canadian CF population. In this model, the number of persons with severe lung disease decreased by 60%, the number of pulmonary exacerbations decreased by 19%, and the number of lung transplants decreased by 146 during the period 2021-2030 if the medication is introduced by 2021. Decreasing the need for acute treatments and lung transplant would be a shift in the role of these treatments in the disease.[1]

Reference:

1. Stanojevic S, et al. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. J Cyst Fibros, article in press, published online August 23, 2020. DOI:https://doi.org/10.1016/j.jcf.2020.07.017

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:

Persons with CF in Canada will have already been prescribed the standard treatments whether or not they initiate treatment with elexa/teza/iva under the current treatment recommendations. They would continue the current treatments aimed at controlling symptoms and disease progression.

If the cost of the new medication is similar to the currently available, less effective CFTR modulators, there is no advantage to starting one of them prior to starting elexa/teza/iva. If coverage for ivacaftor/tezacaftor and ivacaftor/lumacaftor remains the same, these will also not be financially viable options for the majority of Canadian CF 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:

The sequence of therapies will not change if the new therapy fails. If the person's condition changes or further information suggests that the medication may then be effective, it could be tried again, with careful monitoring for effectiveness.

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:

Because the effects of this medication depend on the CFTR genotype, it has currently been found effective in persons with at least one copy of the F508del mutation. Health Canada approval has been requested for persons 12 and up, and studies have included people with all severities of lung disease.

Because CF is a chronic, progressive, and eventually fatal disease, all patients with CF who are eligible for this therapy are at need of an intervention. The current Special Access Program only covers patients with severe lung disease, but limiting it to this population does not address the progressive nature of the disease at an earlier stage, where the progression to severe disease and disability could be prevented or delayed.

Many of the clinical studies only included persons with lung function measured by FEV1 percent predicted between 40-90%. While this design was important for clinical trials, further clinical experience and some research results have found that the medication was useful in patients with FEV1 < 40%. In patients with FEV1 > 90%, there are often early signs of CF lung disease present, such as bronchiectasis, mucus plugging, or early mild declines in FEV1% predicted that could benefit from therapy with elexa/teza/iva. Limiting coverage or access to this therapy by lung function measurements will leave some patients who could benefit at risk.

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:

As the Canadian Cystic Fibrosis clinic system is well established and covers almost all persons with CF in Canada, patients best suited and qualifying for this medication would be identified by their CF care provider based on the genotype of their CFTR mutations and other clinical factors. The criteria for diagnosing CF are well established and standardized, and the appropriate tests are available at CF clinics.

CFTR genotype is standardly performed on persons with CF (with consent) and is available to the practitioner prescribing the medication.

Because CF is a genetic, progressive chronic disease, manifestations of the disease start in early life. Treatment with this potentially disease altering medication should not be held until persons become more symptomatic or until lung function deteriorates.

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

Response:

Any patient who does not have a CFTR mutation genotype that would respond to the medication, or persons with a known allergy or other adverse reaction to this or a similar medication.

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:

Patients would be identified by their CF clinic care provider based on having an eligible CFTR genotype and no contraindications to this therapy.

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:

The treatment guidelines recommend routine medical visits to the CF clinic every three months. Standard parameters such as vital signs, height and weight, pulmonary function testing, and other measures are recorded at these visits. In addition, other tests such as radiological exams and blood work are obtained at regular intervals. These are routinely used to follow CF disease and will also be used to follow clinical response to this medication.

The frequency of pulmonary exacerbations and other conditions requiring urgent care and/or hospitalization would be monitored by the CF Clinic team.

In addition, patients who started the other CFTR modulators have also had other evaluations if indicated (ophthalmologic examinations, measurement of fecal elastase for pancreatic function, sweat chloride measurements, etc.) to look for response to these medications.

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:

The improvements that have been measured in most clinical trials include pulmonary function testing, weight and nutritional status, and quality of life. In clinical practice, patients have reported feeling better, having fewer symptoms such as cough or shortness of breath, missing less work or school due to medical issues, and stabilization of the disease. Increased attention to quality-of-life measures and screening measures to detect mental health issues have led to these aspects also being included in response to treatment clinically.

6.10. How often should treatment response be assessed?

Response:

Because of the routine clinic visits at three-month intervals, treatment response is assessed frequently. For ivacaftor/tezacaftor and ivacaftor/lumacaftor, a visit at one month after the start of therapy was also commonly used to assess for early response and potential side effects.

Canadian protocols for longitudinal assessment of treatment response are being developed.

On a population basis, the Canadian CF Registry will be used to track changes in factors such as hospitalization, lung function decline, mortality, and lung transplant.

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:

As with any treatment, discontinuation should be considered if a severe side effect, allergy, or other adverse event occurs. With this medication, the development of signs of worsening liver disease may require stopping treatment.

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

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

Response:

This treatment should be prescribed by practitioners at an accredited Cystic Fibrosis clinic. It is a twice daily oral treatment, so it will be taken as an outpatient as part of the person's standard routine.

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:

Almost all patients with cystic fibrosis in Canada are followed at accredited Cystic Fibrosis clinics, which are staffed by professionals who have the training and experience in diagnosing, treating, and monitoring persons with CF who would be treated with this medication.

7. Additional information

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

Response:

Cystic fibrosis clinicians who have had patients treated with elexa/teza/iva, either through the Special Access Program (SAP) or clinical trials, have many examples of how their patients' lives and medical condition have been changed after starting this therapy. In order to safeguard patient confidentiality, we cannot report identifying details, but a few common themes are emerging.

Clinic directors in Manitoba, Nova Scotia, Alberta, Saskatchewan, Ontario and British Colombia shared reports of patients who were on the lung transplant waitlist that have been delisted due to marked improvement in lung function. The transplant centers are seeing similar results, with patients being taken off the waitlist because their condition has improved. So far, we've heard of at least 40 patients who have improved enough to be delisted or to have transplant evaluations put on hold.

An older adolescent had to have two similar surgeries: the first, before starting elexa/teza/iva, was complicated by poor wound healing, pain, and a prolonged hospital stay. The second, one month after starting therapy and two months after the first, went smoothly, with faster recovery and a normal length of stay. Another adolescent patient, on palliative care after deciding against lung transplant, has stabilized and now is planning to get his GED and possibly a job instead of preparing for death.

A patient in the Maritimes with recurrent pneumothoraces and frequent and prolonged hospitalizations stabilized after starting elexa/teza/iva through the Special Access Program. He had a dramatic improvement and is no longer being considered for transplant assessment.

Other patients who had repeated courses of antibiotics and repeated hospitalizations have had less frequent or no hospitalizations since starting elexa/teza/iva and many fewer courses of antibiotics. SAP patients, who in order to qualify have to have very severe disease, have had improvements in FEV1% predicted that boost them up into the severe or moderate disease categories – still affected, but more able to participate in activities of daily living, work, and school.

We hear stories from colleagues in the US of patients coming off disability and going back to work. This medication may play the same role in CF as some of the highly effective medications played in HIV/AIDS, turning it from a fatal to a manageable chronic disease. This is probably the most major breakthrough in cystic fibrosis since the discovery of the gene in 1989.

When we meet with the parents of a baby newly diagnosed through newborn screening, they ask us if there is hope. They know that CF is a progressive, fatal disease. With the arrival of the CFTR modulators, we have been able to pass on the hope that, with treatment, the burden of CF will be less than previously and their child's future less clouded by the disease. For adults living with CF, it means being able to plan for a future that didn't previously seem likely and to continue to contribute. For CF clinicians and care teams, it holds out the promise of being able to help our patients reach their goals and spend less time in hospital and fewer treatments and procedures If the projections in the microsimulation transition model[1]

hold, the number of pulmonary exacerbations requiring hospitalization or home IV therapy could drop by 4135 during the period 2021-2030 if the medication becomes available in 2021.

The distribution of severity of lung disease would also change, with more individuals in the mild lung disease category and fewer in the severe lung disease category. Persons in the severe lung disease category are frequently unable to work or go to school, to participate in many activities, and may progress towards death or transplant within a few years.

In the model, the median age of survival is projected to increase by 9.2 years if the medication becomes available soon.

1. Stanojevic S, et al. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. J Cyst Fibros, article in press, published online August 23, 2020. DOI:https://doi.org/10.1016/j.jcf.2020.07.017

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 assistance was provided in completing this submission, except for the email address list of Canadian CF Clinic Directors supplied by CF Canada.

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.

   Some data was obtained form the Canadian Cystic Fibrosis Registry, which is published and available in print or online. PubMed and Google Scholar were used to locate appropriate publications in the medical literature.

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	*Martha L. McKinney, MD MPH FRCPC*
Position	*Pediatric Cystic Fibrosis Clinic Director, Associate Professor, University of Saskatchewan*
Date	*11-02-2021*
☒	**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**
Vertex Pharmaceuticals	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr Pearce Wilcox*
Position	*Professor Department of Medicine UBC, Medical Director Adult CF Program St Paul's Hospital/UBC*
Date	*11/02/2021*
☒	**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**
Vertex Pharmaceuticals	☐	☒	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Julian Tam, MD FRCPC*
Position	*Saskatoon Adult Cystic Fibrosis Clinic Director, Assistant Professor, University of Saskatchewan*
Date	*12-02-2021*
☒	**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**
AstraZeneca – unrestricted research grant	☐	☒	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Lenna Morgan*
Position	*Director, Pediatric CF Clinic, Windsor Regional Hospital*
Date	*February 12, 2021*
☒	**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**
No COIs	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Nancy Porhownik*
Position	*Adult Cystic Fibrosis Clinic Director, Assistant Professor, University of Manitoba*
Date	*11-02-2021*
☒	**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**
No COI	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*April Price*
Position	*Division Head, Associate Professor, Paediatric Respirology* *Paediatric Cystic Fibrosis Clinic Director*
Date	*21-02-21*
☒	**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**
Vertex	☒	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Winnie Leung, MD FRCPC*
Position	*Edmonton Adult Cystic Fibrosis Clinic Medical Director, Associate Clinical Professor, University of Alberta*
Date	*12/02/2021*
☒	**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**
Vertex Pharmaceuticals	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Nancy J. Morrison, MD, FRCPC*
Position	*Adult Cystic Fibrosis Clinic Director, Professor, Dalhousie University*
Date	*12/02/2021*
☒	**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**
*Vertex Pharmaceuticals **	☐	☐	☒	☐

- This is grant funding for a clinical trial – did not receive any personal payments for this.
- Personal payments would be $0-5,000

Declaration for Clinician 9

Clinician Information	
Name	*Abid Lodhi*
Position	*Director, Pediatric Cystic Fibrosis Clinic Regina. Assistant Professor, University of Saskatchewan*
Date	*11-02-2021*
☒	**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**
No COI	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*Jim Lewis*
Position	*Medical Director of Adult CF Clinic in London Ontario.*
Date	*Please add the date form was completed (11-02-2021)*
☒	**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**
No COI	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 11

Clinician Information	
Name	*Michael Derynck, MD, FRCPC*
Position	*Pediatric Cystic Fibrosis Clinic Director, Kingston Health Sciences Centre* *Assistant Professor, Queen's University*
Date	*12-02-2021*
☒	**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**
No conflict of interest	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 12

Clinician Information	
Name	*M. Diane Lougheed*
Position	*Professor of Medicine, Queen's University: Director, Adult CF Clinic, Kingston, ON*
Date	*Please add the date form was completed (11-02-2021)*
☒	**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**
AstraZeneca (investigator initiated research project, paid to Queen's University)	☐	☐	☐	☒
GlaxoSmithKlein(multicentre asthma study, paid directly to Queen's University	☐	☐	☒	☐
Manitoba Workers Compensation Board Grant (paid to Queen's University)	☐	☐	☐	☒

Declaration for Clinician 13

Clinician Information	
Name	*Tamizan Kherani*
Position	*Assistant Professor, Department of Pediatrics, University of Alberta*
Date	*12-02-2021*
☒	**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**
Vertex Pharmaceuticals	☒	☐	☐	☐

1. 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 14

Clinician Information	
Name	*Linda Pedder, MD, FRCP C*
Position	*Medical Director, Cystic Fibrosis Clinic, McMaster Children's Hospital, Hamilton Health Sciences, Associate Professor, McMaster University*
Date	*16/02/21*
☒	**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 Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0673-000**
Generic Drug Name (Brand Name)	**Elexacaftor/tezacaftor/ivacaftor and ivacaftor**
Indication	**Cystic fibrosis, age > 12 years with at least 1 F508del mutation**
Name of the Clinician Group	**Toronto Adult CF Clinic**
Author of the Submission	[redacted]
Contact information	[redacted]

1. About Your Clinician Group

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

The Toronto Adult CF Clinic was established 3 decades ago and since that time has provided care for > 1,000 adults with CF, 600 of whom are still alive. We follow 60% of all adults with CF in Ontario and a quarter of all adults with CF in Canada. There are 5 academic CF Respirologists (Drs. Anand, Chaparro, McIntyre, Stephenson and Tullis) working in the clinic alongside of a multidisciplinary team including specialized CF pharmacists (Kevin Curley).

www.torontoadultcf.com

2. Information Gathering

1. Review of published literature on CFTR modulators (clinical trials and registry studies)
2. Review of published CF clinical guidelines
3. Clinical experience
4. Review of outcomes of the 50 patients in our clinic who are receiving elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) through Special Access Program and manufacturer's compassionate use program.
5. The Cystic Fibrosis Canada Canadian Cystic Fibrosis Registry

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:

Cystic Fibrosis (CF) is the most common fatal, genetic disease in the Canadian population. Mutations in the CF gene cause abnormalities in the CFTR protein which is a channel that that allows chloride and bicarbonate to move across cell membranes. CFTR is responsible for the hydration of mucus secretions in the body. Defects in CFTR cause thick, dehydrated secretions in multiple organs including the lungs, digestive tract, pancreas, liver, reproductive tract, and sinuses. The thick mucus can block the ducts in various organs and harbour bacteria leading to chronic infection. Damage is present at birth in some organs (pancreas, vas deferens) and accumulates over time in others (lung, liver, sinuses) with symptoms progressing over a lifetime. Treatment is lifelong, intensifying over time so that adults with CF can spend much of each day, every day doing therapy. To date, there is no cure for CF. Therapies can be divided into those that treat the consequences of accumulation of this abnormal mucus and those that tackle the actual defects in the CFTR protein.

Therapies that treat the downstream consequences of CF in the lungs include chest physiotherapy and exercise to promote clearance of mucus from the airways, inhaled mucolytics which thin the mucus, inhaled antibiotics, anti-inflammatory agents (inhaled and oral), inhaled bronchodilators, and in patients with severe lung disease, supplemental oxygen and non-invasive ventilation. Lung transplant is required for end stage respiratory failure. Management of the nutritional and gastrointestinal issues includes a high calorie diet, pancreatic enzyme replacement, fat-soluble vitamin replacement, ursodeoxycholic acid for liver disease, agents to treat gastroesophageal reflux and aid in GI motility and insulin for CF diabetes. Involvement of the sinuses requires intranasal corticosteroids and regular irrigation of sinus cavities with saline. The prevalence of anxiety and depression is considerably higher than in the general population and often requires medical therapy as well as counselling.

Therapies that treat the defect in CFTR would include gene therapy (not yet available) and CFTR modulator therapies. CFTR modulator therapies are medications that work on the various defects in the CFTR protein seen as a result of the different CF mutations. Potentiators (e.g ivacaftor (IVA)) increase the open probability of CFTR and are indicated for people with CF who have gating mutations. Correctors (e.g. tezacaftor (TEZ) and lumacaftor (LUM)) fix the folding defect in CFTR and, in conjunction with ivacaftor, are used to correct the defect seen in patients with the F508del mutation, the most common of the >2,000 different CF mutations. Triple combinations of CFTR modulators combine 2 correctors and a potentiator (e.g. elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)) and result in improved correction of chloride transport in people with the F508del mutation. This translates to significant clinical efficacy even in patients with only a single F508del mutation.

Mogayzel PJ, et al. Cystic Fibrosis Pulmonary Guidelines. Am J Respir Crit Care Med 2013;187(7):680–689

Ren CL, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-280.

Habib, AR.R., Kajbafzadeh, M., Desai, S. *et al.* A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. *Sci Rep* **9,** 7234 (2019). https://doi.org/10.1038/s41598-019-43652-2

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:

A perfect therapy would cure CF and thus prevent the multisystem, progressive disease manifestations. This is currently not possible. Thus, important goals of an ideal therapy are:

1. Increase life expectancy
2. Prevent development of lung disease
3. Delay disease progression for people with established disease
4. Improve lung function for people with established disease
5. Reduce frequency of pulmonary exacerbations and avoid need for admission to hospital
6. Reduce need for lung transplantation
7. Improve quality of life (reduce daily symptoms, increase ability to attend school, have a career and be independent)

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:

There have been remarkable advances in CF therapies in the past 30 years and this has been associated with improvements in life expectancy. Some standard of care therapies have been demonstrated to improve life expectancy (e.g. TOBI and Pulmozyme) and reduce pulmonary exacerbations (e.g. TOBI, azithromycin, Pulmozyme and hypertonic saline), but these therapies treat the lung infection and inflammation and thin mucus but do not treat the abnormality in the CFTR protein. Not all patients respond to these medications and in spite of current therapies, CF remains a progressive disease with declining lung function, increasing symptoms, increasing treatment burden and ultimately, the need for lung transplant or premature death.

CFTR modulator therapy is the only therapy available that treats the basic defect in CF. In the 5% of Canadians with CF with a gating mutation, clinical trials and registry studies have demonstrated that IVA reduces exacerbations, decreases the rate of decline in lung function, reduces lung transplants and improves survival – an impressive impact but IVA is only indicated for a limited proportion of patients. CFTR modulators consisting of a corrector and a potentiator (LUM/IVA and TEZ/IVA) are indicated for the 50% of CF patients who carry two copies of the F508del mutation but they have a more modest impact on lung function and pulmonary exacerbations than ivacaftor. Triple combination therapy with 2 correctors and a potentiator (ELX/TEZ/IVA) has been shown to have a significant response in patients who have at least 1 F508del mutation – thereby providing significant clinical benefit to 90% of Canadians with CF.

Bessonova L, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. Thorax 2018;**73:**731-740.

Volkova N, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. J Cyst Fibros. 2020;19(1):68-79.

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:

As CFTR modulator therapy is the only treatment that addresses the basic defect in the function of the CFTR protein, all patients with CF who have the appropriate gene mutations have an unmet need.

ELX/TEZ/IVA has been shown to restore the function of CFTR with the F508del mutation, and the improvement in function is such that there is a significant clinical response even in patients who have only a single copy of F508del, regardless of the mutation on the other allele. In Canada ~90% of people with CF have at least one copy of the F508del mutation so ELX/TEZ/IVA will help the vast majority of people with CF in Canada.

CFTR modulator therapy is not widely available for Canadians with CF. At the present time, ivacaftor (IVA) is the only CFTR modulator therapy that is on the provincial formulary and it is only indicated for CF patients with certain gating mutations (5% of the Canadian CF population).

LUM/IVA is Health Canada-approved for patients with 2 copies of the F508del mutation and TEZ/IVA has the same indication and is also indicated for patients with F508del and certain residual function mutations. However, neither LUM/IVA or TEZ/IVA are on the provincial formularies so only patients with private drug coverage can access these medications. Adults with CF, because of their disease and its resulting limitations, may not be able to have the type of employment that provides insurance coverage, resulting in a

2-tier system of those with access and those without access. In addition, clinical trials comparing ELX/TEZ/IVA with TEZ/IVA in patients over the age of 12 demonstrated further significant improvement in lung function in those on ELX/TEZ/IVA.

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:

Triple combination modulator therapy (ELX/TEZ/IVA) would be added to current standard of care for CF as a first-line therapy for those patients with the appropriate CF mutation (F508del).

Phase 3 trials have demonstrated that the addition of ELX/TEZ/IVA to standard of care resulted in significant improvements in clinically important outcomes of lung function, pulmonary exacerbations, weight and QOL. Consensus guidelines already include CFTR modulator therapies. There are trials underway to test which downstream therapies may be discontinued in patients on ELX/TEZ/IVA but at this point, all standard of care treatments should be maintained.

ELX/TEZ/IVA is an improvement on existing CFTR modulator therapy and would replace LUM/IVA or TEZ/IVA in patients ≥ 12 years based on clinical trial evidence of superior efficacy. ELX/TEZ/IVA is also indicated for a broader CF population as has been shown to be effective in all patients who have at least one F508del mutation.

Mogayzel PJ, et al. Cystic Fibrosis Pulmonary Guidelines. Am J Respir Crit Care Med 2013;187(7):680–689

Ren CL, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-280.

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:

Although all patients should continue on standard of care therapies as appropriate addressing the downstream consequences of CF, ELX/TEZ/IVA should be started in all patients with at least one F508del mutation in CFTR as it is the only therapy that targets the defect in CFTR and is more effective than

LUM/IVA or TEZ/IVA.

Patients who are ≥ 12 years of age and are on LUM/IVA or TEZ/IVA should be switched to ELX/TEZ/IVA. There is no reason to use LUM/IVA or TEZ/IVA except in patients with F/F who are under the age of 12 years as only TEZ/IVA and LUM/IVA are Health Canada-approved in that age group.

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 would be no difference in the sequence of pulmonary therapies however, the addition of ELX/TEZ/IVA would hopefully delay disease progression and thus delay the need for other therapies including lung transplant. There are trials underway to test which downstream therapies may be discontinued but at this point, all standard of care treatments should be maintained.

At this point in time, there are no other CFTR modulators available should patients not respond to ELX/TEX/IVA

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:

CF patients who have at least one copy of the F508del mutation and are ≥ age 12 years are eligible for ELZ/TEZ/IVA and all these patients can benefit from therapy. Younger patients generally have less severe lung disease but can benefit from a reduction in pulmonary exacerbations which will impact lung function decline. Treatments that target the basic defect have the potential to prevent development of disease and should be used early in the course of this progressive disease. Clinical trials were conducted in adolescents and adults as well as those with mild and more severe lung disease and all subgroups responded to ELX/TEZ/IVA. Patients with severe lung disease (FEV_1 <40% pred) on ELX/TEZ/IVA as part of SAP/compassionate program also seem to have a meaningful clinical response (see 7.1).

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:

Eligible patients would be identified by their CF physician at one of the 42 CF clinics in Canada. Newborn screening for CF is now available across the country and allows early referral to CF clinics, confirmation of the diagnosis of CF and initiation of therapy often even before the development of symptoms. The diagnosis of CF may be delayed until adulthood in a small proportion of cases but, given the complexity and specialized nature of CF care, that these patients are referred to and followed in CF clinics.

Genetic testing is done at the time of diagnosis and this would determine eligibility for CFTR modulator therapy. These tests are already part of standard of care.

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

Response:

Patients with severe liver disease (Child-Pugh Class C) should not be started on ELX/TEZ/IVA. It is not yet clear if there would be benefit to using ELX/TEZ/IVA in patients with CF who have had a lung transplant.

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:

There is no way to predict which patients would respond to ELX/TEZ/IVA without a trial of therapy.

There are many possible positive responses that can be seen with CFTR modulator therapy. The most obvious positive effect is short-term improvement in lung function. However, improvement in survival, reduction in lung function decline, reduction in pulmonary exacerbations/hospitalizations are all desirable outcomes although it would take more time to see these effects. Even if a patient failed to show an improvement in FEV_1, stabilization of health and improved quality of life in the context of progressive disease would be a meaningful 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:

The outcomes to assess clinical response in clinical practice are virtually the same as those used in clinical trials. These are measured at every CF clinic visit and documented prospectively in the Canadian CF Patient Registry (see Section 7.1 for further details on the Registry). These include lung function (FEV_1), weight, frequency of pulmonary exacerbations, hospitalizations, and lung transplantation. The Canadian CF Patient Registry can be used to calculate rate of decline in lung function over time.

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:

Objective important outcomes include those measured in clinical trials (lung function, number of exacerbations, body mass index (BMI)). These outcomes are associated with survival. In CF, the minimal clinically important difference of these outcomes has not been determined. However, in this progressive disease, it is more important to demonstrate that therapies can prevent deterioration rather than just showing short-term improvements in lung function and short term improvement does not predict long-term rate of decline in FEV_1.

The Canadian CF Registry allows for examination of lung function decline as well as change in nutritional status and rates of pulmonary exacerbation. Standardized queries can be created for clinics to quickly assess response to therapy in individual patients.

Outcomes that capture the reduction in daily symptoms, improved quality of life and increased functional capacity are important to patients as they impact their day to day lives, including ability to attend school or work.

Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. J Cyst Fibros. 2016;15(4):416-423.

VanDevanter DR, Konstan MW. Outcome measures for clinical trials assessing treatment of cystic fibrosis lung disease. *Clin Investig (Lond)*. 2012;2(2):163-175.

6.10. How often should treatment response be assessed?

Response:

Quarterly clinic visits are standard of care in CF and that is an appropriate frequency to assess response to CFTR modulator therapy. We would also recommend blood work after 1 month on ELX/TEZ/IVA and every 3 months for the first year to ensure no derangements in liver function.

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 therapy (even if temporary) should be considered if severe adverse effects (including elevated liver function tests >5 times upper limit of normal and progression of liver disease). Other reasons for stopping therapy include drug-drug interactions with medications such as with rifampin or anti-seizure medications or development of drug allergy.

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

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

Response:

People with CF on CFTR modulator therapy should be under the care of a CF specialist in one of the 42 accredited CF Clinics across Canada.

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:

Yes. Essentially all people with CF are cared for in CF clinics and it is the limited number of specialised CF physicians in these clinics who will be prescribing this therapy. The standard of care in Canada for CF is quarterly CF clinic visits where weight, lung function and microbiology are measured. Data from clinic visits including genetics, pulmonary function, weight, microbiology, hospitalizations, CF medications, complications (e.g. diabetes, transplant etc) are entered in the Canadian CF Data Registry and this allows for analysis of response to therapy.

7. Additional information

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

Response:

<u>Experience with ELX/TEZ/IVA in Special Access Program compassionate use</u>

We would like to share our experience with ELX/TEZ/IVA in those patients with CF who are eligible for the compassionate use program from the manufacturer and can access this medication via the Special Access Program at Health Canada.

The compassionate access program is limited to those patients homozygous for the F508del mutation (F/F) and those patients with F508del on one allele and a minimal function mutation on the other allele (F/MF). To be eligible for the compassionate program, patients with F/MF must have an FEV_1 below 40% predicted sustained for > 2 months and those with F/F must have FEV_1 of < 30% pred or between 30-40%pred but also > 6 exacerbations in a year and/or a drop in FEV_1 of 20% sustained over at least 2 months.

We have 50 patients enrolled in this program who have been on ELX/TEZ/IVA for at least 1 month. Of the 50 patients, 42 (84%) have been on ELX/TEZ/IVA for at least 6 months with 11 having completed a full year of therapy. All patients have lung function measured before starting therapy (usually the day before first dose) and then at 1, 3,6, 9 and 12 months. Sweat chloride is measured at baseline and 1 and 12 months.

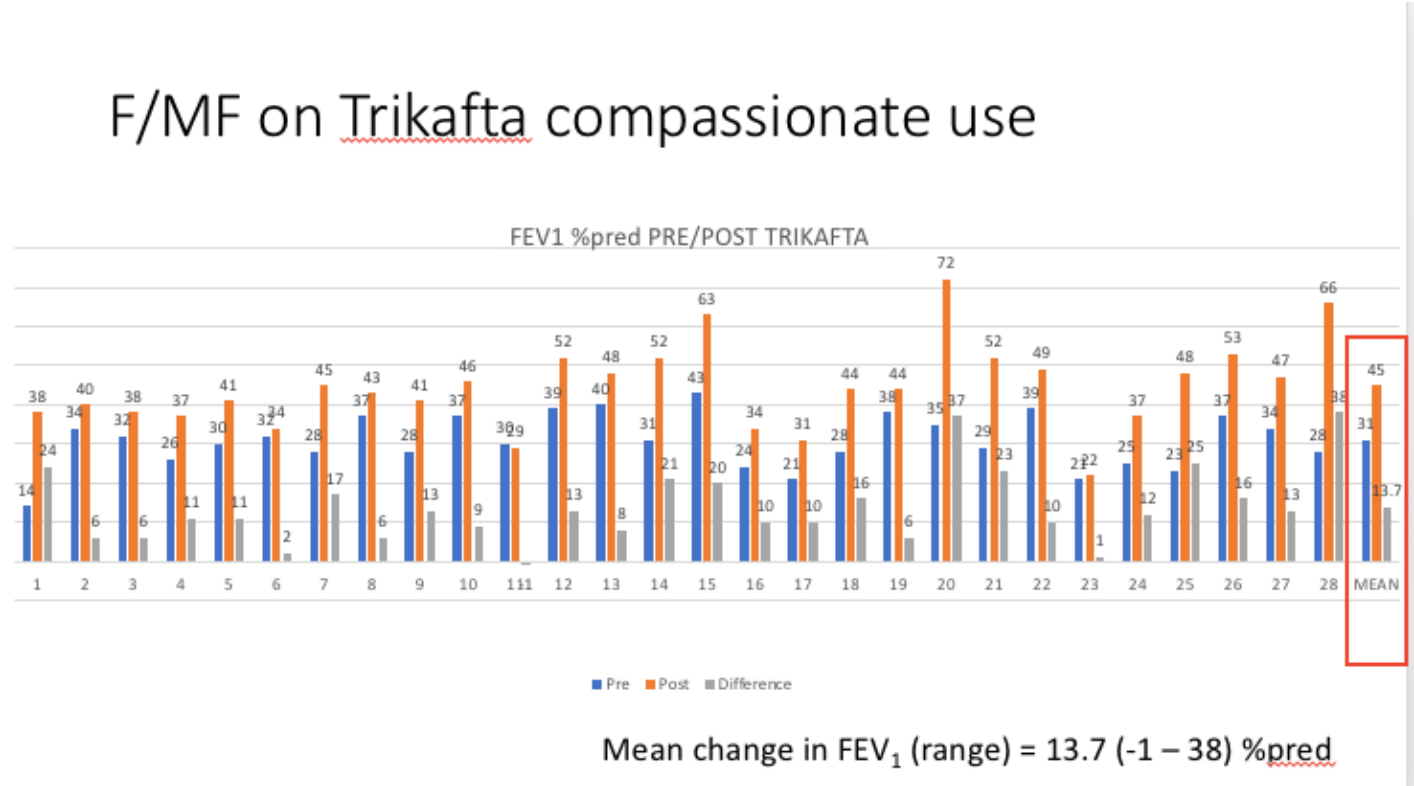
All patients tolerated therapy and there were no patients that had to stop therapy. Side effects were similar in

frequency and nature to those reported in the Phase 3 trials (mostly rash, abdominal pain, diarrhea). The lung function response is summarized below in 3 categories: F/MF, F/F patients who were already on CFTR modulators and F/F not previously on CFTR modulator therapy. In spite of this being a patient population with more severe disease than the population tested in Phase 3 clinical trials, the results are similar with a mean FEV_1 improvement of 13.7% pred in F/MF, 8.5% pred in F/F (on CFTR modulators) and 10.8% pred in F/F (not on prior CFTR modulator therapy). This degree of response is remarkable given the severity of the underlying lung disease in these patients. The degree of improvement in some patients is astonishing – improvements in FEV_1 from 14% predicted to 38% predicted – which in litres represents a three-fold increase in lung function.

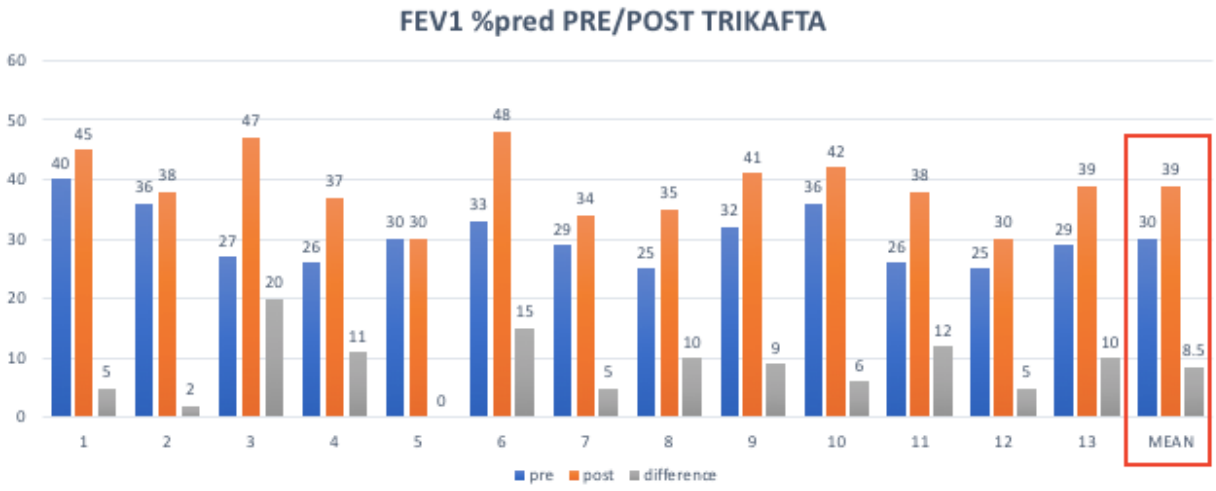
Five patients (10%) did not see a significant improvement in their lung function although all 5 had clinical improvements (reduced pulmonary exacerbations, reduction in symptoms, were able to stop O_2 or be removed from transplant list). Significant weight gains were seen on therapy (an average of 8 kg in the 11 patients treated for a year), with 10/50 patients gaining >10 kg. Malnutrition is common in CF and is a risk factor for death. Thus, weight gain is often an important and desired clinical outcome in our patients.

All 10 patients on ELZ/TEZ/IVA who had been assessed for lung transplant improved so much that they were removed from the transplant list. Sadly, one patient approved for ELX/TEZ/IVA while on the transplant list was transplanted a few days before we heard that they would have access to therapy. All patients who were on supplemental oxygen had improvements so that O_2 requirements decreased and 3 were able to discontinue O_2 completely. What was most remarkable is that none of the 50 patients on ELX/TEZ/IVA have required IV antibiotic therapy or hospitalization for pulmonary exacerbations since starting therapy – including the 11 who have been on therapy for 1 year.

This therapy has been life changing for patients who speak of the joy of being able to resume work or their education, be able to participate more fully in family life and being able to plan for their future.

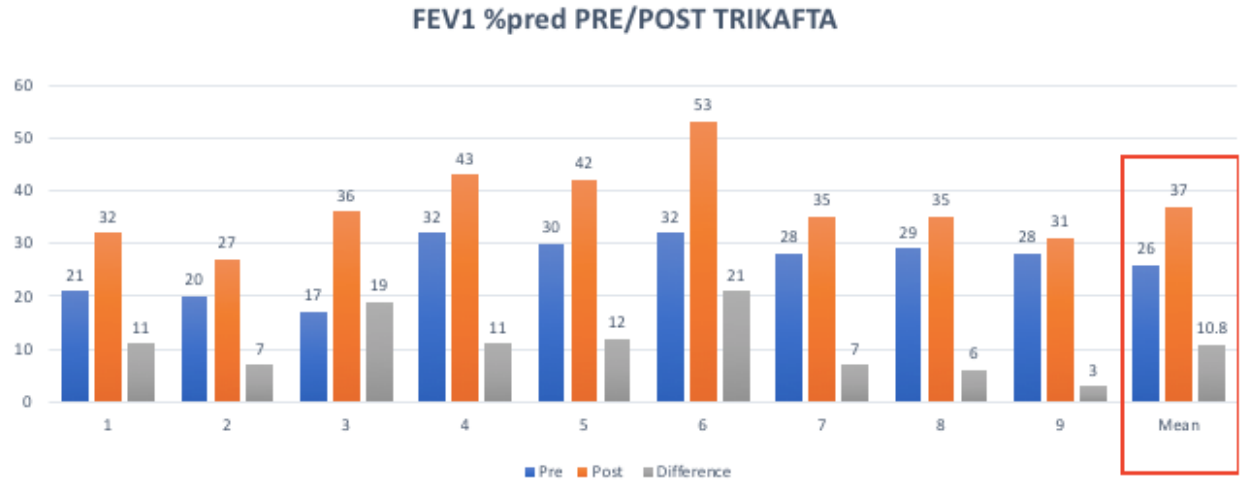


F/F (previous CFTR modulator use) on Trikafta



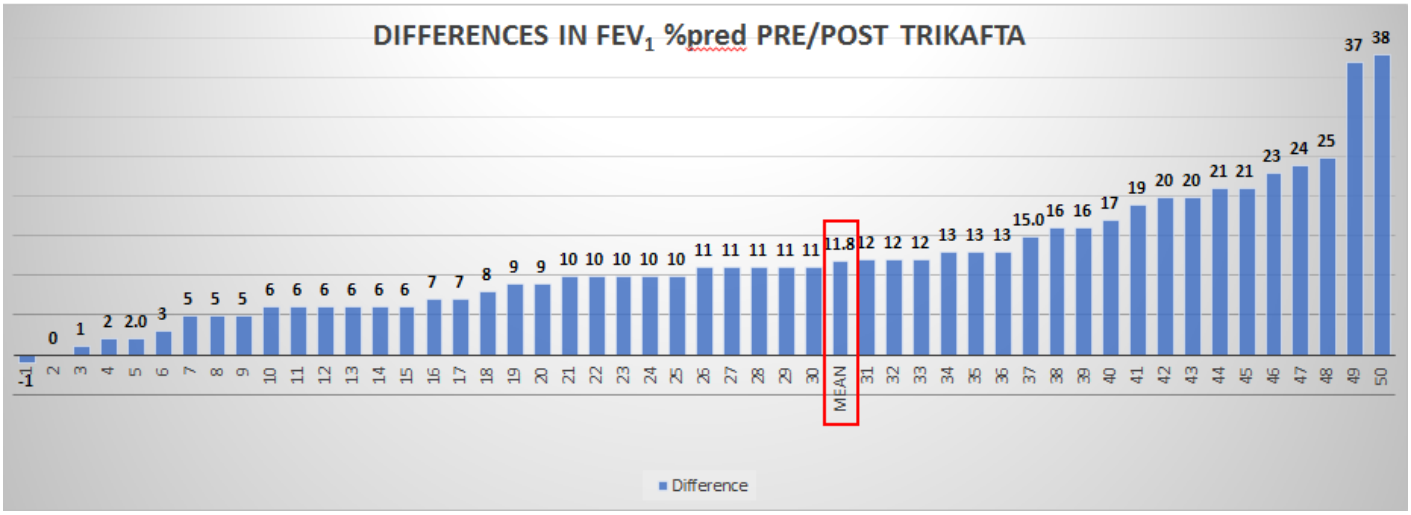
Mean change in FEV_1 (range) = 8.5 (0-20) %pred

F/F (CFTR modulator naïve) on Trikafta



Mean change in FEV_1 (range) = 10.8 (3-21) %pred

F/F and F/MF on Trikafta



Use of Canadian CF Patient Data Registry to determine impact of CFTR modulator therapy

The Canadian CF Patient Data Registry (CCFR) records encounter-based data on a longitudinal cohort of individuals living with CF who are receiving care at one of the 42 Canadian adult/pediatric CF clinics. The CCFR is used to monitor epidemiologic trends over time, conduct research, educate and advocate, and enhance clinical care for the CF community. Data are collected longitudinally across the lifetime of the individual. A summary of the individual's demographic information (including: birth date, death date, sex, race, marital status, employment status, geographic location), health information (including: date of diagnosis, birth date, height, weight, pulmonary function, nutritional status, CF gene markers, CF-related complications, transplantation and related complications), and treatment information (including: hospitalization, courses of home IV antibiotics, medication use, other treatments) are captured within the CCFR. All CF clinics have research ethics board approval from their respective institutions as well as informed consent from patients in order to contribute data to the CCFR. Each CF clinic reports annually to Cystic Fibrosis Canada on the number of patients who decline participation in the Registry, which is <1% of the patients followed at CF clinics in Canada (personal communication with Cystic Fibrosis Canada). It is estimated that the CCFR includes over 95% of the Canadian CF population.

The CCFR is a powerful tool to understand the changing demographics, the evolving needs of the CF population and the impact of key interventions on important health outcomes which are captured in the CCFR at a national level. The CCFR has been used to study the impact of modulator therapy on the Canadian population and captures data on the start and stop date of modulator therapy as well as the reasons for discontinuation. Our research group has used CCFR data to evaluate the impact of modulator therapy on health outcomes in a real-world setting within Canada. **All of the studies mentioned below were investigator-initiated studies and were *not* funded or supported in any way by industry**.

A study led by Dr. Anne Stephenson, a researcher at the Toronto Adult CF Clinic, investigated the impact of IVA on individuals with CF living in Canada using CCFR data. The manuscript, which is currently under review at the *Journal of Cystic Fibrosis* (revisions requested and have been submitted), showed that, on average, FEV_1 significantly increased by 5.7% predicted (absolute change; $p<0.001$) and BMI significantly increased by 6.57 percentiles ($p<0.001$) in Canadians who were started on IVA in a real-world setting. Further, the rate of FEV_1 decline was attenuated to -0.30% predicted/year post-IVA, compared with -0.75% predicted/year pre-ivacaftor which represents a 59% reduction in the rate of decline in lung function post-IVA. There was an 18% decreased risk of exacerbations in the post-IVA period, although this did not reach statistical significance likely due to the small sample size. There was a decreased odds of a positive sputum culture for *P. aeruginosa* in the post-IVA period (odds ratio 0.44, $p<0.001$) compared with pre-IVA period. These results suggest that IVA, when used outside of a clinical trial, has a positive and significant impact on health outcomes in Canadians living with CF.

More recently, Dr. Stephenson's research group has begun analyzing data to evaluate the impact of LUM/IVA and TEZ/IVA on the health of Canadians with CF using the CCFR data. Preliminary data suggests that there is a statistically significant increase in lung function with a reduction in the rate of decline in FEV_1 after initiation of LUM/IVA or TEX/IVA although the final results are not yet available.

With respect to ELX/TEZ/IVA, Dr. Stephenson and her team used CCFR data in order to forecast the impact of triple combination therapy on the Canadian CF population (funded by Cystic Fibrosis Canada). This study used a technique called microsimulation to predict what might happen to Canadians living with CF in the year 2030. The forecasting models looked at 3 key scenarios: (1) if ELX/TEZ/IVA was not available in Canada (2) if ELX/TEZ/IVA was available in 2021 (early) and (3) if access to ELX/TEZ/IVA was delayed until 2025 (delayed). The results show that early introduction of ELX/TEZ/IVA would result in 60% fewer people with severe lung disease, 18% increase in people with mild lung disease and 19% fewer hospitalizations or home intravenous courses for chest infections by 2030 compared to no drug available. It is projected that early introduction of ELX/TEZ/IVA could reduce deaths by 15%, improve the median age of survival by 9.2 years over a 10-year period and reduce the number of transplants that are required for severe lung disease. If access to ELX/TEZ/IVA is delayed, the improvements in health will be substantially reduced across all outcomes therefore, delayed access to this effective medication will result in preventable heath care costs and death.

In conclusion, the CCFR will continue to play an important role in tracking modulator use as well as the impact of these drugs on the Canadian CF population in a real-world setting. Moving forward we will not only evaluate important clinical outcomes such as lung function, nutritional status, and hospitalizations but also the impact on transplantation rates, mortality, and the burden of disease to inform the CF community.

Kawala et al., Real-world use of ivacaftor in Canada: A retrospective analysis using the Canadian Cystic Fibrosis Registry, *J Cyst Fibros* (under review, revisions requested and submitted), 2021.

Stanojevic et al. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis, *J Cyst Fibros*, 2020 Aug 5:S1569-1993(20)30809-2. doi: 10.1016/j.jcf.2020.07.017. Online ahead of print.

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	*Elizabeth Tullis*
Position	*Director, Toronto Adult CF Clinic, Professor, University of*
Date	*11-02-2021*
☒	**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**
Vertex Pharmaceuticals, Inc	☐	☐	☒	☐
Proteostasis Therapeutics Inc	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Anne Stephenson*
Position	*Respirologist and Clinical Scientist, Toronto Adult CF Clinic, St Michael's Hospital*
Date	*11/02/2021*

☒	**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**
Cystic Fibrosis Canada	☐	☐	☐	☒
Vertex Pharmaceuticals Inc	☐	☐	☒	☐

Declaration for Clinician 3

Clinician Information	
Name	*Kieran McIntyre*
Position	*Respirologist and Clinician in Quality Improvement, Toronto Adult CF Clinic, St Michael's Hospital*
Date	*11-02-2021*
☒	**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**
Nothing to disclose	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Cecilia Chaparro*
Position	*Director of Lung Transplantation, UHN and CF Respirologist, Toronto Adult CF Clinic*
Date	*11/02/2021*
☒	**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**
Vertex Pharmaceuticals, Inc	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Anju Anand*
Position	*Respirologist, Toronto Adult CF Clinic, St Michael's Hospital*
Date	*11/02/2021*
☒	**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**
Nothing to disclose	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Kevin Curley*
Position	*CF Pharmacist, Toronto Adult CF Clinic, St Michael's Hospital*
Date	*11/02/2021*
☒	**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**
Vertex Pharmaceuticals, Inc	☒	☐	☐	☐

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	SR0673-000
Generic Drug Name (Brand Name)	**Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™)**
Indication	For people living with cystic fibrosis aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Name of the Clinician Group	Cystic Fibrosis Canada's Accelerating Clinical Trials Network (also called CF CanACT) Executive Committee.
Author of the Submission	[redacted]
Contact information	[redacted]

1. About Your Clinician Group

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

The physicians who are submitting this proposal are part of the Executive Committee of Cystic Fibrosis Canada's Accelerating Clinical Trials Network (also called CF CanACT). CF CanACT operates under the auspices of Cystic Fibrosis Canada. Its purposes are to conduct world class clinical trials in cystic fibrosis (CF) and to attract research of new therapies to Canada. This is integral to bringing new therapeutics and better care to CF patients in Canada.

The physicians are also Clinic Directors of 14 cystic fibrosis Clinics serving 60% of the CF population in Canada. As Clinic Directors, each has personal experience of treating cystic fibrosis patients. In addition, these physicians represent the leading clinical researchers in CF in Canada.

https://cysticfibrosis.ca/our-programs/clinical-trials-network

2. Information Gathering

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

Information included in this submission was gathered by the following means:

1. Cystic Fibrosis Canada's Data Registry which contains individual patient information on people living with cystic Fibrosis in Canada such as survival outcomes, number of transplants, rate of pulmonary exacerbations, lung function, and medications.

2. Outcomes of patients who have participated in clinical trials within the network, especially modulator trials.
3. Scientific publications on cystic fibrosis.
4. Personal experience of the physicians in this submission in treating individuals with cystic fibrosis.

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:

Cystic Fibrosis (CF) is the most commonly inherited genetic condition in Canada effecting over 4,300 Canadians, with an incidence of approximately 1 in 3,600 live births. Since 2018, all babies born in Canada are screened for CF. This accounts for 2/3rd of the 160 annual CF diagnoses. CF is a progressive, degenerative multi-system disease that mainly affects the lungs and digestive system. In the lungs, where the effects are most devastating, a build-up of thick mucus causes severe respiratory problems. Mucus also builds up in the digestive tract, making it difficult to digest and absorb nutrients from food. Consequently, the mainstay of treatment is prevention of lung disease and ensuring good nutrition and growth.

Initially, viewed as a pediatric disease, now over 65% of the CF population are adults. Data from the 2019 Canadian CF Registry report illustrates that CF is responsible for a large burden of care accounting for 20,000 clinic visits, over 25,000 hospital days, 15,000 home IV days and 46 lung transplants each year (1).

Historically, patients would die in early childhood. Newborn screening has allowed the natural history of the disease to be modified and reduce the decline in lung function with the earlier administration of new and improved treatments. This has translated into increased patient survival. Despite this advance, death for CF patients still occurs in early to mid adulthood with the median age of death reported at 42 years (2019), compared to 33 (2018) and 27 years (2000) respectively.

As survival improves the main cause of morbidity and mortality is lung damage due to a vicious cycle of infection, inflammation and lung destruction. This is prevented by regular daily chest physiotherapy, inhaled mucolytics (e.g. hypertonic saline, Pulmozyme™) and chronic suppressive inhaled antibiotic therapy (e.g. TOBI™, Cayston™). This strategy aims to slow the evolving lung damage and the resultant decline in lung function that ultimately lead to respiratory failure and death.

In addition to preservation of lung health, CF treatment focuses on optimising growth and nutrition. Due to pancreatic insufficiency, the majority of patients require pancreatic enzyme supplementation in addition to fat soluble vitamin supplementation. This promotes good nutrition and is critically linked to survival.

Given the multisystem impact of CF, complications arise as the patient ages and so all patients have regular screening for these issues. Of note, CF related diabetes is very prevalent with up to 33% adult patients needing to use insulin to control this. Liver disease is common and, if medical management is unsuccessful, leads to liver transplantation. Additionally, patients are at risk of early development of osteoporosis. Issues with fertility are common with most men being infertile and women sub-fertile. There is an increased risk of cancer particularly bowel cancer as well as inflammatory bowel disease and celiac disease.

CF care is holistic and research has shown that emotional wellness is now a significant problem within this patient group. Data has shown that over 30% of patients and/or caregivers are currently suffering from either anxiety or depression. This has become a high priority in this patient group and is the focus of a national incentive.

The aim of newborn screening and the time-consuming CF treatment regime is to alter the natural history, control symptoms and reduce morbidity associated with recurrent pulmonary exacerbations and hospitalisations. There is no cure. Approved medications aim at altering and slowing the trajectory of lung function decline. Ultimately, when respiratory failure occurs, lung transplantation is the only option to try to extend life expectancy and improve quality of life. Even if available it is associated with its own complications and the 5-year survival is 60% with a median survival of 10 years.

Since 2010, CFTR modulators have been developed to tackle the underlying defect of CF. Although not a cure, they aim to restore the function of the CFTR protein, a chloride and bicarbonate channel, at the cell surface. CFTR modulators are tailored to work to correct specific mutations and are an example of precision (personalized) medicine. The first modulator commercially available was ivacaftor (IVA) which is effective in patients who have “gating” mutations, only 4% of Canadian CF patients. It is an extremely effective medication, restoring CFTR function with clinical benefits of increasing lung function, reducing hospitalizations and improving nutritional status, and real-world evidence of improving survival and decreasing need for lung transplant. It is currently funded both at a 3rd party and provincial level. For patients with 2 copies of the most common CF mutation, F508del (50% of Canadian CF Patients), lumacaftor/ivacaftor (LUM/IVA; Orkambi™) and tezacaftor/ivacaftor (TEZ/IVA; Symdeko™) have been developed. Despite Health Canada approval, these medications are not available provincially (with the exception of Quebec’s ‘patient d’exception’ programme) and consequently only 12% of Canadian CF patients receive these through participation in clinical trials or 3rd party payers.

The advent of a 3rd CFTR modulator provides a triple combination therapy, known as elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; Trikafta™). Phase 3 trials have demonstrated clinically significant incremental improvements in lung function over TEZ/IVA in patients with 2 copies of F508del and expansion of the indication of CFTR modulator therapy to patients who have only 1 copy of the F508del mutation. It will undoubtedly prove to be a highly impactful treatment for the vast majority (~90%) of CF patients in Canada.

Reference:

1. Cystic Fibrosis Canada. (2020). The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Toronto, Canada: Cystic Fibrosis Canada.

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:

As highlighted in section 3.1 a treatment would ultimately address the basic defect causing CF. The ideal treatment is gene therapy which removes the basic defect and restores normal chloride transport on the cell surface. While, studies are attempting to address this, the reality is this treatment is still a decade or more away. By correcting, even imperfectly, the defective protein's function, CFTR modulators provide an excellent therapy that is as close to a cure as the CF world has ever seen. Although, CFTR modulators do not correct the genetic defect, they are able to correct defects in the protein structure and restore chloride transport.

The latest "third generation" CFTR modulator combination is a highly effective therapy producing ground-breaking results for patients with CF. It achieves many of the goals for successful treatment of CF, namely:

- Improves and stabilizes lung function
- Prevents and reduces pulmonary exacerbations
- Improves nutrition and growth
- Minimizes and /or reverses complications of CF disease
- Reduces psychosocial issues
- Improves quality of life
- Allows attendance at school, university and work with minimal disruption
- Reduces burden of care and number of therapies needed to maintain health
- Alters the disease trajectory.

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:

- Current treatments such as inhaled antibiotics and mucus thinning agents target downstream consequences of CF lung disease (e.g. infection, thick, dehydrated mucus) and therefore do not

treat the root cause or reverse the course of disease. These therapies require nebulization and therefore are extremely time-consuming to administer (2-3 hours per day) and thus adversely impact quality of life and work/school productivity. This demanding treatment regimen also influences medication adherence and mental health. Most patients eventually become refractory to inhaled antibiotics due to antibiotic resistance which leads to more frequent infectious exacerbations and eventually lung transplantation.

- Response to currently available, second generation, CFTR modulator therapies (LUM/IVA, TEZ/IVA) for F508del homozygous patients is variable and most patients continue to experience lung disease progression (requiring hospitalizations/lung transplant). Furthermore, there are significant side effects related to the use of LUM/IVA (e.g. chest tightness, blood pressure elevation) and numerous drug-drug interactions.
- Current treatments do not reverse extra-pulmonary manifestations of CF including sinusitis, exocrine pancreatic insufficiency, diabetes, liver disease, bowel manifestations. Most adult CF patients require 15-20 different medications to manage all of the manifestations of this 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 a single copy of F508del paired with another CF mutation (i.e. F508del heterozygous) that is not a gating or residual function mutation have the greatest unmet need as there are currently no approved CFTR modulator therapies available to them. In patients with a single copy of F508del and a “minimal function” mutation, clinical manifestations are severe and the drug under review is considered a breakthrough as it leads to substantial improvements in lung function and respiratory-related quality of life and markedly reduces exacerbations and hospitalizations.
- Patients with two copies of F508del (i.e. F508del homozygous) also have substantial unmet need as only a minority (<12%) have been able to access LUM/IVA or TEZ/IVA due to the lack of public reimbursement in most provinces. Furthermore, in the minority of patients who have been able to access these therapies, response is variable and side effects can be considerable. The drug under review leads to tremendous improvements beyond the effects related to LUM/IVA and TEZ/IVA and has fewer side effects and drug-drug interactions than LUM/IVA.
- Patients with very mild/early disease also have a tremendous unmet need as currently available treatments do not reverse the course of disease or prevent end-organ damage. Initiation of CFTR modulator therapy before irreversible damage occurs to the lungs, pancreas, and other affected organs should be a primary goal to prevent sequelae (e.g. bronchiectasis, chronic airway infection, exocrine pancreatic insufficiency, diabetes) and reduce the need for other lifelong treatments such as inhaled antibiotics, inhaled mucolytics, pancreatic enzymes, and insulin which add significant treatment burden and adversely impact 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:

Triple combination modulator therapy (ELX/TEZ/IVA) addresses the underlying disease process, and would be added on to current standard of care for CF as a first-line therapy for those patients with the appropriate CF mutation. CFTR modulator therapy is specifically targeted to the patient's CF gene mutations.

Current treatment paradigm for CF divides therapies into those that address the basic defect (CFTR modulators) and those that treat the consequences of the defect (inhaled antibiotics, inhaled mucolytics, bronchodilators, anti-inflammatory drugs, physiotherapy). Phase 3 trials have demonstrated that the addition of ELX/TEZ/IVA to standard of care resulted in significant improvements in clinically important outcomes of lung function, pulmonary exacerbations, weight and QOL (1,2). Consensus guidelines already include CFTR modulator therapies (3), but they have not been recommended to replace prior therapies such as inhaled antibiotics that treat consequences of the defect because end-organ damage has already occurred and therefore these treatments remain necessary. Future research will determine if some of these other standard of care therapies can be safely removed for patients on ELX/TEZ/IVA and whether introduction of ELX/TEZ/IVA earlier in life will prevent the need for inhaled antibiotics, inhaled mucolytics, and other standard of care treatments.

ELX/TEZ/IVA is not the first therapy that addresses the underlying defect in CF, but rather it is an improvement on existing CFTR modulator therapies. This therapy would replace other CFTR modulators that are currently available. When compared to the Health Canada-approved CFTR modulator (TEZ/IVA), Phase 3 trials have demonstrated greater efficacy of ELX/TEZ/IVA (2). ELX/TEZ/IVA is also indicated for a broader CF population as has been shown to be effective in all patients who have at least one F508del mutation (1,4). In this sense it is, for F508del heterozygote CF patients, a first-line therapy that addresses the underlying defect in CF.

References:

1. Middleton, P.G.; Mall, M.A.; Drevinek, P.; Lands, L.C.; McKone, E.F.; Polineni, D.; Ramsey, B.W.; Taylour-Cousar, J.L.; Tullis, E.; Vermeulen, F.; et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N. Eng. J. Med*. **2019**, *381*, 1809–1819, doi:10.1056/NEJMoa1908639.
2. Heijerman, H.G.; McKone, E.F.; Downey, D.G.; Van Braeckel, E.; Rowe, S.M.; Tullis, E.; Mall, M.A.; Welter, J.J.; Ramsey, B.W.; McKee, C.M.; et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: A double-blind, randomised, phase 3 trial. *Lancet* **2019**, *394*, 1940–1948, doi:10.1016/S0140-6736(19)32597-8.
3. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, *et al*. Cystic fibrosis pulmonary guidelines: use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc* **2018**;15:271–280.
4. https://investors.vrtx.com/news-releases/news-release-details/positive-phase-3-study-results-trikaftar [Accessed Feb 1, 2021]

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:

Patients starting CFTR modulator therapy should already be receiving standard of care treatments as indicated for the extent and characteristics of their disease (e.g. chest physiotherapy for airway clearance, mucolytics, inhaled antibiotics for chronic airway infection, anti-inflammatory therapies, bronchodilators, pancreatic enzymes, fat soluble vitamins, insulin). ELX/TEZ/IVA should be added to this therapy regardless of treatment response to standard of care as it is the only therapy that targets the defect in CFTR. For patients with at least one copy of F508del currently on IVA, TEZ/IVA or LUM/IVA, it is beneficial to switch to ELX/TEZ/IVA.

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 would be no difference in the sequence of pulmonary therapies however, the addition of ELX/TEZ/IVA would hopefully delay disease progression and thus delay the need for other therapies including lung transplant. There may be the potential that treatment with ELX/TEZ/IVA will result in improvements in clinical status so that other standard of care therapy will no longer be required.

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:

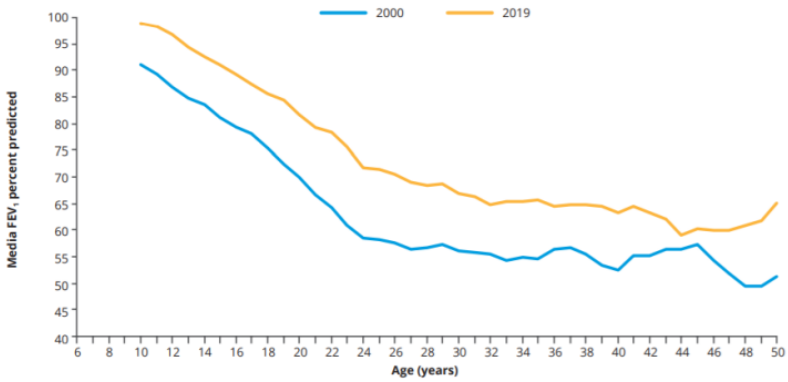
CFTR modulator therapy is specifically targeted to the patient's CF gene mutations. Currently, only patients who have at least one copy of the F508del CF mutation are eligible for ELZ/TEZ/IVA. Other than this criterion, all patients can benefit from this therapy.

Phase 3 trials demonstrated treatment effect in a broad age range (between 12-17 years and over age 18 years) and in those patients with relatively mild disease and also in those with established disease and low lung function (FEV1 below and above 70% predicted). There were no subgroups that did not respond (age, gender, country, presence of Pseudomonas, therapies) (1,2). A recent study has also demonstrated benefit in patients with advanced CF lung disease (3).

CF is a life-long, progressive disease and the chronic lung infection, inflammation and recurrent pulmonary exacerbations lead to progressive decline in lung function. Fifty percent of the decline in lung

function can be attributed to pulmonary exacerbations (4) and so reduction in frequency of exacerbations is an important goal of therapy. The Canadian CF Registry shows that the steepest rate of decline in lung function occurs in the adolescent CF population in patients on current standard of care and thus starting CFTR modulator therapy as early as possible may prevent this from occurring (5).

Median FEV$_1$ percent predicted vs. age of cystic fibrosis individuals (5-year moving window), 2000 and 2019*.



** GLI reference equations used to calculate FEV$_1$ percent predicted values.*

References:

1. Middleton, P.G.; Mall, M.A.; Drevinek, P.; Lands, L.C.; McKone, E.F.; Polineni, D.; Ramsey, B.W.; Taylour-Cousar, J.L.; Tullis, E.; Vermeulen, F.; et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N. Eng. J. Med*. **2019**, *381*, 1809–1819, doi:10.1056/NEJMoa1908639.
2. Heijerman, H.G.; McKone, E.F.; Downey, D.G.; Van Braeckel, E.; Rowe, S.M.; Tullis, E.; Mall, M.A.; Welter, J.J.; Ramsey, B.W.; McKee, C.M.; et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: A double-blind, randomised, phase 3 trial. *Lancet* **2019**, *394*, 1940–1948, doi:10.1016/S0140-6736(19)32597-8.
3. O'Shea KM, O'Carroll OM, Carroll C, Grogan B, Connolly A, O'Shaughnessy L, Nicholson T, Gallagher CG, McKone EF. The efficacy of Elexacaftor/Tezacaftor/Ivacaftor in patients with cystic fibrosis and advanced lung disease. *Eur Respir J* **2020**. doi: 10.1183/13993003.03079-2020. Epub ahead of print. PMID: 33154033.
4. Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E and Ratjen F. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* **2012**;40:61-6.
5. Cystic Fibrosis Canada. (2020). The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Toronto, Canada: Cystic Fibrosis Canada.

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 candidates must have cystic fibrosis, i.e. typical symptoms or a positive newborn screen and either possessing two disease-causing Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations or have a sweat chloride >60 mmol/L (when not on CFTR modulator therapy). (ref CF Dx 2017). To be eligible for ELX/TEZ/IVA, the individual with CF must have at least one F508del mutation. All potential recipients need to have documented genetic testing demonstrating two CFTR mutations, of which at least one is F508del.

Genetic testing and sweat chloride testing should be performed at accredited CF centres, of which there are 42 across Canada, giving wide access to diagnostic testing. Newborn screening, which is responsible for identifying 66% of new diagnoses, has been in place in certain regions of Canada for over a decade, but for a shorter time in other regions. As such, current CF patients are a mix of those diagnosed by newborn screening and those diagnosed because of symptomatic presentation. Some patients present at a later age either due to missed diagnosis or milder symptoms. Such late diagnoses are expected to be less frequent over time because of newborn screening.

The mechanism of action of the drug is to increase the function of F508del mutant CFTR. Mutant CFTR results in loss of lung function, malnutrition, elevated sweat chloride values, and male infertility, as the most common symptoms. Ultimately it is loss of lung function that accounts for the majority of premature deaths.

Given that there are many patients with lung function (spirometry, typically Forced Expiratory Volume in one-second (FEV_1)) that is low (<40%) waiting for lung transplantation who have improved on this treatment to the point that they no longer need transplantation, there should be no lower limit of lung function to be eligible. Given that 1) lung function is often normal despite progression of structural lung damage, and that this damage begins in early life despite newborn screening, and 2) that this therapy results in a significant decrease in the incidence of pulmonary exacerbations (acute worsening of symptoms requiring antibiotics) that contribute to progressive lung damage, there should be no upper limit of lung function for eligibility.

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

Response:

As demonstrated in studies of CF infants diagnosed by newborn screening, structural lung damage begins early in life (1). As such, there is no “silent” or pre-symptomatic disease. All cystic fibrosis patients with at least one F508del mutation should be eligible. Drug-drug interactions may require that certain other medications be changed or the dosage be changed, but these are few and used infrequently in the CF population**.**

Those patients who have undergone lung transplantation will not receive lung function benefits. However, their sinus disease, which can be debilitating, is expected to improve with ELX/TEV/IVA (2). Improving sinus disease can diminish the risk of developing chronic rejection post-lung transplantation, so ELX/TEV/IVA should be considered in those lung transplant recipients with significant sinus disease. Their sweat chloride values will improve, thus avoiding episodes of severe dehydration that can occur.

References:

1. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM; AREST CF Investigators. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* **2013** May 23;368(21):1963-70. doi: 10.1056/NEJMoa1301725. PMID: 23692169.
2. DiMango E, Overdevest J, Keating C, Francis SF, Dansky D, Gudis D. Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis. *J Cyst Fibros*. **2020** Jul 18:S1569-1993(20)30794-3. doi: 10.1016/j.jcf.2020.07.002. Epub ahead of print. PMID: 32694034.

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:

The clinical trials have demonstrated that those patients with at least one F508del mutation, regardless of the second mutation, respond to this therapy, as noted by improvements in lung function, weight, and reduced pulmonary exacerbations requiring antibiotics. Those with reduced lung function are more likely to see increases in lung function, compared to those with normal lung function. As CFTR modulators are systemic medications, they impact CFTR function in the sweat glands as measured by the concentration of chloride in sweat (sweat chloride). Although this does not have clinical significance (other than reduced risk for dehydration and heat stroke), this is biomarker of the effect of CFTR modulator and Phase 3 trials show that ELX/TEZ/IVA use is associated with a reduction in sweat chloride below the diagnostic threshold for CF. Changes in sweat chloride are generally predictive of lung function changes at a population (but not an individual) level (1).

Reference:

1. Fidler MC, Beusmans J, Panorchan P, Van Goor F. Correlation of sweat chloride and percent predicted FEV_1 in cystic fibrosis patients treated with ivacaftor. *J Cyst Fibros*. **2017** Jan;16(1):41-44. doi: 10.1016/j.jcf.2016.10.002. Epub 2016 Oct 20. PMID: 27773592.

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:

The outcomes of interest are those measured regularly at the quarterly CF clinic visits as part of standard of care. At each clinic visit, patients have spirometry to measure lung function, have their weight and height measured, and provide a sputum sample for culture. Assessment by the CF physician would review their respiratory and other CF symptoms and determine the presence of pulmonary exacerbations at or between clinic visits. Thus, additional visits or testing is not required to assess response to therapy with CFTR modulators.

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:

Meaningful clinical responses include:

1. Improvement in lung function (FEV_1)
2. Stabilization of lung function over time (i.e. prevention of the usual decline in lung function)
3. Reduction in the number of pulmonary exacerbations
4. Reduction or stabilization of respiratory symptoms
5. Improvement in nutritional status
6. Improvement in quality of life scores.

As the treatment goal of this progressive disease is to slow decline in lung function and reduce mortality, the most important outcomes are 2 and 3.

6.10. How often should treatment response be assessed?

Response:

Treatment response time intervals depend on the outcome measure used. For outcome measures 1,2 4 and 5, assessments should be performed in the first 3 months of therapy; every 3 to 6 months in the first year of treatment and on a yearly basis subsequently. Outcome measures 3 and 6 should be assessed on a yearly basis.

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 therapy should be considered in patients who have clinically significant adverse effects that persist and recur after stopping and re-initiating therapy.

Examples of these reactions include (but are not limited to):

1. Elevation of liver function tests beyond the higher range of fluctuations observed in CF patients
2. Allergic reactions to treatment

However, the risk-benefit of discontinuing treatment should be considered on a case-by-case basis depending on the severity of the adverse event and risk of stopping treatment.

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

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

Response:

Treatment should be limited to CF patients attending the cystic fibrosis clinics accredited by CF Canada.

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:

As outlined for question 6.12, treatment of CF patients with this drug should be limited to CF specialists practicing at CF clinics certified by Cystic Fibrosis Canada.

7. Additional information

7.1.

Response:

Currently there are 62 CF patients in Canada who have gained access to ELX/TEZ/IVA through their involvement in Vertex-sponsored clinical trials. The impact of this therapy has been so dramatic and life-altering that they have expressed intense guilt about their friends and siblings with CF not having access to this breakthrough therapy as well. Some of our patients who remain in the open-label safety phase of the trial have been on the drug for >120 weeks (2.25 years) and the efficacy reported in the pivotal Phase 3 clinical trials have been sustained and the drug continues to be very well tolerated.

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.

   The only help provided for this submission was administrative support from the Manager of CF CanACT to collate responses.

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.**

   The CF CanACT network to which the physicians belong is supported by a grant from Cystic Fibrosis Canada and the Cystic Fibrosis Foundation in the USA.

Declaration for Clinician 1

Clinician Information	
Name	*Bradley Quon*
Position	*Associate Professor of Medicine, University of British Columbia, Respirologist Adult CF Physician St. Paul's Hospital, Medical Lead CF CanACT*
Date	*04-02-2021*
☒	**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**
Vertex Pharmaceuticals	☒	☐	☐	☐
AbbVie	☒	☐	☐	☐
Horizon Therapeutics	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Mark Chilvers*
Position	*Paediatric Respirologist, BC Children's Hospital, Vancouver, BC.*
Date	*04-02-2021*
☒	**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**
Vertex	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Felix Ratjen*

Position	*Head, Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Professor, University of Toronto.*
Date	*03-02-2021*
☒	**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**
Vertex	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Larry lands*
Position	*Director, Pediatric CF Clinic, Montreal Children's Hospital*
Date	*03-02-2021*
☒	**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**
Vertex	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Diana Elizabeth Tullis*

Position	*Professor of Medicine, University of Toronto, CF Respirologist ST Michael's Hospital*
Date	*03-02-2021*
☒	**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**
Vertex	☐	☐	☒	☐
Proteostasis	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐