Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data.

March 19, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input

Name of Drug: elexacaftor+tezacaftor+ivacaftor
Indication: To treat cystic fibrosis
Name of Patient Group: Cystic Fibrosis Canada
Author of Submission: Nicki Perkins

1. About Your Patient Group

Cystic Fibrosis Canada www.cysticfibrosis.ca

2. Information Gathering

The success of patient trials done in the United States and Europe show that the drug in question, Trikafta, is very effective in treating patients with a responsive cystic fibrosis gene other than the currently approved gene DF508. In my case it is the gene numbered: M1101K. This is a gene that has responded tremendously to Trikafta. It is the gene that is found in the Hutterite population and unfortunately marginalized as a subpopulation. M1101K is a rare class II variant, found in 0.2% of CF patients registered in CFTR2 worldwide registry. However, in Canada, M1101K is found in 1.7% of individuals with CF.

The information I have received has been from my clinic team (Southern Alberta Cystic Fibrosis Adult Clinic) at the university of Calgary, Alberta in the Cumming School of Medicine.

“The Hutterite population is a genetic isolate with an increased incidence of cystic fibrosis (CF). Previously we identified three CF haplotypes defined by polymorphisms flanking the CF transmembrane conductance regulator (CFTR) gene. delta F508 was present on one of the haplotypes in only 35% of CF chromosomes. We hypothesized that the other two CF haplotypes, one of which was the most common and the other of which is rare, each harbored different non-delta F508 mutations. Single-strand conformation polymorphism analysis detected a missense mutation, M1101K, in both chromosomes of a Hutterite patient carrying the two non-delta F508 haplotypes. M1101K appears to have originated on an uncommon CFTR allele and to be infrequent outside the Hutterite population. The presence of M1101K on two haplotypes is likely the result of a CFTR intragenic recombination which occurred since the founding, 10-12 generations ago, of the Hutterite population. The crossover was located between exons 14a and 17b, an interval of approximately 15 kbp. delta F508 and M1101K accounted for all the CF mutations in patients from 16 CF families representing the three subdivisions of the Hutterite population.” – National Institute of Health

The studies showing the efficacy of Trikafta with this gene are located here.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10618485/

https://pubmed.ncbi.nlm.nih.gov/33303536/

3. Disease Experience

WHAT IS CYSTIC FIBROSIS?

Cystic fibrosis (CF) is the most common fatal genetic disease affecting Canadian children and young adults. At present, there is no cure.

CF causes various effects on the body, but mainly affects the digestive system and lungs. The degree of cystic fibrosis severity differs from person to person, however, the persistence and ongoing infection in the lungs, with destruction of lungs and loss of lung function, will eventually lead to death in the majority of people with CF.

Typical complications caused by cystic fibrosis are:

- Difficulty digesting fats and proteins
- Malnutrition and vitamin deficiencies because of inability to absorb nutrients

- Progressive lung damage from chronic infections and aberrant inflammation
- CF related diabetes
- Sinus infections

More than 4,300 Canadian children, adolescents, and adults with cystic fibrosis attend specialized CF clinics. Half of the Canadians who died with CF in the past five years were under the age of 37.

Cystic fibrosis affects the cells that produce mucus, sweat and digestive juices. These secreted fluids are normally thin and slippery. But in people with CF, a defective gene causes the secretions to become sticky and thick. Instead of acting as lubricants, the secretions plug up tubes, ducts and passageways, especially in the lungs and pancreas. Eventually the patient will succumb to the disease from respiratory failure.

This disease is an entity of itself, it roars, it scares, it hurts, it depresses, and it progressively worsens. Life becomes unrecognizable and death for some becomes a friend. As this disease progresses most of life's freedoms are taken away one by one. You move from the ability to attend school or got to work to fearing the task of climbing a flight of stairs because the idea of it puts you into panic overdrive for fear of collapsing at the top or being embarrassed because you have to pull to the side to catch your breath. From here you move into the "I can't keep weight on" phase and have to get a feeding tube surgically implanted so that you can survive, then your lungs become so damaged that you have to go on oxygen from that point forward you have to live with the fact that you are in end stage CF. Finally, you decide to go for transplant or just stop fighting which means your time is now finite and CF holds a straight flush, Ace high on the river card, you are done. All the while you are trying to survive the rest of your life, relationships, education, career, family, and friends. I live in a very sick body, a body that is slowly quitting. I can't stop it, I can't slow it down, I can't even get a holiday from it. When I go to bed, I am sick and when I wake up, I am sick. I'm not trying to depress you I'm trying to shed light on a disease that needs to be cured and eradicated from this earth. It is a torturous existence when it takes hold of you. Four times a year I attend clinic and for 2 reasons it is a highly emotional day for me. The first is that I see other patients who are healthier than me and I see the other ones who are worse than me. The terrifying part of this is that the healthy patients represent my past, and the sick ones represent my future. It makes me nauseous to even put this reality down on paper. The second is that we have a lot of time to between clinic team members, so we review our chart just to see what our team says about us. When I was 33 years old, I sat down to read mine and in it was a letter to the insurance company that pays my LTD that I thankfully qualified for by working at the U of C for five years after my university graduation (a feat of its own) and it said things like:

"Her FEV1 still remains <40% of predicted normal which thereby classifies her as having severely advanced CF."

"Cystic Fibrosis is permanent, severe and progressive. Nicole Perkins must live with the lifelong prognosis of worsening pulmonary functional impairment. The threat of progressive symptomatology forces Nicole to maintain a daily CF routine with exercise, chest physiotherapy, enteral tube feedings, and essential medications."

"The long-term expectation is that there will be gradual increasing severity of her disease. Her CF status is not reversible but rather progressive to worsening. The result might be that she will require home oxygen therapy and eventually lung transplantation."

Could you imagine being 33 years old and reading this diagnosis? Unfortunately, I don't have to imagine, I read it in black and white, my future prognosis.

Fast forward almost 20 years and I am all that, along with having CF related diabetes. My day is spent just trying to breathe.

So here I am. Trying desperately gain access to this, miracle drug. My plead is to you. I want to be able to benefit from this amazing treatment. I don't want a transplant. I don't want oxygen tanks glued to my hip just to get groceries. I don't want CF to push me out of my own life. Am I asking too much? Maybe but what else am I supposed to do…wait to die? I understand and fully accept this life I have, and some days I can see the light, I have hope, but some days that light at the end of the tunnel is a train. Like a grounded tangled kite, I long to fly again. I want my wings back. I want my breath back. I want my life back.

I was born with Cystic Fibrosis in 1972. I was sick for 4 years before I was finally diagnosed. I lived a relatively unencumbered childhood and teen years. I am pancreatic insufficient so I must take enzymes with everything I eat and drink in order to absorb the calories needed to survive. I need 4000 calories a day just to fight this disease. I have had a difficult life with Cystic fibrosis with hundreds of hospitalizations, procedures, tests, appointments, medication along with the mental struggle of knowing I would die at a young age.

When I was diagnosed the doctors gave me a 2-year life expectancy. At that time the treatments for CF were very limited and quite basic. I would need pages to describe to you how awful this disease is.

I am in end stage CF and have a lung function of only 24% or in layman terms I am only able to breathe in less than 750ml of air. A healthy adult is able to breathe in, at minimum, 4 liters. A simple way to get a feel of what it is like to have CF - take that straw out of your pop, put it in your mouth, plug your nose and breathe for one minute. I am currently on the double lung transplant list at the Transplant centre in Edmonton, Alberta. I am on oxygen 24 hours a day and a simple flight of stairs absolutely wears me out, not to mention the calories I burn just breathing. Life is so hard at this moment. I have watched my friends get access to this amazing drug and have their lives flipped upside down. No more coughing, no more mucous clogging the airways, less hospitalizations, no more night feeds, many have been able to return to work. I am just so jealous. The drug is a life changer. I have no idea what it would be like to not cough all day and all night. I am almost 52 and circling the drain. I AM LITERALLY DYING TO TRY THIS DRUG.

4. Experiences With Currently Available Treatments

Current treatments for cystic fibrosis have come a very long way over my lifetime, but that is all they are, treatments. The constant need for chronic antibiotic therapy has worn out my body. I need more and more medicine that is working less and less for me. I take 12 oral medications, I inject 3 different types of insulin, I breathe in 5 different medications. My fight to survive is minute by minute. My transplant team wants me to eke out the most from my lungs because transplant brings upon a whole other type of struggle. Nothing is guaranteed. I had a friend who died waiting and she had 10% lung function. Could you imagine living in that body? Without breath nothing else matters. The treatments up until this point have been combatting the progressive destruction from the disease. Trikafta is a completely new modality. It modifies the defective gene to try to get it working properly. In 90% of the CF population, it has stopped the progression. Children born today will most likely live a long and fruitful life, something denied to me and the other old CF'ers. In fact, being 51 years old is a miracle. I have worked extremely hard to save myself. I have even started a foundation to help CF patients in Calgary, AB. www.sfcf.ca I have had a lot of professional success with the naming of a research lab at the Snyder Institute for Chronic Disease at the University of Calgary in my honour, being at the top. https://snyder.ucalgary.ca/research/core-resources/nicole-perkins-microbial-communities-core-labs . I was also chosen as Philanthropist of the year in 2014 for the city of Calgary. Philanthropist of the Year 2014 I have raised almost 3 million dollars for CF research and programs at the local level. I really want to continue my work but due to my poor health, I have had to put the foundation work on hold**. I feel like I am a great contributor to society despite my disability.**

Exercise, nutrition, rest, meditation, positive attitude and a team of support has got me to 51. Trikafta could possibly give me 10 or more years before needing the transplant. I will still need the transplant, but boy I would love to put it off for as long as I can. It terrifies me. The 5-year survival is only 50%. More importantly, a life not spent coughing out gobs of glue like mucous every hour of the day sounds like a dream to me. **I have never known wellness.**

5. Improved Outcomes

Based on the studies with Vertex, the manufacturer of this drug, for the M1101K gene, Trikafta will:

- Thin out the mucous so I can easily cough it out.
- Allow me to breathe a clear breath with no curdling or death rattle happening.
- Time to find some joy.
- Take away some of my fear.
- Improve my diabetes.
- Allow my body to better absorb the much-needed nutrients.
- Improve my mental health.
- Give me a brand-new outlook on the back nine of my life.
- MAYBE not need oxygen 24/7. That would be remarkable.
- Getting rid of the mucous from my lungs and pancreas will take a heavy burden off my back.

- Improve my life in potentially infinite ways and to feel, for once, in my life like I won't die in a month.
- The most important outcome would be to stop the progression of this disease and postpone the need for a double lung transplant. Get me off the list…for a while.

6. Experience With Drug Under Review

I have had NO opportunity to access this drug because my gene is considered a rare, but responsive gene, to Trikafta.

7. Companion Diagnostic Test

The best test to show the efficacy of Trikafta is the sweat test. Patients are hooked up to a system that measures the amount of chloride in our sweat. Mine is currently 120. I have several friends who have their numbers in the 20's.

Sweat chloride levels:

Less than 30 mmol/L: CF is unlikely.

30 to 59 mmol/L: CF is possible, further testing may be required.

60 or greater mmol/L: diagnostic of CF.

Other markers of improvement are in the number of bacteria colonized in the lungs. I normally have 10^6 parts per million of pseudomonas aeruginosa in the mucous. This has been decreased by thousands in the studies.

8. Anything Else?

I am dying to gain access. It could change my world.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

No

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

   No

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
<Enter Name Here>				

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

Name: Nicki Perkins
Position: Patient
Patient Group: Cystic Fibrosis Canada
Date: February 26, 2024

CADTH

Project Number: SR0837-000
Name of Drug: elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)
Indication: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data.
Name of Patient Group: Cystic Fibrosis Canada
Author of Submission: Dr. Paul Eckford, Chief Scientific Officer

1. Information Gathering

In completing this submission, Cystic Fibrosis Canada conducted focus groups with Canadians with rare mutations who are being treated with Trikafta, Canadians with rare mutations who do not have access to Trikafta, and caregivers of Canadians with rare mutations that cause cystic fibrosis. We also utilized findings from our 2021 patient and caregiver survey on access to Trikafta, which received over 1200 responses from our community. We made queries and referred to data sets from the Canadian Cystic Fibrosis Registry.

We also included findings from Phase I of *The Social and Economic Impact of Cystic Fibrosis in Canada: A Burden of Disease Study* (herein called "Burden of Disease Study") conducted by Dalhousie University and Cystic Fibrosis Canada, in partnership with the Conference Board of Canada and funded in part by Cystic Fibrosis Canada and the Canadian Institutes in Health Research (CIHR). Through this study we conducted a community survey months before Trikafta became widely available in Canada. Where permission was granted, survey findings were linked to individual registry records, which allows us to stratify data across disease severity, geographic location, age, sex, and other informative data points. The study measures the burden of CF at the individual, caregiver, health systems and societal levels. It is said to be one of the most comprehensive studies of the burden of CF in the world. A Phase II follow up study is underway and will provide data that demonstrate the socio-economic impact Trikafta has had on the Canadian CF population since the Phase I study.

We also provide insights from relevant medical and scientific publications and perspectives that speak to the health and health related challenges that Canadians who have rare mutations that lead to cystic fibrosis face.

2. Disease Experience

According to the Canadian Cystic Fibrosis Registry, now over 50 years old, life-changing treatments are increasingly reaching the 4,445 Canadians with cystic fibrosis (CF) and that Canadians born with CF today will live longer than those who came before them. But there's another, less-rosy side to the story: more than half of Canadians who died of CF in 2022 didn't reach their 40th birthday. Many are still very ill and one in seven living with the disease today is ineligible for the treatments making such a positive difference for others with CF.

For the first time, the estimated median age of survival has reached the milestone of 60 years of age. In other words, half of babies born with CF today are expected to live beyond their 60th birthday, compared to their 52nd birthday as reported in the 2017 edition of the report and 37th birthday in 2002.

The number of Canadians with CF who are taking CFTR modulator therapies has increased by 70%. This was approximately 2,500 people in 2022, compared to approximately 1,500 in 2021 when about 250 people with at least one copy of the most common mutation that leads to CF – F508del - were granted pre-market authorization access to ELX-TEZ-IVA through Health Canada's Special Access Program.

The drug received a positive reimbursement recommendation from CADTH in the summer of 2021 for use in those 12 years of age and older who had at least one copy of the most common mutation that leads to CF and had lung functions

(ppFEV1) of 90% or less, after which all of Canada's public drug programs reimbursed the drug within two months of CADTH's recommendation. Three of these drug plans – Alberta, Saskatchewan and Manitoba – did not include the 90% or less lung function criteria, instead providing broad access to anyone with at least one copy of the F508del mutation who was 12 years of age or older. More Canadians gained access in 2022 when ELX-TEZ-IVA was approved for those who were six years of age or older and the 90% or less lung function requirement was lifted.

Steady growth in the median age of survival is an indicator of the advancements in CF care, our investments in research, new treatments and the efforts that patients put into maintaining their health. Yet while the data are pointing in the right

direction, cystic fibrosis is still a fatal disease, people still have a high treatment burden and there is still much work to be done.

There are continued challenges of living with CF from a healthcare and quality of life perspective, including those who are unable to benefit from recent life-changing treatments:

- In contrast to the survival milestone, the 40 Canadians who died of CF in 2022 had a median age of 38.
- Canadians with CF collectively had 17,000 clinic visits, spent 10,000 days in hospital, and spent nearly 6,000 days on intravenous antibiotics in 2022 alone. While these numbers represent decreases over previous years, they indicate a disease with a significant toll on daily life as well as Canada's healthcare system.
- One in five Canadian adults with CF has depression or anxiety recorded as a complication in the CF Registry, reflecting international work showing elevated rates of these mental health conditions in the CF community.

Data from the Canadian Cystic Fibrosis Registry on Canadians with CF who don't currently have a Health Canada indication for modulators show that:

- 246 have mutations known to respond to ELX-TEZ-IVA.
- 114 have mutations predicted to not respond to ELX-TEZ-IVA.
- 179 have mutations that have unknown responses to ELX-TEZ-IVA.

Table 1: ELX-TEZ-IVA (Trikafta) eligibility, known and predictive response status of Canadians with CF by mutation class and jurisdiction

Cohort	**Province of CF clinic care**				
	Canada	**BC**	**AB**	**SK**	**MB**
1. Eligible for ELX-TEZ-IVA	3851 (86.52%)	376 (87.65%)	484 (85.06%)	117 (89.31%)	102 (90.27%)
2. Eligible for ivacaftor	61 (1.37%)	10-15 (2-4%)	5 (0.88%)	<5 (<3%)	<5 (<4%)
3. Responsive to ELX-TEZ-IVA	246 (5.53%)	20 (4.66%)	47 (8.26%)	7 (5.34%)	5-10 (4-9%)
4. Not predicted to respond to ELX-TEZ-IVA	114 (2.56%)	<5 (<1%)	13 (2.28%)	0 (0.00%)	0 (0.00%)
5. Unknown response to ELX-TEZ-IVA	179 (4.02%)	19 (4.43%)	20 (3.51%)	5-10 (3-8%)	<5 (<4%)
Total number of individuals	**4451 (100%)**	**429 (10%)**	**569 (13%)**	**131 (3%)**	**113 (3%)**

Table 2: ELX-TEZ-IVA (Trikafta) eligibility, known and predictive response status of Canadians with CF by mutation class and jurisdiction

Cohort	Province of CF clinic care				
	ON	**QC**	**NS**	**NB**	**NL**
1. Eligible for ELX-TEZ-IVA	1321 (86.74%)	1111 (85.07%)	243 (90.33%)	37 (90.24%)	60 (85.71%)
2. Eligible for ivacaftor	61 (1.37%)	10-15 (2-4%)	5 (0.88%)	<5 (<3%)	<5 (<4%)
3. Responsive to ELX-TEZ-IVA	246 (5.53%)	20 (4.66%)	47 (8.26%)	7 (5.34%)	5-10 (4-9%)
4. Not predicted to respond to ELX-TEZ-IVA	114 (2.56%)	<5 (<1%)	13 (2.28%)	0 (0.00%)	0 (0.00%)
5. Unknown response to ELX-TEZ-IVA	179 (4.02%)	19 (4.43%)	20 (3.51%)	5-10 (3-8%)	<5 (<4%)
Total number of individuals	**4451 (100%)**	**429 (10%)**	**569 (13%)**	**131 (3%)**	**113 (3%)**

The data presented above are similar to the cohorts requested by France's Dr. Pierre-Régis Burgel for a global rare mutations project. Dr. Brugel has done extensive research on how people with CF who have rare mutations respond to ELX-TEZ-IVA. He started France's compassionate use program for the drug, which gives anyone with a rare mutation that may respond to ELX-TEZ-IVA the

right to try it, provided they don't have two mutations known to not respond. The program is further described in Section 8 of this submission. In a 2023 study Dr. Brugel, et al, found that:

> *Although focused on CFTR expression and processing (and not channel function),* ***our study confirms the relevance of assessing the response of rare mutations to modulators (in a personalized medicine approach)*** *and suggests the existence of a location-dependent pattern of response to modulators that may contribute to further clarifying the mechanism of action of the correctors.* ***Understanding the molecular and functional consequences of rare CF mutations is fundamental for the adoption of precision therapeutic approaches for such CF patients.***

We agree that we must assess the response for rare mutations to modulators to facilitate access to precision medicines, and that needs to happen now. For many people living with CF, CFTR modulator therapies offer a significant advantage in managing their disease, but Canadians with rare mutations have no existing pathway to long-term access at present. These people are getting sicker while those who have access are getting better. These people face layers of inequities – being born with a rare mutation, not being diagnosed early because their rare mutations are not always on newborn screening panels, insufficient numbers for clinical trials for many, Canada's lack of regulatory and policy frameworks to evaluate predictive in vitro laboratory evidence, and reimbursement systems that do not or will not cover the therapy for anyone outside of the narrow Health Canada indication.

A member of our community focus group of individuals living with rare CF mutations described to us the all too familiar story of access denied by the current system:

> *Last year I had a pneumonectomy…they removed one of my lungs because of necrosis to try to buy me time before putting me on the lung transplant list, but my lung function continued to drop. When I got to under 30% lung function my doctor started trying to get me Trikafta…it showed that it worked in other people with one of my mutations.*

> *The process was a nightmare. My doctor wrote to Health Canada to see if I could get it through the <Special Access Program>, but that program is only for drugs that do not have Health Canada approval. Trikafta does, just not for me.*
>
> *After that my doctor tried to get it through <the provincial drug plan>. I was denied on the first application and the appeal, even though my health was tanking. – Person with CF who lives with a rare mutation*

Moreover, many people who carry rare mutations come from diverse and often racialized backgrounds. These people are already disadvantaged by health care systems that were not designed with them in mind. In some instances, people have been told that it is unlikely that they or their children have cystic fibrosis because of their ethnic background, even when there are incidences of the disease in these populations.

Using data from the European Cystic Fibrosis Registry, an article published in the Journal of Cystic Fibrosis in 2023 (Zahav et al) shows the results of a study on disease severity in people with cystic fibrosis who have residual function (RF) mutations (mutations where there is at least some, though not normal levels, of CFTR function and may result in what is considered more 'mild' CF disease). Minimal function (MF) mutations have no, or nearly no CFTR function and are often considered to have the most severe CF disease.

> *Of the 44,594 eligible patients (median age 19.5 years, IQR 10–29.8), 6,636 (14.6%) carried RF mutations, and 37,958 (85.1%) MF mutations. Patients carrying RF mutations were older, diagnosed at a later age, had lower sweat chloride at diagnosis and better FEV1pp at each age group.*
>
> ***However, their FEV1pp declined with age and rates of chronic Pseudomonas aeruginosa increased with age. A significant number of patients with RF had FEV1pp similar to patients with MF at each age group. 4.5% of RF patients were treated with oxygen and 2.61% had a lung transplant. With increasing age, 26.6% of RF patients were treated with pancreatic enzymes associated with a more severe lung disease. RF patients had shortened life spans, with mortality starting around the age of 20 years.***
>
> ***Conclusions: Patients carrying RF mutations experience a decline of pulmonary function with age, leading to life- shortening. Standard of care therapies and augmenting CFTR function may improve their survival and quality of life.***

Table 3 compares data from the 2020 and 2022 Canadian Cystic Fibrosis Registry reports. It illustrates the impact ELX-TEZ-IVA has had on the Canadian cystic fibrosis population since ELX-TEZ-IVA was first introduced in Canada. It includes data on when ELX-TEZ-IVA was first introduced for those 12 years of age and older in the summer of 2021. The 2022 report does not, for the most part, include data on 6+, introduced in the fall of 2022, nor does it contain data for 2-5 year olds, for which access started in early 2024.

Table 3: Comparison of key health outcomes of Canadians 12 years of age and older since the introduction of ELX-TEZ-IVA.

	2020	**2022**	**Difference**	**Percentage change**
Number of Canadians with cystic fibrosis	4332	4445	Increase of 113	3%
Number of clinic visits	18,000+	16,750	Decrease of 1250+ days	-7%

Number of hospital days	17,100+	10,478	Decrease of 6662+ days	-39%
Number of home IV days	13,600+	5964	Decrease of 7636+ days	-56%
Number of organ transplants	21	7	Decrease of 14 transplants	-67%

While these are tremendous outcomes, there is still work to be done to improve access to ELX-TEZ-IVA and to have it funded for everyone who can benefit, especially for those with rare mutations. The Canadian Drug Expert Committee (CDEC) has the opportunity to help these people get access to a therapy that may very well save and change their lives. Do not let Canada's lagging regulatory and policy initiatives delay access for these people. Do not let Canada's implementation inertia steal their lives away.

3. Experiences With Currently Available Treatments

There are hundreds of therapies that aid in symptom management in the categories of: antibiotics, supplemental vitamins, aerosol bronchodilators, mucolytics and pancreatic enzymes, anti-inflammatories, and steroids. Most cystic fibrosis patients take pancreatic enzymes, multi-vitamins and nutritional supplements to maintain normal growth.

> *So many of my meds are not covered, so I pay out of pocket. Things like vitamins, which are $80 a month, enzymes and nebulized meds like hypertonic saline are not covered. They cost me hundreds of dollars a month.*

> *I know the drug <Trikafta> costs a lot, but when I see the outcomes that people are having and hear about people coming off of other meds I can't help but wish that was me. – Person with CF who lives with a rare mutation.*

Cystic fibrosis patients work tirelessly every day to improve the clearance of secretions from their lungs. This is done by performing airway clearance techniques at least twice a day for about 30-60 minutes per session. Inhaled medications are used to open the airways while inhaled antibiotic treatments are used to control infections. The total time spent on maintaining lung health is well over two hours each day for most CF patients.

> *My routine is very rigorous. I think one of the reasons I stayed healthy so long is that I exercise for hours a day, on the treadmill, my rowing machine, whatever. But when I got a bad infection that all changed. I started going downhill quickly, and my doctor was trying to find things that could help. He told me about this medicine – Trikafta – that was working miracles. But I couldn't get it. I didn't have the right <mutation>. Eventually I was able to get into the clinical trial. After the initial purge I started to feel instantly better, and it has only gotten better from there. Now I can exercise at a much more intense level, which is going to help me in the long-term. – Person with CF with a rare mutation*

Patients not on ELX-TEZ-IVA frequently have periods of infection and acute inflammation called exacerbations that require a hospital stay of at least two weeks and that frequently last up to four weeks. Exacerbations often result in a drop in lung function that is not fully recovered once the exacerbation resolves, resulting in poorer long-term health and greater disability each time. The steroids that are used to reduce the inflammation and help patients recover from the exacerbation ultimately damage organs in the long run and may be a contributing factor to the development of cystic fibrosis related diabetes (CFRD), which occurs in approximately 33% of all Canadian cystic fibrosis adults.

Many of the other drugs that patients need to take on a regular basis also have negative side-effects. Antibiotics can cause kidney damage and total lifetime dose must be controlled; others permanently stain the teeth. Chronic use of antibiotics

leads to resistance and as patients age, a need to try multiple antibiotics to find one that works. Because patients are on so many drugs, drug to drug interactions become difficult to manage and can interfere with optimum therapy.

> *I have had problems with about five therapies. An inhaled steroid shut down my adrenal glands and I could not move throughout the day. I am an adult who is less than 5 feet tall because my growth and weight were suppressed due to meds,*
>
> *I had extremely rare side effects to four antibiotics and couldn't walk anymore. I was red and had swollen bumps all over, flu-like symptoms and couldn't even go to the bathroom. After three days of this I had to go to hospital, which is when I found out I had Stevens-Johnson syndrome <SJS>, which is rare, caused by a reaction to a medication, and affected my skin and mouth. I was in so much pain. Usually, people with SJS need to be put in a coma so they can get through the pain.*
>
> *Walking came back easily with steroids, but the rest of the symptoms took three months to clear. I had burns on my hands, blisters, and peeling, all due to an antibiotic.*
>
> *Due to adverse reactions, I can't take these antibiotics, so I now have limited choice to help with lung infections. That is very scary. – Person with CF who has a rare mutation.*

For many, cystic fibrosis brings physiological changes and challenges. This includes Distal Intestinal Obstruction Syndrome (DIOS), blockage of the liver and pancreas ducts, inability to conceive children, early onset osteoporosis, nasal polyps and sinusitis.

> *When I went to the adult clinic like you kind of, you know, you hit the point where you're not as resilient as a kid. And <my> lung function started going down a little bit at a time.*
>
> *But in the past like 3 years it's felt more…more severe like my lung function is kind of, it's progressing, it's progressing and it's progressing. I've had a few more hospital visits than I'm used to. And that's been hard because a lot of the time every time I go to the hospital, I've had a lot of nasal issues.*
>
> *I had to get surgery to get all my <sinus> polyps removed. It <had been> really bad for about four years <the doctor> said. I had like 15% function in my nose, so I couldn't smell anything for a long time. And then I got the polyps removed. And since the surgery, my nose has been even more of a problem. And so, every time I go see the ENT, he goes, what are you, are you on Trikafta?*
>
> *And every time I would be like, no, I can't have it.*
>
> *But that's become a question now whenever a health issue arises…often doctors who aren't familiar with me will go well, are you on Trikafta?*
>
> *It's like, no, I can't have that. – Person with CF who has a rare mutation*

As we face a new day in CF with a new treatment that can make a difference for some people, there is a significant population – one in every seven people with CF – whose genetic mutations mean they cannot access these treatments, and more whose CF has progressed past the point of full benefit. These people cannot be left behind.

4. Improved Outcomes

ELX-TEZ-IVA is now indicated for approximately 87% of Canadians with cystic fibrosis, those who carry at least one copy of the most common mutation, F508del. It is the single biggest advancement in treating cystic fibrosis in the history of the disease and has been proven to significantly improve health outcomes. The remarkable impact the drug has had on what has been an inevitably fatal disease has led to intense media interest, interests from other patient communities, and the interest of funders. Due to its tremendous efficacy, it made its way from first Health Canada application to being funded

for those 12+ with at least one copy of the most common mutation by all of Canada's public drug programs in just 11 months, forever changing the lives of those who can access it, as well as those who cannot. The former will overwhelmingly live longer. The latter overwhelmingly won't.

In our focus groups. Canadians with CF who have rare mutations and their caregivers shared their thoughts on how ELX-TEZ-IVA might change their or their loved one's lives:

> *We want <our child to have a long and adventurous life>. We would give anything to remove barriers to getting <our child> access. As a twin, <their> trajectory is together. We want to see them sitting on porch when <they> are old. – Parent of a child with CF who has a rare mutation*

> *Just because <my child> is healthy today does not mean <they> will be healthy in the future. We have no guarantee. This is a progressive disease. The future is so unknown. I want <my child> to have a future. – Parent of a child with CF who has a rare mutation*

While we are starting to see the significant benefit of ELX-TEZ-IVA for those with the most common mutation in Canada, in other jurisdictions, we are starting to also see significant benefit for many who have rare mutations. This provides both hope and despair for Canadians with rare mutations.

> *I feel like I am constantly trying to grab on to hope but it is slipping through our fingers and knowing where this disease is going…it could help me, and right now there just is nothing available. I can't even imagine what it would be like to have this drug handed to me. – Person with CF who has rare mutation*

> *For all of my life I have taken very good care of self. My parents always said that one day there would be a treatment for me, to have hope. The symptoms hit me hard in my twenties. I am still focused getting a magical therapy…Trikafta is that therapy, at least for now. I advocated for access only to find out that I can't get it. I thought it would help me and still think it might. I have worked my life like I didn't have CF, but I do and I can't get a drug that will keep me going in my career, in my relationship and with life. I need it because I have worked hard. I want those extra years. Like others with CF who have the drug, I deserve those extra years. – Person with CF who lives with a rare mutation.*

Canadians with rare mutations and their loved ones are acutely aware of the inequalities that our healthcare and drug access systems have placed on them, and that these inequalities lead to poorer health outcomes. This is particularly painful when it comes to access to ELX-TEZ-IVA. It is devastating to watch others get better due to this drug while there is no pathway to access for those with rare mutations. Many reported feeling scared for their futures and their families. They want a chance at life and right now they don't have it.

> *Healthcare workers assume <my child> is on it and <my child> is not. This is a painful reminder of being left out. <My child> made friends with CF and they were passing away, and now with Trikafta, they will likely out live <my child>. We know it works in <people who have the same rare mutation> as <my child>, but <my child> can't get it. Should I allow <my child> to perish because Canada won't make the exception that other countries have? – Parent of a child with CF who lives with a rare mutation*

> *I have built a good life and have always put in a lot to manage my disease, like hours a day every day for over thirty years. I work full-time, pay taxes, and have found love. But my health is not good right now. It is declining, and I am afraid that if I don't get Trikafta soon I will need to go on the lung transplant list. What will happen to everything I have built? What will happen to my job? What will happen to my <partner>?*

5. Experience With Drug Under Review

Very few Canadians with rare mutations that lead to cystic fibrosis have access to ELX-TEZ-IVA. Most who have access participated in clinical trials. While clinical trials for ELX-TEZ-IVA in individuals with 18 rare CF mutations had Canadian patient participation and we know that overall, based on a manufacturer press release, the study met its primary endpoint and showed that ELX-TEZ-IVA resulted in rapid, statistically significant, and clinically meaningful improvements in lung function compared to placebo (9.2 percentage point increase in ppFEV1), we do not yet know how many Canadians participated, or if all mutations showed the same response in the study. We look forward to the release of the full study details. What we do know is that the individuals in these trials who also participated in our focus groups significantly benefitted from access to this drug and continue to benefit for now. In recommending and providing broad access to Trikafta, CDEC and Canada's public drug programs can help ensure that these people can benefit from this transformational therapy long-term.

Several people in the focus groups had mutations on the FDA's approved list of mutations, meaning that if they lived in the US, they would have secured long-term access years ago. As a result of broad access in other countries, there is published RWE in the literature of ELX-TEZ-IVA response in patients with many of these same mutations. CDEC must consider all this evidence in its deliberations. To deny access based on limited Canadian data would be wrong, especially for those with ultra-rare mutations for which there may be only a handful of people world-wide.

Some who are on ELX-TEZ-IVA have self-funded the drug either out of pocket or through donations. None of these approaches will provide mid-or-long-term access. Unless public and private drug programs agree to fund ELX-TEZ-IVA broadly for those with rare mutations, these people will soon lose access to therapy, which means not only will they lose all of the benefits and quality of life improvements they have experienced, loss of therapy can also cause a springboard effect through which they may become even sicker than they were before trying ELX-TEZ-IVA. These people are in very tenuous situations. In our focus groups we spoke to Canadians with rare mutations that are currently being treated with ELX-TEZ-IVA, as well as those who are not. The experiences of those who are on therapy are detailed below:

> *Life has been hard for me, and it was getting harder. It's not just Trikafta, there were two to three modulators before it. I was constantly told that I don't qualify. Hearing everyone else's successes…it has been hard to keep going. – Person with CF who lives with a rare mutation*

> *Through my clinic, in March 2022 I qualified for one of <the manufacturer's> clinical trials…it started out well. Prior to me initiating the treatment I know that my sweat chloride test was 105 or 109, in that range, and when I came back to next clinic after what I think was 2 to 4 weeks and we did the sweat chloride tests it was down to 18 in one arm and 14 in the other.*

> *My cough, I went through the purge period for about three to four days, and coughed my lungs out, that, it cleared up and I have never really had an issue since. - Person with CF who lives with a rare mutation.*

> *I got Trikafta through <individual donations> and am <rationing> it because I can't afford it myself. So, I only take one pill a day. Still, I have had great results. I know that it is working for me because I can do things I couldn't do before, but I can't guarantee my supply. I can't pay for it long-term. I don't know if I can keep going with this but I do know that it is working for me. – Person with CF who has a rare mutation*

Like most others who are on ELX-TEZ-IVA, all in our focus groups who have rare mutations and are taking ELX-TEZ-IVA responded exceptionally well to therapy, even those who have mutations for which evidence is scarce.

> *Even though there isn't <much evidence> on my mutation, Trikafta improved my lung function by 10% within a month and is keeping it steady. It dropped my sweat <chloride> down and helps me be less breathless. I can walk and talk at the same time now. I wasn't able to do that before… now that I am more stable and my PFTs are up, I am off the transplant list and the transplant doc does not want to book an appointment for a year. – Person with CF who lives with a rare mutation*

> *I am pregnant! It happened unexpectedly within a month and a half of me <taking> Trikafta. It was always my dream to be a mom, but I wasn't well enough and it is hard for women with CF to get pregnant. I also never thought I'd have a future, so I didn't want to do that to <a child>.*
>
> *To having a baby and making plans…these are not things I ever thought I would be able to do…but now it's not "I have this appointment or that appointment"…I can focus on something other than just my medical appointments.*
>
> *I am having a baby. Now I have to think of the future. – Person with CF who lives with a rare mutation*

Canadians with CF who live with rare mutations deserve the right to try ELX-TEZ-IVA, including those where evidence is lacking. Indeed, there should be avenues to try ELX-TEZ-IVA for those who don't have mutations known to not respond. This could be through an access program that generates RWE, or through laboratory testing on patient cells. It should not be incumbent upon the family of a sick patient to fundraise for access.

> *My family had no choice but to fundraise for Trikafta. Through generous donations I was able to get it. My lung function went up by 10% in the first month, I have gained weight and have energy and have hope for the future…<planning> for the future, something I have never had done because who knows when you're going get sick next, to go to hospital next…you don't know if you will have a future.*
>
> *But I had to fight for this drug, I could have died trying to get it and I don't know what will happen when*
>
> *it runs out. It's like every step of the way they told me that there was no evidence to support me getting*
>
> *the drug.*
>
> *Let me be your evidence. – Person with CF who lives with a rare mutation*

Even with evidence in hand, Canadians with rare mutations that may respond to ELX-TEZ-IVA have been denied access. Despite overwhelming findings on the positive clinical impact that ELX-TEZ-IVA has on some of these individuals, our systems are not built for them. In fact, they are built against them.

Public and private drug plans won't generally consider these people for coverage because their mutation does not have a Health Canada indication, nor a Health Technology Assessment. Some of these people have ultra-rare mutations for which "gold standard evidence" of clinical trials cannot ever be generated unless Health Canada was to embrace N=1 studies. And still some fall outside of the lines, or their time will run out before N=1 studies can help them.

When we think of the best-case scenario, we know that public and private drug programs have the ability to cover Trikafta off-label for those with rare mutations, but they choose not to because of the risk of carrying a person who may or may not respond to therapy. But what is the risk of not covering these people? It is ultimately dangerous and will likely involve lung transplantation, if they are lucky. While risky, the ultimate choice is lung transplantation or certain death.

That Canada's public drug programs would choose death over potential of life speaks to the lack of compassion in our system of access. There are so many opportunities to help these people access this life-changing medication, but our review bodies and access systems – including CADTH – were built to review drugs for the masses and innovations of the past, not precision medicines like ELX-TEZ-IVA. We know the system is recognizing the need for change and is starting to act to implement innovative frameworks to fairly consider these types of evidence for these types of people who fall outside of the lines, but we need action now because people with rare CF mutations who could benefit from ELX-TEZ-IVA are getting sicker every day. They are pleading to us for help, and many may die waiting for the system to bring them the therapy they deserve, the therapy that so many others are benefiting from. Our public drug plans could and should provide broad access. They can make a difference here and now. These lives hang in the decisions you make, as well as the decisions that you don't make.

6. Companion Diagnostic Test

Since the discovery of the gene responsible for cystic fibrosis in Toronto in 1989 and the development of new technologies, it has become possible to detect the mutations in the gene through laboratory tests, using blood samples or cheek swabs. Samples are sent to specialized molecular diagnostic laboratories for analysis. Over 2,100 mutations in the gene responsible for cystic fibrosis have been described in the CFTR Mutation Database. The CFTR2 database lists mutations of known clinical consequence from the major CF registries around the world. CFTR2 includes over 800 variants to date, nearly all of which are disease-causing. About 130 of these mutations occur in the database less than 6 times. Many more ultrarare mutations exist that are not yet even described in CFTR2.

Medical diagnostic laboratories typically conduct newborn screening for the most common mutations in Canada. Such tests detect the mutations in the majority of the Canadian cystic fibrosis population. If medically indicated, complete exome sequencing will usually identify cystic fibrosis mutations missed by screening panels, though for a small number of individuals two disease-causing mutations aren't found. The falling costs of such tests make it more feasible than in the past to sequence CFTR mutations. Both the coverage and the availability of genetic testing vary across Canada, and there remain small numbers of individuals in the Registry who lack data on two disease-causing mutations for a variety of reasons. But these individuals can't fall through the cracks. Existing mechanisms must be fully utilized to understand if they will benefit from ELX-TEZ-IVA. If they will benefit, they must have a pathway to access. That is the duty and care our public drug programs have for these people. It is time that our public drug programs acknowledged this.

ELX-TEZ-IVA is the first CFTR modulator therapy available to treat patients with at least one copy of the most common cystic fibrosis mutation, F508del, and it is increasingly showing benefit in patients with a multitude of rare and ultra-rare mutations. The vast majority of individuals for whom ELX-TEZ-IVA is currently indicated, are known by their clinic or can be queried by their clinic using the Canadian Cystic Fibrosis Registry, even if the patients themselves aren't necessarily aware of their genotype. In addition to the complete CFTR genotype for most patients, the registry also houses rich clinical information on nearly every Canadian with cystic fibrosis including demographic information, clinical measurements, hospitalizations, treatments, and medications (including dates of initiation and cessation, where appropriate, for CFTR modulators).

There were 80 new diagnoses of cystic fibrosis in 2022 that were recorded in the CF Registry. Of these, 55 (68.8%) were made through provincial newborn screening (NBS) programs. In total, 4,354 (98.0%) of individuals with cystic fibrosis reported on in 2022, had a recorded diagnosis date, and of those, 2,659 (61.1%) were diagnosed before the age of one year, and 3,196 (73.4%) were diagnosed by the age of two years. Adult diagnoses, those diagnosed at 18 years and older, accounted for only 355 (8.2%) of all individuals reported on in 2022, and likely would primarily be individuals with milder CF disease born before newborn screening was accessible in all jurisdictions in Canada or those who immigrated to Canada.

Nearly all individuals with cystic fibrosis reported on in 2022 (4,404 out of 4,445; 99.1%) had at least one CFTR gene mutation recorded. 2,021 (45.5%) have two copies of the F508del mutation (referred to as homozygous F508del) and 1,842 (41.4%) carry a single copy of the F508del mutation (referred to as heterozygous F508del). In total, almost 87% carry at least one copy of the F508del mutation. Among the remaining 13%, approximately 4-5% of these people have mutations that do not produce protein and therefore do not respond to ELX-TEZ-IVA, but the other 7-8% are either known to respond to ELX-TEZ-IVA or may respond to ELX-TEZ-IVA if given the right to try it.

While all provinces and territories screen newborns for cystic fibrosis, as indicated above, some individuals with rare mutations continue to fall through the cracks. These people may face significant challenges in being diagnosed late with more advanced disease than those diagnosed at birth and given access to standard of care treatments early.

> *<Our child with CF> was diagnosed when <they were> 3 weeks old, kind of a fluke, which was really amazing. That was in 1997 when <they were> born.*
>
> *My parents lost a child when he was 11 months old in 1959 and my dad was a pharmacist and he went into medical school after that and they became aware of this disease that became <known as> cystic fibrosis. My dad had an article that he read and thought that that sounded like <the symptoms> they were dealing with.*
>
> *…he was very healthy and got a cold and went into the hospital. Both of my parents did not anticipate him passing away. In fact, they both weren't there when he did, which was very sad in my family. And so, they always suspected that he had cystic fibrosis.*

So, <our child> was diagnosed with CF when <they were> three. I had a lot of trouble nursing my older daughter, so when <our child with CF> was born, I just said I'm not gonna go through that again. They had lactation consultants at the hospital at that time and they helped me. They actually came to my home and nursing actually with <our child with CF> turned out completely different and went really well, but <our child with CF> wasn't responding and gaining weight. So basically, failure to thrive.

And so, at three weeks of age, that lactation consultant said to me: "I don't want to alarm you, but there's no reason why your baby should not be gaining weight. I think you should go back to your doctor".

And that's when my mom intervened and said, "you know what? I want this baby tested for cystic fibrosis". I thought my mom was out of her mind. She had that sense from the previous experience that she went through.

But we did go back to the doctor and that's how <our child received> a kind of fluky diagnosis at three weeks of age, which was a blessing. – Parent of a child with CF that lives with a rare mutation

Receiving "fluky" diagnoses was a theme among those in our focus groups:

And I think and I know the system is quite complicated for newborn screening and it's not perfect and all of that. But there is a piece there that if you are really saying that you're looking at a person and you're saying this is precision medicine or an individual person, you would <think to> look at the biological parents.

And so, once we got the sweat test, we had to repeat it a few times. It took I think four months to finally find the mutations. It took a long time, I was told. I thought I wasn't sure what the time usually takes, but they couldn't find them. But I think back now and I say, well, if they had said, well both parents of are of <our heritage's> descent, what's the most common mutation in <the country we came from>? Most likely one of them would have been <the mutation my child has> and it is.

And so race was just sort of erased from all of it. And I think that's the piece that really bothers me. I think, you know… it's that color blindness, right, which is systemic racism. And so that was a big part of the misdiagnosis, and it took me being able to speak up and advocate.
…I think about my parents who were new to the country, didn't know the system <and the> language barriers <they experienced>. If that had been me, could they have, would they have been able to advocate for me? – Parent of a child with CF who lives with a rare mutation

7. Anything Else?

In May of 2023 Health Canada consulted on its agile licensing agenda, which contained a number of regulatory and guideline changes. Neither the proposed regulations nor the guidance documents enable the use of precision medicine laboratory data to demonstrate efficacy in individual patients in regulatory decision making. This is vital to improving access to gene-based therapies, not only for Canadians with rare diseases, but also for important rare or ultra-rare sub-populations of more common diseases where clinical trial data is limited or non-existent.

The proposed agile regulations do not fully align with international regulators when it comes to assessing drugs for rare diseases. However, if adopted, agile licensing would allow for reviews of certain drugs that address unmet medical need to rely on the authorization of a trusted foreign regulator. This would mean that Canada could adopt the December 2020 decision of the US Food and Drug Agency – now over three years old – to add 176 rare mutations to ELX-TEZ-IVA's indication based exclusively on in vitro data.

Canada should also look to the UK's National Health Services (NHS) and France's L'Agence nationale de sécurité du médicament et des produits de santé (L'ANSM) to inform our decision-making. Both used laboratory evidence to expand access for people with rare mutations.

L'ANSM is the program the CF world is watching, a model that we believe Canada should follow. Their compassionate use program covers CF patients who do not have two mutations deemed to be unresponsive to ELX-TEZ-IVA. If patients have some clinical benefit, they may stay on treatment after the initial assessment period. Twenty-two of the 45 responders in the initial study have mutations not currently approved by the FDA, indicating that **significantly more CF patients may benefit from treatment than have access in Canada, or even the United States.**

Canada already has infrastructure in place to support such a program. A partnership of Cystic Fibrosis Canada and The Hospital for Sick Children, the Program for Individualized Cystic Fibrosis Therapy (CFIT) is well positioned to improve access for people with rare mutations right now. Established in 2015, CFIT is creating a bank of nasal epithelial cells and stem cells (iPSCs) from CF patients. With these cell samples available as models for researchers, new therapies can be tested and perfected to treat CF patients in the future. CFIT cultures patient nasal cells much like lung cells and can conduct functional studies with the components ELX, TEZ and IVA to demonstrate if a patient will respond. Proof of concept has been achieved in patients with Health Canada indicated mutations starting on CF modulators, and this assay is correlated with clinical response, identifying over 90% of individuals with a clinical response to CF modulator drugs. This data will be published soon.

CFIT uses similar protocols to those in use at the Personalized Cystic Fibrosis Therapy and Research Center (PCFC) at Cincinnati Children's Hospital, as well as efforts in France and Italy. The CFIT group meets with their international colleagues periodically to share information. Private drug plans in the US consider response data for patients with rare mutations and no FDA indication generated by the PCFC and some provide reimbursement to ELX-TEZ-IVA to these patients.

To date and to our knowledge, no Canadian public or private payer has expanded access using this type of patient specific data because there is no Health Canada indication and no CADTH recommendation. Federal and provincial access programs are not designed for this type of evidence and typically do not consider applications under these situations where the drug is approved only for other mutations. But a Health Canada indication and HTA recommendation from CADTH could change this. What our community needs is access for all individuals who lack two copies of mutations known not to respond to ELX-TEZ-IVA. This would save and change lives for all who can benefit and help generate real world evidence that could help more people, while avoiding treating those who we know won't benefit. If this is not possible, an indication and recommendation for anyone with a mutation where there is some form of evidence (clinical trials data, real world experience or in vitro data) would help create a pathway to access via our public access programs for those where strong potential to benefit can be demonstrated.

It is possible and it is already happening in other countries. The Israeli Ministry of Health used CFIT data and organoid data to grant off-label short-term access to ELX-TEZ-IVA for those with rare mutations. That Canadian *in vitro* data was used to inform decision- making by a foreign ministry is excellent. However, to date these data have not been used to expand access in Canada, which shows how absurd our current evidence practices are.

Moreover, Health Canada, CADTH and INESSS have joint guidance on how to report on real-world evidence. Page 57 of the guidance document shows that a consensus was achieved on March 1, 2023 on how to treat in vitro data, however we don't know what that guidance is, or where that guidance is: a year later, the guidance document has yet to be updated. That there is guidance on in vitro data that has been sitting somewhere for over a year and has not been published shows how slow Canada's drug regulatory review bodies are to step into the present. It also shows that Canadians with rare mutations may not be able to access a lifesaving and life-changing drug, simply due to inefficient bureaucratic processes and paperwork. This is unacceptable. Lives are at stake.

If Canadians with rare mutations that lead to cystic fibrosis lived in one of the other countries that provide access they would have access now. But they don't: they live in Canada and Canada's systems continue to let them down. CDEC has an opportunity to change this.

There are some additional mechanisms that can be used to get access for Canadians with rare mutations that lead to CF. In September 2023 CADTH implemented procedures for Time-Limited Reimbursement Recommendations. Page three of the documents notes that:

> *A time-limited recommendation is a recommendation to publicly fund a drug or drug regimen for a certain period of time based on the condition that the sponsor will conduct 1 or more clinical studies that address the uncertainty and that CADTH will conduct a reassessment of the additional evidence. CADTH's future reassessment will lead to a final reimbursement recommendation.*
>
> *… Developments with global regulatory authorities are leading to faster and more agile review processes (e.g., conditional terms and conditions associated with approvals based on early-phase clinical data).* ***These regulatory initiatives are an important consideration for CADTH and our expert committees as we seek to modernize our review processes to allow for greater confidence in CADTH recommendations where there is uncertainty in the clinical evidence.***

Time limited reviews are only available to drugs that have been or are undergoing review through Health Canada's advance consideration process – which ELX-TEZ-IVA for rare mutations is going through – under the Notice of Compliance with Conditions (NOC/c) or the approval is accompanied by terms and conditions. The policy also requires manufacturers to seek evidence plans. Cystic Fibrosis Canada does not know if these requirements are in place. What we do know is that ELX-TEZ-IVA is a drug that is changing the face of cystic fibrosis. It is altering the course of the disease and saving lives, but only to those who have access.

We urge CDEC to consider access to ELX-TEZ-IVA for Canadians with rare mutations that do or may respond to the drug under the above-mentioned frameworks. If CDEC did, there is good case to make for our public drug programs to use the pan-Canadian Pharmaceutical Alliance's Temporary Access Program (pTAP) – or the principles of it – to provide rapid access to Canadians with rare mutations, and perhaps develop a model similar to France's. When in doubt of whether a person might respond to ELX-TEZ-IVA, our payers can work with CFIT to use in vitro laboratory evidence to predict a response.

On March 22, 2023 – almost exactly a year from the day we are providing this submission - the Government of Canada launched the National Strategy for Drugs for Rare Diseases. CADTH plays a big role in this strategy, and the strategy should inform and guide CDEC's deliberations. Not only will CADTH lead the development of the Canadian Drug Agency (CDA), it will become the Canadian Drug Agency. One of CADTH's strategic pillars is to "unleash the value of technology across its lifespan" to "lead in the science and practice of evidence appraisal". At this important time of transition, CADTH must stay true to this principle. As its presence grows on the world stage, CADTH must catch up to what its peers are doing. When it comes to access to ELX-TEZ-IVA for Canadians with CF who have rare mutations, CADTH isn't leading. It isn't even following.

If Canadians with rare mutations that do or may respond to ELX-TEZ-IVA lived in a future version of Canada's drug review and reimbursement system, most would almost certainly would get access. But they live in this moment in time, which means they may not get access purely because Canada's decision-makers have fallen behind their international peers in both embracing emerging science and in creating systems that work for where we are now, not where we should have been years ago.

When 87% of the Canadian CF population now have futures they never thought they'd have, most Canadians with rare mutations do not. They are still waiting for Canada to catch up with what other countries are doing, to create a pathway to access. These people should not be denied access and destined for sickness, disability and pre-mature death because our decision-makers have dragged their heels. Canada's drug access decision-makers are so focused on developing – but not implementing - policies that could help people with rare mutations that they have forgotten that these people need help now.

CDEC has developed and is developing frameworks and policies to guide its decision-making, which we applaud. We call on CDEC to use these decision-making tools now to save lives. Regardless of the mutation one might have, cystic fibrosis can't wait.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

   No, Cystic Fibrosis Canada prepared this submission.

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

   We worked with Dalhousie University to conduct Phase I of our burden of disease study, which is a socio-economic study of the financial and time burden that cystic fibrosis has on individuals, caregivers, the health system and society.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca Canada Inc.	x			
Horizon Therapeutics				x
Pfizer Canada Inc.	x			
Trudell Medical International		x		
Vertex Pharmaceuticals	x			
Vertex Pharmaceuticals (Canada) - Head Office				x
Viatris			x	

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

Name: Dr. Paul Eckford
Position: Chief Scientific Officer
Patient Group: Cystic Fibrosis Canada **Date**: March 19, 2024

CADTH

Project Number: SR0837-000
Name of Drug: elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)
Indication: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data.
Name of Patient Group: Cystic Fibrosis Canada
Author of Submission: Dr. Paul Eckford, Chief Scientific Officer

1. About Your Patient Group

Since being founded by parents in 1960, Cystic Fibrosis Canada has grown into a leading organization with a central role engaging people living with cystic fibrosis, parents and caregivers, volunteers, researchers and healthcare professionals, government and donors. We have advanced research and care that has quadrupled life expectancy. We work together to change lives through treatment, research, information and support. Despite our progress we are not yet done.

Cystic Fibrosis Canada funds basic, discovery science and clinical research, and has helped establish core facilities across the country. We provide financial support to the forty multi-disciplinary cystic fibrosis clinics that see nearly all Canadians living with cystic fibrosis and maintain close relationships with the clinical and research communities. We have invested over $275M in research and clinical care support. Our close relationships with the research, clinical and patient communities give us an excellent understanding the disease and how it impacts Canadians with CF, as well as those who serve them. We are the most respected and trusted source for information on cystic fibrosis in Canada and provide an information and resource service to the community that includes publishing a comprehensive resource compendium for the community. In addition, we maintain close relationships with our sister organizations around the world, which allow for the rapid sharing of information and adoption of best practices. In 2018, we launched the Cystic Fibrosis Canada Accelerating Clinical Trials (CF CanACT) network that now includes 10 sites comprising 13 of the 40 cystic fibrosis clinics serving over 60% of Canadians with cystic fibrosis, and 100% through the network referral program. CF CanACT also works closely with our international partners to conduct protocol reviews, share Data Safety Monitoring Boards, and help speed clinical trial progress.

Cystic Fibrosis Canada manages the Canadian Cystic Fibrosis Registry (the Registry). The Registry contains the clinical information of nearly all Canadians with cystic fibrosis, living or deceased, with data going back to the 1970's. The Registry publishes an annual report that describes the current status of the cystic fibrosis population in Canada and national trends over time. The data in the Registry is also used by investigators in Canada and around the world to better understand the disease and the impact of therapeutic efforts as well as to propose improvements to care. When the registry was established 50 years ago, the median age of survival for Canadians with CF was in the mid-teens. Largely due to multi-disciplinary care and access to standard of care drugs, half of Canadians with CF live to be 60 years old, but this could change if clinical care and access to CF medicines diminishes.

We work closely with our patient community to advocate to improve their health and well-being. Cystic Fibrosis Canada's National Advocacy Network has over a hundred well-trained advocates and a basket of tools to help them in their efforts. We've been able to help the cystic fibrosis community by amplifying their voices through coordinated efforts that have addressed both national and regional priorities.

Cystic Fibrosis Canada's contributions have led to significant improvements in care and quality of life for people living with cystic fibrosis. As a result, Canada has one of the highest median ages of survival in the world.

Cystic Fibrosis Canada is pleased to provide patient group input to CADTH's consideration of ELX-TEZ-IVA (Trikafta™) for the treatment of cystic fibrosis (CF) in patients two years of age or older who have an F508del or a responsive CFTR mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. We appreciate the consideration CADTH gave to our submission on the 12+ population, as well as our clinicians and researchers' responses to the draft criteria. We are very pleased with the thoughtful approach the Common Drug Review (CDR) Committee took in reviewing the 6+ file, including accepting the outcomes of the Promise Study, which provided a compelling set of real-world evidence (RWE) that ultimately informed the CDR's 2022 recommendation to eliminate the 90% or less lung function initiation criterion it recommended in 2021 for 12+. CF clinicians and researchers share this sentiment. We also appreciate CADTH's positive reimbursement recommendation for 2-5 year olds with the most common mutation that causes CF, F508del. Access to CF modulators for t is anticipated to preserve lung function, giving young CF patients today a much different disease course with improved quality and length of life.

We are hopeful that CDEC's deliberations are equally as thoughtful for Canadians with CF who have rare mutations that may respond to Trikafta. Cystic Fibrosis Canada is calling on CDEC to recommend the broadest access possible for this life-changing therapy for these individuals. These individuals have been getting sicker while those who have access to Trikafta are getting better and, despite the growing amount of international evidence to support broad access, we are extremely concerned that Canada has not moved more quickly to adopt frameworks to enable access when so many other countries have.

2. Information Gathering

In completing this submission, Cystic Fibrosis Canada conducted focus groups with Canadians with rare mutations who are being treated with Trikafta, Canadians with rare mutations who do not have access to Trikafta, and caregivers of Canadians with rare mutations that cause cystic fibrosis. We also utilized findings from our 2021 patient and caregiver survey on access to Trikafta, which received over 1200 responses from our community. We made queries and referred to data sets from the Canadian Cystic Fibrosis Registry.

We also included findings from Phase I of *The Social and Economic Impact of Cystic Fibrosis in Canada: A Burden of Disease Study* (herein called "Burden of Disease Study") conducted by Dalhousie University and Cystic Fibrosis Canada, in partnership with the Conference Board of Canada and funded in part by Cystic Fibrosis Canada and the Canadian Institutes in Health Research (CIHR). Through this study we conducted a community survey months before Trikafta became widely available in Canada. Where permission was granted, survey findings were linked to individual registry records, which allows us to stratify data across disease severity, geographic location, age, sex, and other informative data points. The study measures the burden of CF at the individual, caregiver, health systems and societal levels. It is said to be one of the most comprehensive studies of the burden of CF in the world. A Phase II follow up study is underway and will provide data that demonstrate the socio-economic impact Trikafta has had on the Canadian CF population since the Phase I study.

We also provide insights from relevant medical and scientific publications and perspectives that speak to the health and health related challenges that Canadians who have rare mutations that lead to cystic fibrosis face.

3. Disease Experience

According to the Canadian Cystic Fibrosis Registry, now over 50 years old, life-changing treatments are increasingly reaching the 4,445 Canadians with cystic fibrosis (CF) and that Canadians born with CF today will live longer than those who came before them. But there's another, less-rosy side to the story: more than half of Canadians who died of CF in 2022 didn't reach their 40th birthday. Many are still very ill and one in seven living with the disease today is ineligible for the treatments making such a positive difference for others with CF.

For the first time, the estimated median age of survival has reached the milestone of 60 years of age. In other words, half of babies born with CF today are expected to live beyond their 60th birthday, compared to their 52nd birthday as reported in the 2017 edition of the report and 37th birthday in 2002.

The number of Canadians with CF who are taking CFTR modulator therapies has increased by 70%. This was approximately 2,500 people in 2022, compared to approximately 1,500 in 2021 when about 250 people with at least one copy of the most common mutation that leads to CF – F508del - were granted pre-market authorization access to ELX-TEZ-IVA through Health Canada's Special Access Program.

The drug received a positive reimbursement recommendation from CADTH in the summer of 2021 for use in those 12 years of age and older who had at least one copy of the most common mutation that leads to CF and had lung functions (ppFEV1) of 90% or less, after which all of Canada's public drug programs reimbursed the drug within two months of CADTH's recommendation. Three of these drug plans – Alberta, Saskatchewan and Manitoba – did not include the 90% or less lung function criteria, instead providing broad access to anyone with at least one copy of the F508del mutation who was 12 years of age or older. More Canadians gained access in 2022 when ELX-TEZ-IVA was approved for those who were six years of age or older and the 90% or less lung function requirement was lifted.

Steady growth in the median age of survival is an indicator of the advancements in CF care, our investments in research, new treatments and the efforts that patients put into maintaining their health. Yet while the data are pointing in the right

direction, cystic fibrosis is still a fatal disease, people still have a high treatment burden and there is still much work to be done.

There are continued challenges of living with CF from a healthcare and quality of life perspective, including those who are unable to benefit from recent life-changing treatments:

- In contrast to the survival milestone, the 40 Canadians who died of CF in 2022 had a median age of 38.
- Canadians with CF collectively had 17,000 clinic visits, spent 10,000 days in hospital, and spent nearly 6,000 days on intravenous antibiotics in 2022 alone. While these numbers represent decreases over previous years, they indicate a disease with a significant toll on daily life as well as Canada's healthcare system.
- One in five Canadian adults with CF has depression or anxiety recorded as a complication in the CF Registry, reflecting international work showing elevated rates of these mental health conditions in the CF community.

Data from the Canadian Cystic Fibrosis Registry on Canadians with CF who don't currently have a Health Canada indication for modulators show that:

- 246 have mutations known to respond to ELX-TEZ-IVA.
- 114 have mutations predicted to not respond to ELX-TEZ-IVA.
- 179 have mutations that have unknown responses to ELX-TEZ-IVA.

Table 1: ELX-TEZ-IVA (Trikafta) eligibility, known and predictive response status of Canadians with CF by mutation class and jurisdiction

Cohort	**Province of CF clinic care**				
	Canada	**BC**	**AB**	**SK**	**MB**
1. Eligible for ELX-TEZ-IVA	3851 (86.52%)	376 (87.65%)	484 (85.06%)	117 (89.31%)	102 (90.27%)

2. Eligible for ivacaftor	61 (1.37%)	10-15 (2-4%)	5 (0.88%)	<5 (<3%)	<5 (<4%)
3. Responsive to ELX-TEZ-IVA	246 (5.53%)	20 (4.66%)	47 (8.26%)	7 (5.34%)	5-10 (4-9%)
4. Not predicted to respond to ELX-TEZ-IVA	114 (2.56%)	<5 (<1%)	13 (2.28%)	0 (0.00%)	0 (0.00%)
5. Unknown response to ELX-TEZ-IVA	179 (4.02%)	19 (4.43%)	20 (3.51%)	5-10 (3-8%)	<5 (<4%)
Total number of individuals	**4451 (100%)**	**429 (10%)**	**569 (13%)**	**131 (3%)**	**113 (3%)**

Table 2: ELX-TEZ-IVA (Trikafta) eligibility, known and predictive response status of Canadians with CF by mutation class and jurisdiction

Cohort	**Province of CF clinic care**				
	ON	**QC**	**NS**	**NB**	**NL**
1. Eligible for ELX-TEZ-IVA	1321 (86.74%)	1111 (85.07%)	243 (90.33%)	37 (90.24%)	60 (85.71%)
2. Eligible for ivacaftor	29 (1.90%)	7 (0.54%)	5-10 (1-4%)	<5 (<10%)	0 (0.00%)
3. Responsive to ELX-TEZ-IVA	62 (4.07%)	91 (6.97%)	<5 (<2%)	<5 (<10%)	5 (7.14%)
4. Not predicted to respond to ELX-TEZ-IVA	41 (2.69%)	49 (3.75%)	8 (2.97%)	0 (0.00%)	<5 (<6%)
5. Unknown response to ELX-TEZ-IVA	70 (4.60%)	48 (3.68%)	10 (3.72%)	<5 (<10%)	<5 (<6%)
Total number of individuals	**1523 (34%)**	**1306 (29%)**	**269 (6%)**	**41 (1%)**	**70 (2%)**

The data presented above are similar to the cohorts requested by France's Dr. Pierre-Régis Burgel for a global rare mutations project. Dr. Brugel has done extensive research on how people with CF who have rare mutations respond to ELX-TEZ-IVA. He started France's compassionate use program for the drug, which gives anyone with a rare mutation that may respond to ELX-TEZ-IVA the right to try it, provided they don't have two mutations known to not respond. The program is further described in Section 8 of this submission. In a 2023 study Dr. Brugel, et al, found that:

> *Although focused on CFTR expression and processing (and not channel function),* ***our study confirms the relevance of assessing the response of rare mutations to modulators (in a personalized medicine approach)*** *and suggests the existence of a location-dependent pattern of response to modulators that may contribute to further clarifying the mechanism of action of the correctors.* ***Understanding the molecular and functional consequences of rare CF mutations is fundamental for the adoption of precision therapeutic approaches for such CF patients.***

We agree that we must assess the response for rare mutations to modulators to facilitate access to precision medicines, and that needs to happen now. For many people living with CF, CFTR modulator therapies offer a significant advantage in managing their disease, but Canadians with rare mutations have no existing pathway to long-term access at present. These people are getting sicker while those who have access are getting better. These people

face layers of inequities – being born with a rare mutation, not being diagnosed early because their rare mutations are not always on newborn screening panels, insufficient numbers for clinical trials for many, Canada's lack of regulatory and policy frameworks to evaluate predictive in vitro laboratory evidence, and reimbursement systems that do not or will not cover the therapy for anyone outside of the narrow Health Canada indication.

A member of our community focus group of individuals living with rare CF mutations described to us the all too familiar story of access denied by the current system:

> *Last year I had a pneumonectomy…they removed one of my lungs because of necrosis to try to buy me time before putting me on the lung transplant list, but my lung function continued to drop. When I got to under 30% lung function my doctor started trying to get me Trikafta…it showed that it worked in other people with one of my mutations.*
>
> *The process was a nightmare. My doctor wrote to Health Canada to see if I could get it through the <Special Access Program>, but that program is only for drugs that do not have Health Canada approval. Trikafta does, just not for me.*
> *After that my doctor tried to get it through <the provincial drug plan>. I was denied on the first application and the appeal, even though my health was tanking. – Person with CF who lives with a rare mutation*

Moreover, many people who carry rare mutations come from diverse and often racialized backgrounds. These people are already disadvantaged by health care systems that were not designed with them in mind. In some instances, people have been told that it is unlikely that they or their children have cystic fibrosis because of their ethnic background, even when there are incidences of the disease in these populations.

Using data from the European Cystic Fibrosis Registry, an article published in the Journal of Cystic Fibrosis in 2023 (Zahav et al) shows the results of a study on disease severity in people with cystic fibrosis who have residual function (RF) mutations (mutations where there is at least some, though not normal levels, of CFTR function and may result in what is considered more 'mild' CF disease). Minimal function (MF) mutations have no, or nearly no CFTR function and are often considered to have the most severe CF disease.

> *Of the 44,594 eligible patients (median age 19.5 years, IQR 10–29.8), 6,636 (14.6%) carried RF mutations, and 37,958 (85.1%) MF mutations. Patients carrying RF mutations were older, diagnosed at a later age, had lower sweat chloride at diagnosis and better FEV1pp at each age group.*
>
> ***However, their FEV1pp declined with age and rates of chronic Pseudomonas aeruginosa increased with age. A significant number of patients with RF had FEV1pp similar to patients with MF at each age group. 4.5% of RF patients were treated with oxygen and 2.61% had a lung transplant. With increasing age, 26.6% of RF patients were treated with pancreatic enzymes associated with a more severe lung disease. RF patients had shortened life spans, with mortality starting around the age of 20 years.***
>
> ***Conclusions: Patients carrying RF mutations experience a decline of pulmonary function with age, leading to life- shortening. Standard of care therapies and augmenting CFTR function may improve their survival and quality of life.***

Table 3 compares data from the 2020 and 2022 Canadian Cystic Fibrosis Registry reports. It illustrates the impact ELX-TEZ-IVA has had on the Canadian cystic fibrosis population since ELX-TEZ-IVA was first introduced in Canada. It includes data on when ELX-TEZ-IVA was first introduced for those 12 years of age and older in the summer of 2021. The 2022 report does not, for the most part, include data on 6+, introduced in the fall of 2022, nor does it contain data for 2-5 year olds, for which access started in early 2024.

Table 3: Comparison of key health outcomes of Canadians 12 years of age and older since the introduction of ELX-TEZ-IVA.

	2020	2022	Difference	Percentage change
Number of Canadians with cystic fibrosis	4332	4445	Increase of 113	3%
Number of clinic visits	18,000+	16,750	Decrease of 1250+ days	-7%
Number of hospital days	17,100+	10,478	Decrease of 6662+ days	-39%
Number of home IV days	13,600+	5964	Decrease of 7636+ days	-56%
Number of organ transplants	21	7	Decrease of 14 transplants	-67%

While these are tremendous outcomes, there is still work to be done to improve access to ELX-TEZ-IVA and to have it funded for everyone who can benefit, especially for those with rare mutations. The Canadian Drug Expert Committee (CDEC) has the opportunity to help these people get access to a therapy that may very well save and change their lives. Do not let Canada's lagging regulatory and policy initiatives delay access for these people. Do not let Canada's implementation inertia steal their lives away.

4. Experiences With Currently Available Treatments

There are hundreds of therapies that aid in symptom management in the categories of: antibiotics, supplemental vitamins, aerosol bronchodilators, mucolytics and pancreatic enzymes, anti-inflammatories, and steroids. Most cystic fibrosis patients take pancreatic enzymes, multi-vitamins and nutritional supplements to maintain normal growth.

> *So many of my meds are not covered, so I pay out of pocket. Things like vitamins, which are $80 a month, enzymes and nebulized meds like hypertonic saline are not covered. They cost me hundreds of dollars a month.*
>
> *I know the drug <Trikafta> costs a lot, but when I see the outcomes that people are having and hear about people coming off of other meds I can't help but wish that was me. – Person with CF who lives with a rare mutation.*

Cystic fibrosis patients work tirelessly every day to improve the clearance of secretions from their lungs. This is done by performing airway clearance techniques at least twice a day for about 30-60 minutes per session. Inhaled medications are used to open the airways while inhaled antibiotic treatments are used to control infections. The total time spent on maintaining lung health is well over two hours each day for most CF patients.

> *My routine is very rigorous. I think one of the reasons I stayed healthy so long is that I exercise for hours a day, on the treadmill, my rowing machine, whatever. But when I got a bad infection that all changed. I started*

going downhill quickly, and my doctor was trying to find things that could help. He told me about this medicine – Trikafta – that was working miracles. But I couldn't get it. I didn't have the right <mutation>. Eventually I was able to get into the clinical trial. After the initial purge I started to feel instantly better, and it has only gotten better from there. Now I can exercise at a much more intense level, which is going to help me in the long-term. – Person with CF with a rare mutation

Patients not on ELX-TEZ-IVA frequently have periods of infection and acute inflammation called exacerbations that require a hospital stay of at least two weeks and that frequently last up to four weeks. Exacerbations often result in a drop in lung function that is not fully recovered once the exacerbation resolves, resulting in poorer long-term health and greater disability each time. The steroids that are used to reduce the inflammation and help patients recover from the exacerbation ultimately damage organs in the long run and may be a contributing factor to the development of cystic fibrosis related diabetes (CFRD), which occurs in approximately 33% of all Canadian cystic fibrosis adults.

Many of the other drugs that patients need to take on a regular basis also have negative side-effects. Antibiotics can cause kidney damage and total lifetime dose must be controlled; others permanently stain the teeth. Chronic use of antibiotics leads to resistance and as patients age, a need to try multiple antibiotics to find one that works. Because patients are on so many drugs, drug to drug interactions become difficult to manage and can interfere with optimum therapy.

I have had problems with about five therapies. An inhaled steroid shut down my adrenal glands and I could not move throughout the day. I am an adult who is less than 5 feet tall because my growth and weight were suppressed due to meds,

I had extremely rare side effects to four antibiotics and couldn't walk anymore. I was red and had swollen bumps all over, flu-like symptoms and couldn't even go to the bathroom. After three days of this I had to go to hospital, which is when I found out I had Stevens-Johnson syndrome <SJS>, which is rare, caused by a reaction to a medication, and affected my skin and mouth. I was in so much pain. Usually, people with SJS need to be put in a coma so they can get through the pain.

Walking came back easily with steroids, but the rest of the symptoms took three months to clear. I had burns on my hands, blisters, and peeling, all due to an antibiotic.

Due to adverse reactions, I can't take these antibiotics, so I now have limited choice to help with lung infections. That is very scary. – Person with CF who has a rare mutation.

For many, cystic fibrosis brings physiological changes and challenges. This includes Distal Intestinal Obstruction Syndrome (DIOS), blockage of the liver and pancreas ducts, inability to conceive children, early onset osteoporosis, nasal polyps and sinusitis.

When I went to the adult clinic like you kind of, you know, you hit the point where you're not as resilient as a kid. And <my> lung function started going down a little bit at a time.

But in the past like 3 years it's felt more…more severe like my lung function is kind of, it's progressing, it's progressing and it's progressing. I've had a few more hospital visits than I'm used to. And that's been hard because a lot of the time every time I go to the hospital, I've had a lot of nasal issues.

I had to get surgery to get all my <sinus> polyps removed. It <had been> really bad for about four years <the doctor> said. I had like 15% function in my nose, so I couldn't smell anything for a long time. And then I got the polyps removed. And since the surgery, my nose has been even more of a problem. And so, every time I go see the ENT, he goes, what are you, are you on Trikafta?

And every time I would be like, no, I can't have it.

But that's become a question now whenever a health issue arises…often doctors who aren't familiar with me will go well, are you on Trikafta?

It's like, no, I can't have that. – Person with CF who has a rare mutation

As we face a new day in CF with a new treatment that can make a difference for some people, there is a significant population – one in every seven people with CF – whose genetic mutations mean they cannot access these treatments, and more whose CF has progressed past the point of full benefit. These people cannot be left behind.

5. Improved Outcomes

ELX-TEZ-IVA is now indicated for approximately 87% of Canadians with cystic fibrosis, those who carry at least one copy of the most common mutation, F508del. It is the single biggest advancement in treating cystic fibrosis in the history of the disease and has been proven to significantly improve health outcomes. The remarkable impact the drug has had on what has been an inevitably fatal disease has led to intense media interest, interests from other patient communities, and the interest of funders. Due to its tremendous efficacy, it made its way from first Health Canada application to being funded for those 12+ with at least one copy of the most common mutation by all of Canada's public drug programs in just 11 months, forever changing the lives of those who can access it, as well as those who cannot. The former will overwhelmingly live longer. The latter overwhelmingly won't.

In our focus groups. Canadians with CF who have rare mutations and their caregivers shared their thoughts on how ELX-TEZ-IVA might change their or their loved one's lives:

We want <our child to have a long and adventurous life>. We would give anything to remove barriers to getting <our child> access. As a twin, <their> trajectory is together. We want to see them sitting on porch when <they> are old. – Parent of a child with CF who has a rare mutation

Just because <my child> is healthy today does not mean <they> will be healthy in the future. We have no guarantee. This is a progressive disease. The future is so unknown. I want <my child> to have a future. – Parent of a child with CF who has a rare mutation

While we are starting to see the significant benefit of ELX-TEZ-IVA for those with the most common mutation in Canada, in other jurisdictions, we are starting to also see significant benefit for many who have rare mutations. This provides both hope and despair for Canadians with rare mutations.

I feel like I am constantly trying to grab on to hope but it is slipping through our fingers and knowing where this disease is going…it could help me, and right now there just is nothing available. I can't even imagine what it would be like to have this drug handed to me. – Person with CF who has rare mutation

For all of my life I have taken very good care of self. My parents always said that one day there would be a treatment for me, to have hope. The symptoms hit me hard in my twenties. I am still focused getting a magical therapy…Trikafta is that therapy, at least for now. I advocated for access only to find out that I can't get it. I thought it would help me and still think it might. I have worked my life like I didn't have CF, but I do and I can't get a drug that will keep me going in my career, in my relationship and with life. I need it because I have worked hard. I want those extra years. Like others with CF who have the drug, I deserve those extra years. – Person with CF who lives with a rare mutation.

Canadians with rare mutations and their loved ones are acutely aware of the inequalities that our healthcare and drug access systems have placed on them, and that these inequalities lead to poorer health outcomes. This is particularly painful when it comes to access to ELX-TEZ-IVA. It is devastating to watch others get better due to this drug while there

is no pathway to access for those with rare mutations. Many reported feeling scared for their futures and their families. They want a chance at life and right now they don't have it.

> *Healthcare workers assume <my child> is on it and <my child> is not. This is a painful reminder of being left out. <My child> made friends with CF and they were passing away, and now with Trikafta, they will likely out live <my child>. We know it works in <people who have the same rare mutation> as <my child>, but <my child> can't get it. Should I allow <my child> to perish because Canada won't make the exception that other countries have? – Parent of a child with CF who lives with a rare mutation*

> *I have built a good life and have always put in a lot to manage my disease, like hours a day every day for over thirty years. I work full-time, pay taxes, and have found love. But my health is not good right now. It is declining, and I am afraid that if I don't get Trikafta soon I will need to go on the lung transplant list. What will happen to everything I have built? What will happen to my job? What will happen to my <partner>?*

6. Experience With Drug Under Review

Very few Canadians with rare mutations that lead to cystic fibrosis have access to ELX-TEZ-IVA. Most who have access participated in clinical trials. While clinical trials for ELX-TEZ-IVA in individuals with 18 rare CF mutations had Canadian patient participation and we know that overall, based on a manufacturer press release, the study met its primary endpoint and showed that ELX-TEZ-IVA resulted in rapid, statistically significant, and clinically meaningful improvements in lung function compared to placebo (9.2 percentage point increase in ppFEV1), we do not yet know how many Canadians participated, or if all mutations showed the same response in the study. We look forward to the release of the full study details. What we do know is that the individuals in these trials who also participated in our focus groups significantly benefitted from access to this drug and continue to benefit for now. In recommending and providing broad access to Trikafta, CDEC and Canada's public drug programs can help ensure that these people can benefit from this transformational therapy long-term.

Several people in the focus groups had mutations on the FDA's approved list of mutations, meaning that if they lived in the US, they would have secured long-term access years ago. As a result of broad access in other countries, there is published RWE in the literature of ELX-TEZ-IVA response in patients with many of these same mutations. CDEC must consider all this evidence in its deliberations. To deny access based on limited Canadian data would be wrong, especially for those with ultra-rare mutations for which there may be only a handful of people world-wide.

Some who are on ELX-TEZ-IVA have self-funded the drug either out of pocket or through donations. None of these approaches will provide mid-or-long-term access. Unless public and private drug programs agree to fund ELX-TEZ-IVA broadly for those with rare mutations, these people will soon lose access to therapy, which means not only will they lose all of the benefits and quality of life improvements they have experienced, loss of therapy can also cause a springboard effect through which they may become even sicker than they were before trying ELX-TEZ-IVA. These people are in very tenuous situations. In our focus groups we spoke to Canadians with rare mutations that are currently being treated with ELX-TEZ-IVA, as well as those who are not. The experiences of those who are on therapy are detailed below:

> *Life has been hard for me, and it was getting harder. It's not just Trikafta, there were two to three modulators before it. I was constantly told that I don't qualify. Hearing everyone else's successes…it has been hard to keep going. – Person with CF who lives with a rare mutation*

> *Through my clinic, in March 2022 I qualified for one of <the manufacturer's> clinical trials…it started out well. Prior to me initiating the treatment I know that my sweat chloride test was 105 or 109, in that range, and when I came back to next clinic after what I think was 2 to 4 weeks and we did the sweat chloride tests it was down to 18 in one arm and 14 in the other.*

My cough, I went through the purge period for about three to four days, and coughed my lungs out, that, it cleared up and I have never really had an issue since. - Person with CF who lives with a rare mutation.

I got Trikafta through <individual donations> and am <rationing> it because I can't afford it myself. So, I only take one pill a day. Still, I have had great results. I know that it is working for me because I can do things I couldn't do before, but I can't guarantee my supply. I can't pay for it long-term. I don't know if I can keep going with this but I do know that it is working for me. – Person with CF who has a rare mutation

Like most others who are on ELX-TEZ-IVA, all in our focus groups who have rare mutations and are taking ELX-TEZ-IVA responded exceptionally well to therapy, even those who have mutations for which evidence is scarce.

Even though there isn't <much evidence> on my mutation, Trikafta improved my lung function by 10% within a month and is keeping it steady. It dropped my sweat <chloride> down and helps me be less breathless. I can walk and talk at the same time now. I wasn't able to do that before… now that I am more stable and my PFTs are up, I am off the transplant list and the transplant doc does not want to book an appointment for a year. – Person with CF who lives with a rare mutation

I am pregnant! It happened unexpectedly within a month and a half of me <taking> Trikafta. It was always my dream to be a mom, but I wasn't well enough and it is hard for women with CF to get pregnant. I also never thought I'd have a future, so I didn't want to do that to <a child>.

To having a baby and making plans…these are not things I ever thought I would be able to do…but now it's not "I have this appointment or that appointment"…I can focus on something other than just my medical appointments.

I am having a baby. Now I have to think of the future. – Person with CF who lives with a rare mutation

Canadians with CF who live with rare mutations deserve the right to try ELX-TEZ-IVA, including those where evidence is lacking. Indeed, there should be avenues to try ELX-TEZ-IVA for those who don't have mutations known to not respond. This could be through an access program that generates RWE, or through laboratory testing on patient cells. It should not be incumbent upon the family of a sick patient to fundraise for access.

My family had no choice but to fundraise for Trikafta. Through generous donations I was able to get it. My lung function went up by 10% in the first month, I have gained weight and have energy and have hope for the future…<planning> for the future, something I have never had done because who knows when you're going get sick next, to go to hospital next…you don't know if you will have a future.

But I had to fight for this drug, I could have died trying to get it and I don't know what will happen when

it runs out. It's like every step of the way they told me that there was no evidence to support me

getting the drug.

Let me be your evidence. – Person with CF who lives with a rare mutation

Even with evidence in hand, Canadians with rare mutations that may respond to ELX-TEZ-IVA have been denied access. Despite overwhelming findings on the positive clinical impact that ELX-TEZ-IVA has on some of these individuals, our systems are not built for them. In fact, they are built against them.

Public and private drug plans won't generally consider these people for coverage because their mutation does not have a Health Canada indication, nor a Health Technology Assessment. Some of these people have ultra-rare mutations for which "gold standard evidence" of clinical trials cannot ever be generated unless Health Canada was to embrace N=1 studies. And still some fall outside of the lines, or their time will run out before N=1 studies can help them.

When we think of the best-case scenario, we know that public and private drug programs have the ability to cover Trikafta off-label for those with rare mutations, but they choose not to because of the risk of carrying a person who may or may not respond to therapy. But what is the risk of not covering these people? It is ultimately dangerous and will likely involve lung transplantation, if they are lucky. While risky, the ultimate choice is lung transplantation or certain death.

That Canada's public drug programs would choose death over potential of life speaks to the lack of compassion in our system of access. There are so many opportunities to help these people access this life-changing medication, but our review bodies and access systems – including CADTH – were built to review drugs for the masses and innovations of the past, not precision medicines like ELX-TEZ-IVA. We know the system is recognizing the need for change and is starting to act to implement innovative frameworks to fairly consider these types of evidence for these types of people who fall outside of the lines, but we need action now because people with rare CF mutations who could benefit from ELX-TEZ-IVA are getting sicker every day. They are pleading to us for help, and many may die waiting for the system to bring them the therapy they deserve, the therapy that so many others are benefiting from. Our public drug plans could and should provide broad access. They can make a difference here and now. These lives hang in the decisions you make, as well as the decisions that you don't make.

Companion Diagnostic Test

Since the discovery of the gene responsible for cystic fibrosis in Toronto in 1989 and the development of new technologies, it has become possible to detect the mutations in the gene through laboratory tests, using blood samples or cheek swabs. Samples are sent to specialized molecular diagnostic laboratories for analysis. Over 2,100 mutations in the gene responsible for cystic fibrosis have been described in the CFTR Mutation Database. The CFTR2 database lists mutations of known clinical consequence from the major CF registries around the world. CFTR2 includes over 800 variants to date, nearly all of which are disease-causing. About 130 of these mutations occur in the database less than 6 times. Many more ultrarare mutations exist that are not yet even described in CFTR2.

Medical diagnostic laboratories typically conduct newborn screening for the most common mutations in Canada. Such tests detect the mutations in the majority of the Canadian cystic fibrosis population. If medically indicated, complete exome sequencing will usually identify cystic fibrosis mutations missed by screening panels, though for a small number of individuals two disease-causing mutations aren't found. The falling costs of such tests make it more feasible than in the past to sequence CFTR mutations. Both the coverage and the availability of genetic testing vary across Canada, and there remain small numbers of individuals in the Registry who lack data on two disease-causing mutations for a variety of reasons. But these individuals can't fall through the cracks. Existing mechanisms must be fully utilized to understand if they will benefit from ELX-TEZ-IVA. If they will benefit, they must have a pathway to access. That is the duty and care our public drug programs have for these people. It is time that our public drug programs acknowledged this.

ELX-TEZ-IVA is the first CFTR modulator therapy available to treat patients with at least one copy of the most common cystic fibrosis mutation, F508del, and it is increasingly showing benefit in patients with a multitude of rare and ultra-rare mutations. The vast majority of individuals for whom ELX-TEZ-IVA is currently indicated, are known by their clinic or can be queried by their clinic using the Canadian Cystic Fibrosis Registry, even if the patients themselves aren't necessarily aware of their genotype. In addition to the complete CFTR genotype for most patients, the registry also houses rich clinical information on nearly every Canadian with cystic fibrosis including demographic information, clinical measurements, hospitalizations, treatments, and medications (including dates of initiation and cessation, where appropriate, for CFTR modulators).

There were 80 new diagnoses of cystic fibrosis in 2022 that were recorded in the CF Registry. Of these, 55 (68.8%) were made through provincial newborn screening (NBS) programs. In total, 4,354 (98.0%) of individuals with cystic fibrosis reported on in 2022, had a recorded diagnosis date, and of those, 2,659 (61.1%) were diagnosed before the age of one year, and 3,196 (73.4%) were

diagnosed by the age of two years. Adult diagnoses, those diagnosed at 18 years and older, accounted for only 355 (8.2%) of all individuals reported on in 2022, and likely would primarily be individuals with milder CF disease born before newborn screening was accessible in all jurisdictions in Canada or those who immigrated to Canada.

Nearly all individuals with cystic fibrosis reported on in 2022 (4,404 out of 4,445; 99.1%) had at least one CFTR gene mutation recorded. 2,021 (45.5%) have two copies of the F508del mutation (referred to as homozygous F508del) and 1,842 (41.4%) carry a single copy of the F508del mutation (referred to as heterozygous F508del). In total, almost 87% carry at least one copy of the F508del mutation. Among the remaining 13%, approximately 4-5% of these people have mutations that do not produce protein and therefore do not respond to ELX-TEZ-IVA, but the other 7-8% are either known to respond to ELX-TEZ-IVA or may respond to ELX-TEZ-IVA if given the right to try it.

While all provinces and territories screen newborns for cystic fibrosis, as indicated above, some individuals with rare mutations continue to fall through the cracks. These people may face significant challenges in being diagnosed late with more advanced disease than those diagnosed at birth and given access to standard of care treatments early.

> *<Our child with CF> was diagnosed when <they were> 3 weeks old, kind of a fluke, which was really amazing. That was in 1997 when <they were> born.*
>
> *My parents lost a child when he was 11 months old in 1959 and my dad was a pharmacist and he went into medical school after that and they became aware of this disease that became <known as> cystic fibrosis. My dad had an article that he read and thought that that sounded like <the symptoms> they were dealing with.*
>
> *…he was very healthy and got a cold and went into the hospital. Both of my parents did not anticipate him passing away. In fact, they both weren't there when he did, which was very sad in my family. And so, they always suspected that he had cystic fibrosis.*
>
> *So, <our child> was diagnosed with CF when <they were> three. I had a lot of trouble nursing my older daughter, so when*
> *<our child with CF> was born, I just said I'm not gonna go through that again. They had lactation consultants at the hospital at that time and they helped me. They actually came to my home and nursing actually with <our child with CF> turned out completely different and went really well, but <our child with CF> wasn't responding and gaining weight. So basically, failure to thrive.*
>
> *And so, at three weeks of age, that lactation consultant said to me: "I don't want to alarm you, but there's no reason why your baby should not be gaining weight. I think you should go back to your doctor".*
>
> *And that's when my mom intervened and said, "you know what? I want this baby tested for cystic fibrosis". I thought my mom was out of her mind. She had that sense from the previous experience that she went through.*
>
> *But we did go back to the doctor and that's how <our child received> a kind of fluky diagnosis at three weeks of age, which was a blessing. – Parent of a child with CF that lives with a rare mutation*

Receiving "fluky" diagnoses was a theme among those in our focus groups:

> *And I think and I know the system is quite complicated for newborn screening and it's not perfect and all of that. But there is a piece there that if you are really saying that you're looking at a person and you're saying this is precision medicine or an individual person, you would <think to> look at the biological parents.*
>
> *And so, once we got the sweat test, we had to repeat it a few times. It took I think four months to finally find the mutations. It took a long time, I was told. I thought I wasn't sure what the time usually takes, but they couldn't find them. But I think back now and I say, well, if they had said, well both parents of are of <our heritage's> descent, what's the most common mutation in <the country we came from>? Most likely one of them would have been <the mutation my child has> and it is.*

And so race was just sort of erased from all of it. And I think that's the piece that really bothers me. I think, you know… it's that color blindness, right, which is systemic racism. And so that was a big part of the misdiagnosis, and it took me being able to speak up and advocate.

…I think about my parents who were new to the country, didn't know the system <and the> language barriers <they experienced>. If that had been me, could they have, would they have been able to advocate for me? – Parent of a child with CF who lives with a rare mutation

8. Anything Else?

In May of 2023 Health Canada consulted on its agile licensing agenda, which contained a number of regulatory and guideline changes. Neither the proposed regulations nor the guidance documents enable the use of precision medicine laboratory data to demonstrate efficacy in individual patients in regulatory decision making. This is vital to improving access to gene-based therapies, not only for Canadians with rare diseases, but also for important rare or ultra-rare sub-populations of more common diseases where clinical trial data is limited or non-existent.

The proposed agile regulations do not fully align with international regulators when it comes to assessing drugs for rare diseases. However, if adopted, agile licensing would allow for reviews of certain drugs that address unmet medical need to rely on the authorization of a trusted foreign regulator. This would mean that Canada could adopt the December 2020 decision of the US Food and Drug Agency – now over three years old – to add 176 rare mutations to ELX-TEZ-IVA's indication based exclusively on in vitro data.

Canada should also look to the UK's National Health Services (NHS) and France's L'Agence nationale de sécurité du médicament et des produits de santé (L'ANSM) to inform our decision-making. Both used laboratory evidence to expand access for people with rare mutations.

> L'ANSM is the program the CF world is watching, a model that we believe Canada should follow. Their compassionate use program covers CF patients who do not have two mutations deemed to be unresponsive to ELX-TEZ-IVA. If patients have some clinical benefit, they may stay on treatment after the initial assessment period. Twenty-two of the 45 responders in the initial study have mutations not currently approved by the FDA, indicating that **significantly more CF patients may benefit from treatment than have access in Canada, or even the United States.**

Canada already has infrastructure in place to support such a program. A partnership of Cystic Fibrosis Canada and The Hospital for Sick Children, the Program for Individualized Cystic Fibrosis Therapy (CFIT) is well positioned to improve access for people with rare mutations right now. Established in 2015, CFIT is creating a bank of nasal epithelial cells and stem cells (iPSCs) from CF patients. With these cell samples available as models for researchers, new therapies can be tested and perfected to treat CF patients in the future. CFIT cultures patient nasal cells much like lung cells and can conduct functional studies with the components ELX, TEZ and IVA to demonstrate if a patient will respond. Proof of concept has been achieved in patients with Health Canada indicated mutations starting on CF modulators, and this assay is correlated with clinical response, identifying over 90% of individuals with a clinical response to CF modulator drugs. This data will be published soon.

CFIT uses similar protocols to those in use at the Personalized Cystic Fibrosis Therapy and Research Center (PCFC) at Cincinnati Children's Hospital, as well as efforts in France and Italy. The CFIT group meets with their international colleagues periodically to share information. Private drug plans in the US consider response data for patients with rare mutations and no FDA indication generated by the PCFC and some provide reimbursement to ELX-TEZ-IVA to these patients.

To date and to our knowledge, no Canadian public or private payer has expanded access using this type of patient specific data because there is no Health Canada indication and no CADTH recommendation. Federal and provincial access programs are not designed for this type of evidence and typically do not consider applications under these

situations where the drug is approved only for other mutations. But a Health Canada indication and HTA recommendation from CADTH could change this. What our community needs is access for all individuals who lack two copies of mutations known not to respond to ELX-TEZ-IVA. This would save and change lives for all who can benefit and help generate real world evidence that could help more people, while avoiding treating those who we know won't benefit. If this is not possible, an indication and recommendation for anyone with a mutation where there is some form of evidence (clinical trials data, real world experience or in vitro data) would help create a pathway to access via our public access programs for those where strong potential to benefit can be demonstrated.

It is possible and it is already happening in other countries. The Israeli Ministry of Health used CFIT data and organoid data to grant off-label short-term access to ELX-TEZ-IVA for those with rare mutations. That Canadian *in vitro* data was used to inform decision- making by a foreign ministry is excellent. However, to date these data have not been used to expand access in Canada, which shows how absurd our current evidence practices are.

Moreover, Health Canada, CADTH and INESSS have joint guidance on how to report on real-world evidence. Page 57 of the guidance document shows that a consensus was achieved on March 1, 2023 on how to treat in vitro data, however we don't know what that guidance is, or where that guidance is: a year later, the guidance document has yet to be updated. That there is guidance on in vitro data that has been sitting somewhere for over a year and has not been published shows how slow Canada's drug regulatory review bodies are to step into the present. It also shows that Canadians with rare mutations may not be able to access a lifesaving and life-changing drug, simply due to inefficient bureaucratic processes and paperwork. This is unacceptable. Lives are at stake.

If Canadians with rare mutations that lead to cystic fibrosis lived in one of the other countries that provide access they would have access now. But they don't: they live in Canada and Canada's systems continue to let them down. CDEC has an opportunity to change this.

There are some additional mechanisms that can be used to get access for Canadians with rare mutations that lead to CF. In September 2023 CADTH implemented procedures for Time-Limited Reimbursement Recommendations. Page three of the documents notes that:

> *A time-limited recommendation is a recommendation to publicly fund a drug or drug regimen for a certain period of time based on the condition that the sponsor will conduct 1 or more clinical studies that address the uncertainty and that CADTH will conduct a reassessment of the additional evidence. CADTH's future reassessment will lead to a final reimbursement recommendation.*
>
> *… Developments with global regulatory authorities are leading to faster and more agile review processes (e.g., conditional terms and conditions associated with approvals based on early-phase clinical data).* ***These regulatory initiatives are an important consideration for CADTH and our expert committees aes we seek to modernize our review processes to allow for greater confidence in CADTH recommendations where there is uncertainty in the clinical evidence.***

Time limited reviews are only available to drugs that have been or are undergoing review through Health Canada's advance consideration process – which ELX-TEZ-IVA for rare mutations is going through – under the Notice of Compliance with Conditions (NOC/c) or the approval is accompanied by terms and conditions. The policy also requires manufacturers to seek evidence plans. Cystic Fibrosis Canada does not know if these requirements are in place. What we do know is that ELX-TEZ-IVA is a drug that is changing the face of cystic fibrosis. It is altering the course of the disease and saving lives, but only to those who have access.

We urge CDEC to consider access to ELX-TEZ-IVA for Canadians with rare mutations that do or may respond to the drug under the above-mentioned frameworks. If CDEC did, there is good case to make for our public drug programs to use the pan-Canadian Pharmaceutical Alliance's Temporary Access Program (pTAP) – or the principles of it – to provide rapid access to Canadians with rare mutations, and perhaps develop a model similar to France's. When in doubt of

whether a person might respond to ELX-TEZ-IVA, our payers can work with CFIT to use in vitro laboratory evidence to predict a response.

On March 22, 2023 – almost exactly a year from the day we are providing this submission - the Government of Canada launched the National Strategy for Drugs for Rare Diseases. CADTH plays a big role in this strategy, and the strategy should inform and guide CDEC's deliberations. Not only will CADTH lead the development of the Canadian Drug Agency (CDA), it will become the Canadian Drug Agency. One of CADTH's strategic pillars is to "unleash the value of technology across its lifespan" to "lead in the science and practice of evidence appraisal". At this important time of transition, CADTH must stay true to this principle. As its presence grows on the world stage, CADTH must catch up to what its peers are doing. When it comes to access to ELX-TEZ-IVA for Canadians with CF who have rare mutations, CADTH isn't leading. It isn't even following.

If Canadians with rare mutations that do or may respond to ELX-TEZ-IVA lived in a future version of Canada's drug review and reimbursement system, most would almost certainly would get access. But they live in this moment in time, which means they may not get access purely because Canada's decision-makers have fallen behind their international peers in both embracing emerging science and in creating systems that work for where we are now, not where we should have been years ago.

When 87% of the Canadian CF population now have futures they never thought they'd have, most Canadians with rare mutations do not. They are still waiting for Canada to catch up with what other countries are doing, to create a pathway to access. These people should not be denied access and destined for sickness, disability and pre-mature death because our decision-makers have dragged their heels. Canada's drug access decision-makers are so focused on developing – but not implementing - policies that could help people with rare mutations that they have forgotten that these people need help now.

CDEC has developed and is developing frameworks and policies to guide its decision-making, which we applaud. We call on CDEC to use these decision-making tools now to save lives. Regardless of the mutation one might have, cystic fibrosis can't wait.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

   No, Cystic Fibrosis Canada prepared this submission.

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

   We worked with Dalhousie University to conduct Phase I of our burden of disease study, which is a socio-economic study of the financial and time burden that cystic fibrosis has on individuals, caregivers, the health system and society.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca Canada Inc.	x			
Horizon Therapeutics				x
Pfizer Canada Inc.	x			
Trudell Medical International		x		
Vertex Pharmaceuticals	x			
Vertex Pharmaceuticals (Canada) - Head Office				x
Viatris			x	

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

Name: Dr. Paul Eckford
Position: Chief Scientific Officer
Patient Group: Cystic Fibrosis Canada **Date**: March 19, 2024

Clinician Input

CADTH Project Number: SR0837-000

Generic Drug Name (Brand Name): Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™)

Indication: **Trikafta for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data.**

Name of Clinician Group: Cystic Fibrosis Canada's Accelerating Clinical Trials Network (also called CF CanACT) Executive Committee.

Author of Submission: Dr. Jonathan Rayment (on behalf of CF CanACT)

1. About Your Clinician Group

The Physicians who are submitting this proposal are Steering Committee members of Cystic Fibrosis Canada's Accelerating Clinical Trials Network (CF CanACT). CF CanACT operates under the auspices of Cystic Fibrosis Canada and its purpose is to conduct world class clinical trials in Cystic Fibrosis (CF) in Canada. This is integral to bringing new therapeutics and better care to CF patients in Canada.

The Physicians represent 10 Cystic Fibrosis Clinics across Canada comprising 60% of the CF population. In addition, the Physicians at CF CanACT represent the leading clinical researchers in CF in Canada**.**

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

2. Information Gathering

Information supporting this submission was gathered from the following sources:

1. Cystic Fibrosis Canada's Canadian CF Registry (CCFR) which contains individual patient information on almost all people living with CF in Canada.
2. Outcomes of patients who have participated in clinical trials within the network, especially CFTR modulator trials.
3. Publications from the scientific literature.
4. Information from the Cystic Fibrosis Individualized Therapy Program (CFIT)
5. Personal experience of the CF physicians treating patients with CF.

3. Current Treatments and Treatment Goals

Cystic Fibrosis (CF) is the most commonly inherited genetic condition in Canada affecting approximately Canadians, with an incidence of approximately 1 in 3,600 live births. CF is a progressive, degenerative multi-system disease that affects the lungs, digestive system reproductive system and other systems of the body. 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 pancreas and 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.

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 to significantly 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 38 years (2022), compared to 27 years (2000) (1), which is a significant improvement but nowhere near acceptable.

Historically, CF care focused on symptom management and prevention of the long-term complications of the disease (e.g. malnutrition, chronic infection, lung function decline etc.), with an aim to slow disease progression. This paradigm of "symptomatic therapy" to prevent sequelae is the cornerstone of modern CF care. Unfortunately, standard of care treatments such as inhaled antibiotics and mucus thinning agents target the symptomatic consequences of CF lung disease (e.g. infection, thick, dehydrated mucus), but do not treat the underlying cause or reverse the course of disease. These treatments often require nebulization and therefore are extremely time-consuming to administer (2-3 hours per

day). Thus, they adversely impact quality of life and school productivity at a critical time of childhood development. This demanding treatment regimen also influences medication adherence and mental health.

In contrast, **CFTR modulators are revolutionary, disease modifying medications that have been developed to tackle the underlying molecular defect of CF**. Although not a cure, these medications 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. **Elexacaftor/tezacaftor/ivacaftor (ELX-TEZ-IVA) is the most recent CFTR modulator, approved by Health Canada for people with CF aged 2 years and older who have one or two copies of the F508del CFTR mutation (the most common *CFTR* mutation; 87% of the Canadian CF population).** Clinical trial and real-world evidence studies demonstrate remarkable efficacy of this medication in this population.

Currently, people with CF who have rare mutations (i.e. do not have a copy of the F508del *CFTR* mutation) have the greatest unmet need as there are currently no approved CFTR modulator therapies available to them. Currently in Canada, from data from the Canadian CF Registry (CCFR) there are approximately Canadians with CF lack a copy of F508del, or another mutation that currently has a Health Canada indication for a CFTR modulator(1). These individuals currently have no realistic access to ELX-TEZ-IVA, as even though off-label prescription is a possibility, the medication is cost-prohibitively expensive for the majority of Canadians to self-fund. As such, these people still rely on the traditional “symptomatic therapies” that has been traditionally used in CF care but is not revolutionary.

ELX-TEZ-IVA

The 246 people thought to have a mutation that would benefit from ELX-TEZ-IVA have one of the 177 mutations approved by the FDA for ELX-TEZ-IVA in the USA but not in Canada (2). This includes individuals with one of the 10 ivacaftor-approved mutations that are expected to have additional benefit by transitioning to ELX-TEZ-IVA, and have access approved by the FDA in the USA. In most patients included in the FDA 177 mutations, clinical manifestations are severe without ELX-TEZ-IVA treatment, and the drug under review is considered a breakthrough as it leads to substantial improvements in lung and respiratory-related quality of life and markedly reduces exacerbations and hospitalizations.

Treatment goals

As highlighted in the above section, an ideal treatment in CF would fully address the basic molecular defect in CF and restore normal chloride transport on the cell surface. If applied at an early enough age, complete, early and continuous restoration of CFTR function would prevent the multisystem downstream effects that are ultimately fatal for people living with CF. Researchers continue work towards developing tools to completely and permanently correct CFTR function. This may be effectively achieved by perfected small molecule interventions, or nucleic acid-based therapies.

Clinically important outcomes in CF have been established over the past several years for ELX-TEZ-IVA in many clinical trials. ELX-TEZ-IVA generally:

- Improves and/or stabilizes lung function
- Prevents and/or reduces pulmonary exacerbations
- Improves and/or stabilizes nutrition and growth
- Minimizes and/or reverses other multisystem complications of CF disease
- Improves emotional wellness
- 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

As the overall population of people with CF becomes healthier with improved treatment, it is important to recognize that the efficacy outcomes used in previous trials may not be applicable to ongoing drug trials. This paradigm of disease prevention is consistent with the overall treatment approach to CF outlined in section 3.1.

References:

1. Cystic Fibrosis Canada Registry data. (2022). https://www.cysticfibrosis.ca/uploads/2022-Annual-Data-Report-WEB-AODA.pdf

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217660s000lbl.pdf

4. Treatment Gaps (unmet needs)

Current symptomatic therapies do not reverse extra-pulmonary manifestations of CF including sinusitis, exocrine pancreatic insufficiency, diabetes, liver disease, osteoporosis and bowel manifestations. Early and continuous restoration of CFTR function throughout the lifetime by CFTR modulator drugs, such as ELX-TEZ-IVA, in all individuals who could benefit has the potential to minimize many of the pulmonary and extrapulmonary manifestations of CF, extending both the length and quality of life in these individuals significantly. In 2024, there is a clear divide between people with CF who have access to ELX-TEZ-IVA, who have an improved disease course, and those who do not have access and have a traditional CF disease course. Especially in individuals with ultrarare mutations, where low prevalence limits the possibility of obtaining traditional clinical trial evidence, the potential for benefit assessed should be assessed by published real world evidence (RWE), *in vitro* laboratory data, or individual trials of therapy.

5. Place in Therapy

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

ELX-TEZ-IVA is currently first line, standard of care for Canadians with CF with at least one copy of F508del (1,2). Clinical care guidelines already include CFTR modulator therapies (3,4), but they do not recommend discontinuation of prior therapies such as inhaled antibiotics that treat consequences of the defect because end-organ damage has already occurred in most patients now starting on these therapies. However, in younger people with CF where damage may be less extensive, discontinuation of previous symptomatic therapies is currently under investigation.

As outlined above, individuals without a copy of the F508del CFTR mutation are currently limited to symptomatic therapies for the management of the manifestations of their CF. A clear pathway has been developed in Canada for the integration of CFTR modulators into the care pathways of people with CF(4). For those who carry ultrarare mutation and may derive benefit, ELX-TEZ-IVA could be easily added to standard of care.

The major question here is how to define the patients who would derive benefit from this revolutionary, but incredibly expensive medication. This is addressed in the next section.

Consensus guidelines and Standard of Care guidelines already include CFTR modulator therapies (3,4), 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 in most patients now starting on these therapies, and therefore these treatments remain necessary. Future research and clinical trials 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.
For these reasons, ELX-TEZ-IVA is a first-line therapy that addresses the underlying defect in CF.

References:

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

This question is the crux of this response. It is the opinion of this body that **medically and ethically, any patient who carries at least one CFTR mutation that is responsive to ELX-TEZ-IVA should have access to this disease modifying therapy.**

However, as outlined above, non-F508del CF is an ultrarare disease, with fewer than 600 people in Canada with CF who carry non-F508del mutations. This means that the evidence to define an "ELX-TEZ-IVA-responsive" mutation in this group likely needs to come from outside of the traditional randomized control trial (RCT) framework. This definition needs to balance the extremely high cost of this medication with its well described ability to change the lives of people with CF.

As is typically the case in ultrarare diseases, while the number of individuals for each mutation is very small, collectively the group of individuals who could benefit is quite significant. As each patient's life may depend on access to this medication, it is **incumbent on regulators to use all available evidence, or generate the evidence needed to allow access to this life-saving drug**. As such, we support alternative, scientifically rigorous, non-clinical trial approaches to defining mutation responsiveness to define access.

Indeed we concur with the recent editorial favouring access for all individuals based on a lack of two mutations known to be non-responsive, rather than a requirement for the presence in a patient of mutations shown to be responsive (1).

Note, the CanACT response is not providing a list of suggested "responsive" mutations. As the evidence supporting ELX-TEZ-IVA responsiveness is evolving continuously, any list provided today would be outdated by the time of review. Rather, **we suggest that mutation responsiveness, and therefore medication access, should be assessed on an individual basis in the context of available evidence, which could be based on one of four categories**:

1/ traditional clinical trial evidence,
2/ high quality observational real world evidence (RWE),
3/ data from *in vitro* testing of drug response on immortalized cell-line or patient-derived epithelial cells
4/ convincing evidence of individual response to a trial of therapy.

Clinical Trials
As the clinical trials network for people with CF in Canada, we acknowledge both the important place traditional clinical trials have in the evidence base for the safety and efficacy of ELX-TEZ-IVA, and the challenges of recruitment of individuals with ultrarare mutations. The remarkable clinical efficacy of ELX-TEZ-IVA has been proven beyond doubt in RCTs in the F508del mutation carrying population. However, the feasibility of traditional RCTs in the less prevalent mutations is limited.

A press release(2) from a recent pharma-sponsored ELX-TEZ-IVA trial reported very high-level results of a Phase 3, randomized, placebo-controlled clinical trial in people with 18 rare non-F508del responsive CFTR mutations While the variants in the study have not yet been publicly disclosed by the manufacturer, other sources have reported them as: **2789+5G>A, 3849+10KB C>T, 3272-26A>G, A455E, D1152H, G85E,** L1077P**, L206W,** L997F**, M1101K,** P5L**, R1066H, R117C, R347H**, R347P, S945L, T338I, and V232D (3). Bolded variants in the list are reported in the Canadian CF Registry (CCFR) to occur in the Canadian population. Some variants such as M1101K, 3849+10KB C>T and A455E have significant populations in Canada.

This was the first RCT study to specifically address the clinical efficacy of ELX-TEZ-IVA in a non-F508del population, however, it required a large, multinational approach to achieve successful recruitment. One can assume that the mutations chosen for the trial were both those anticipated to have the potential to demonstrate benefit to the drug, and where

sufficient recruitment could be achieved. There are hundreds of other rare and ultrarare CFTR mutations that could be responsive, but future trials on these mutations would be exponentially more challenging to achieve statistical power. Additional traditional RCTs to support further expansion to this group of ultrarare mutations seems unfeasible and is unlikely at this time.

One other specific mutation recently addressed in a non-pharma, open-label trial is N1303K (4). Results from this trial are currently in a preprint form demonstrates a significant improvement in lung function (ppFEV1 +9.5%, p<0.001) despite no change in sweat chloride (-1.1mmol/L, p=0.61). These fascinating data clearly support the expansion of access to people with at least one N1303K mutation; however, this study was an exception is N1303K is a relatively common "rare" mutation, which allowed recruitment of the requisite number of participants in the study. Similar studies are not feasible for more rare mutations.

Yet while there may be small numbers of individuals for some of these mutations, collectively the group of individuals who could benefit is quite significant. And each patient's life may depend on **regulators enabling CF clinicians to use all available evidence or generate the evidence that a patient will benefit from this life-saving drug**. As such, we support alternative, scientifically rigorous approaches to defining Nonclinical trials. We must look to other types of evidence to show potential response in CF patients to this drug that has demonstrated through multiple phase 1-3 trials to be generally safe and well tolerated in CF patients

Real World Evidence

A variety of real-world evidence data are emerging from jurisdictions where access to CFTR modulators is broader. These data should be used to support evidence around mutation responsiveness. For example, the **French Compassionate Program enabled direct access to patients for the right to try ELX-TEZ-IVA if they had any two non-F508del variants**, were over 12 years of age and had advanced lung disease (FEV1pp <40% or under evaluation for lung transplantation) (5). Clinical measures were evaluated by a clinician adjudication committee to assess an objective response resulting in either, 1) a positive response and continued access, 2) an unclear response with further access and follow-up, or 3) a lack of response and discontinuation of access. Upon completion of the initial phase, 45/84 participants (54%) were deemed responders to ELX-TEZ-IVA, with significant clinical benefits. Phase two of the Program expanded to individuals aged 6+ and removed the requirement of severe lung disease (6). In this second phase, individuals harbouring two mutations already demonstrated in other patients to be non-responsive to ELX-TEZ-IVA treatment did not participate in the program. We await the imminent publication of the next cohort of RWE from this program.

RWE evidence continues to evolve and new data should be incorporated into any future access decisions. For example, analyses are underway for a registry study in the United States of the responsiveness of people carrying non-F508del FDA-labelled mutations. These data are not yet published but will provide a wealth of understanding of genotype-specific RWE and should not require re-application.

In vitro *responsiveness data*

It is well-known in the Canadian CF patient community that in the US in 2020, the FDA label of ELX-TEZ-IVA was expanded to include people with 177 CF-causing mutations known to cause defects in the CFTR protein, based on positive *in vitro* data in the Fischer Rat Thyroid (FRT) overexpression system (7). European and Canadian research groups are also providing evidence to suggest that greater sensitivity may be afforded by patient-derived tissue models in predicting therapeutic outcomes. Data continues to emerge around the great potential value of these systems to understand the potential of certain mutations to respond in the clinical setting

The *in vitro* response size considered likely to translate to clinical benefit was recently evaluated using FRT cell data from the Clinical and Functional Translation of CFTR (CFTR2) project (http://cftr2.org/). *In vitro* functional data for 226 different CFTR variants studied in FRT cells was linked to clinical data from greater than 54,671 individuals with CF (8). The study showed strong correlations between CFTR chloride channel function and key clinical outcomes, including sweat chloride and ppFEV1 predicted measures. Further, the authors concluded from comparisons of mutant CFTR function in FRT cells and clinical trial data, that the functional improvement of mutant CFTR to 10% of the mean non-CF value has the potential

to lead to improved ppFEV1 measurements. However, the well-recognized impact of genetic background and environmental impacts on CF disease progression is not captured in FRT cells, prompting the implementation of patient-derived tissues to predict therapeutic outcomes with precision.

A sub-study of the French Compassionate Program (see below) for people with CF provides RWE for the predictive potential of CFTR functional assays conducted using patient derived tissue models (5,9). These findings showed that a relatively modest improvement in mutant CFTR channel function measured in patient specific nasal cells (approximately 10% of non-CF), is sufficient to have a major impact on lung function. Notably, individuals harboring certain mutations, including N1303K, showed *in vitro* responses to ELX-TEZ-IVA above this threshold in nasal cultures but not in the FRT based program described above. These same individuals went on to exhibit improvement in lung function (ppFEV1) after treatment. Hence, these findings suggest that *in vitro* studies in patient-derived tissue models can exhibit superior sensitivity in reporting the CFTR mutations capable of responding to ELX-TEZ-IVA.

A Canadian program called CFIT (Cystic Fibrosis Individualized Therapy Program), funded by Cystic Fibrosis Canada and the SickKids Foundation, and located at the Hospital for Sick Children in Toronto conducts functional studies on patient nasal epithelial cells (10) has curated a bioresource of patient specific nasal epithelial cells representing diverse disease-causing genotypes from 144 Canadians. In addition to cells from individuals harbouring the major mutation, F508del, the bioresource contains cells from people harbouring rare CF causing mutations. CFIT studies of nasal cells from Canadians harbouring rare mutations (G85E and M1101K), found to be ELX-TEZ-IVA-responsive in FRT cells were also found to be responsive in patient-specific nasal cultures (11). Nasal cells from an international participant in the CFIT bioresource, possessing the rare mutation: N1303K, showed a robust *in vitro* response, in contrast to the negative results for this mutation using the FRT platform. These CFIT *in vitro* data from nasal cells predicted a positive clinical response and this prediction was subsequently confirmed as an improvement in ppFEV1>10% (5).

In a recent prospective study, the Canadian CFIT program compared the *in-vitro* responses to CFTR modulators in individual nasal cell cultures to matched clinical responses for fifty-nine unique treatments (45 people with CF) with the same therapy. This comparison showed that a positive in-vitro response greater than 10% of non-CF levels, identified 92% of people with a clinical response to CFTR modulators. These findings support the proposed use of the 10% threshold to identify people with rare mutations who have the potential to benefit from approved therapies. These results are being prepared for submission for peer-review.

In summary, the **CFIT bioresource, a made-in-Canada solution, is poised to support precision medical care for CF individuals with rare CF-causing mutations by providing patient-specific evidence for therapeutic efficacy**.

Individual Trials of Therapy

A Canadian program modeled after the French Compassionate Program could assess response in Canadian patients to mutations that may be present in the Canadian population but were not part of the French cohort. Even if not so formalized on a national level, trials of therapy could be rationally applied to assess individual responsiveness. Particularly, in individuals with mutations where the potential efficacy of ELX-TEZ-IVA is unknown, a clearly defined trial of therapy with predefined outcome measures could be employed to measure response to therapy - with the possibility of discontinuing the medication if no response is seen. Even in the absence of evidence outlined above, this approach could and should be considered.

Lung Transplant

While participants who had undergone lung transplantation were excluded from the original pivotal RCTs, expansion of access for this group is rational. Patients While those who have undergone lung transplantation will not receive lung function benefits. However, , they may still benefit from CF modulator therapy. Their For example, sinus disease, which can be debilitating, is expected to improve with ELX-TEZ-IVA (12). Improving sinus disease can diminish the risk of developing chronic rejection post-lung transplantation, so ELX-TEZ-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.

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5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The **Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis**, details the processes for monitoring of CF modulator use in all CF patients, including those with rare mutations (currently being prescribed off-label), and this guidance is in use across all 40 CF clinics in Canada. The schedule of baseline evaluation and monitoring in patients age 6+, and age <6 from the Consensus

Guideline are shown in table 6a and 6b, respectively. 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 age 6+ have spirometry to measure lung function (FEV1pp), have their weight and height measured for BMI percentile calculation, 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. Quality of life questionnaires (e.g. CFQ-R for respiratory symptoms, GAD-7 for anxiety) are required and others (e.g. SNOT-22 [or SNOT-5 for younger patients] for sinus disease) can also be employed.

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 and/or sinus symptoms
5. Improvement in nutritional status

As the treatment goal of this progressive disease is to slow decline in lung function and reduce mortality, the most important outcomes are 1, 2 and 3. For lung transplant recipients, improvement in sinus symptoms, reduced antibiotic need, and extrapulmonary benefits would be the most important outcomes.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The ***Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis***, details the processes for discontinuation of CF modulator use in all CF patients, including those with rare mutations (currently being prescribed off-label), and this guidance is in use across all 40 CF clinics in Canada. Only CF clinicians currently prescribe, initiate, monitor and discontinue use of modulator drugs like ELX-TEZ-IVA in CF patients, and this process should be maintained. 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 rare adverse 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 risks of stopping treatment. Considerations on side effects, drug-drug interactions, pregnancy/lactation, lung or liver transplantation, and implications of continuation and discontinuation of therapy are detailed in the Consensus Guideline

Patients with rare mutations where there is a paucity of clinical trials data, RWE or in vitro data supporting benefit or lack of benefit of ELX-TEZ-IVA use, or where genotyping cannot define a genetic variant responsible for a patient's CF but repeated sweat chloride measurements fall within the CF range, should have the opportunity to try this therapy and determine if they benefit clinically. These individuals can be monitored and decisions can be made on continuation or discontinuation of therapy based on the process detailed in the Consensus Guideline for all other CF patients prescribed CF modulators. No CF patient should remain on CF modulator therapy if there is no clinical benefit or stabilization of disease. As noted in the Consensus Guideline, in younger patients some of the standard clinical measures (eg FEV1pp) are not appropriate and the clinical goal is to maintain health over the long term rather than improve current lung function per se. The age of the patient should be considered as well as the aggregate of clinical measures described in the Consensus Guideline, rather than any single measure of benefit.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

There must be robust monitoring of patients initiated on CF modulator drugs like ELX-TEZ-IVA, regardless of the evidence used to gain access, to ensure that these drugs are only used in patients who stand to benefit from therapy. The

Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis, details the processes for monitoring, continuation and discontinuation of CF modulator use in all CF patients, including those with rare mutations currently being prescribed ELX-TEZ-IVA off-label, and this guidance is in use across all 40 CF clinics in Canada. Only CF clinicians currently prescribe, initiate, monitor and discontinue use of modulator drugs like ELX-TEZ-IVA in CF patients, and this process should be maintained.

6. Additional Information

7. 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.

3. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.
   a) Assistance with information on the Programme for Individualized Cystic Fibrosis Therapy (CFIT) was provided by Dr Christine Bear, who leads this programme.
   b) Cystic Fibrosis Canada staff provided support and assistance in the development of this submission.

4. 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.
   a) Numbers of CF patients in Canada who may benefit from expansion of the indication for ELX-TEZ-IVA was provided by CF Canda from data housed within the CCFR.

5. 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 who 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

Name: Jonathan Rayment
Position: Medical Lead CF, CF CanACT; Paediatric Respirologist, BC Children's Hospital, Vancouver
Date: <19-03-2024>

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Vertex		x		

Personal COI reported: Speakers' fees and conference travel support.
Note: I also have an unrestricted research grant (~$2M) from the Vertex IIS program.

Declaration for Clinician 2

Name: Felix Ratjen
Position: Paediatric Respirologist, SickKids Hospital, Toronto
Date:18-03-2024

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex	X			
Alnylam	X			
Enavate Sciences	X			
Tavanta	X			

Declaration for Clinician 3

Name: Brad Quon
Position: Medical and Research Director, St. Paul's Hospital Adult CF Clinic, Vancouver
Date: 18-03-2024

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex	X			

Declaration for Clinician 4

Name: Larry Lands
Position: Site Director, McGill University Health Centre CF Clinic, Montreal
Date: 18-03-2024

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex		X		
Laurent Pharmaceuticals			X	

CADTH Project Number: SR0837-000
Generic Drug Name (Brand Name): elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)
Indication: Trikafta for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data
Name of Clinician Group: Edmonton Adult Cystic Fibrosis Clinic and Calgary Adult Cystic Fibrosis Clinic
Author of Submission: Winnie Leung, MD and Ashten Langevin, PharmD

1. About Your Clinician Group

The Edmonton and Calgary Adult Cystic Fibrosis Clinics provide interdisciplinary care and treatment for adults with cystic fibrosis.

2. Information Gathering

1) Personal experience treating people with cystic fibrosis
2) Personal experience treating people with cystic fibrosis who received elexacaftor/tezacaftor/ivacaftor and ivacaftor (ETI)
3) Review of the medical and scientific literature related to cystic fibrosis
4) The Cystic Fibrosis Canada Canadian Cystic Fibrosis Registry – data on Canadians with cystic fibrosis including clinical data and outcomes – Cystic Fibrosis Canada. (2023). *The Canadian Cystic Fibrosis Registry 2022 Annual Data report.* Retrieved from www.cysticfibrosis.ca

3. Current Treatments and Treatment Goals

Cystic Fibrosis (CF) is a progressive life-limiting genetic disease that affects over 4400 Canadians. The basis for CF is an abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein. Dysfunctional CFTR protein affects multiple organ systems, most importantly the respiratory and digestive systems. There is no cure for this lifelong chronic disease.

CF care in Canada is delivered by specialized multidisciplinary CF clinics located across Canada. The goal of CF therapy is to maintain health (delay disease progression, improve lung function, reduce the risk for pulmonary exacerbations, prevent the need for organ transplant), maintain or improve quality of life and to prolong life. Treatment for CF involves many different treatments due to the multiple organ systems affected by the disease. Non-drug treatments include nasal sinus saline irrigation, airway clearance and high protein high calorie nutrition. Drug treatments include acute and chronic antibiotics, mucolytics, bronchodilators, pancreatic enzymes, fat-soluble vitamin supplements, anti-inflammatories, insulin for those with CF-related diabetes, ursodiol for those with CF-related liver disease and more. Oxygen, non-invasive positive pressure ventilation, and lung transplant are treatments for those with end-stage CF lung disease. The aforementioned therapies treat the effects of the dysfunctional CFTR protein that causes CF.

Trikafta (ETI) is licensed by Health Canada for the treatment of CF in patients age 2 years and older who have a least one F508del mutation in the CFTR gene. ETI is a highly effective modulator therapy (HEMT) which has transformed cystic fibrosis care in cystic fibrosis patients. Unlike the above therapies that treat the downstream consequences of dysfunctional CFTR protein, ETI works to improve the transport, function and stability of the CFTR protein. In short, ETI improves CFTR protein function. Clinical trials in those with ≥1 F508del mutation show massive functional response as demonstrated by improvements in sweat chloride [a test of function channel activity used to diagnose CF], improvement in lung function, nutrition, quality of life and reduction in pulmonary exacerbations.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There exists a current gap in care for Canadians with CF who have an ETI CFTR responsive mutation based on *in vitro* and/or clinical data but no F508del allele. These individuals would derive great benefit from HEMT, but currently can only access treatments that target the downstream effects of dysfunctional CFTR protein. Expanding the Health Canada approval of ETI to Canadians with CF who have an ETI CFTR responsive mutation based on *in vitro* and/or clinical data but no F508del allele would align with the US FDA indication and French compassionate program.

Many ETI CFTR responsive mutations are considered rare alleles, and therefore limited data is available in clinical studies. There is limited real-world experience with ETI in people with CF (pwCF) in Alberta with a CFTR responsive mutation without a F508del mutation because ETI is too cost-prohibitive to pay out of pocket without medication coverage and medication coverage is restricted based on the approved indication.

Nevertheless, the limited experience demonstrates that ETI in those with a CFTR responsive mutation without F508del has significant benefit. A case report outlines 2 adult CF patients, homozygous for M1101K alleles which is a known ETI CFTR responsive mutation, with tremendous response to ETI therapy. This allele is highly prevalent in our prairie-based CF populations. In Alberta the M1101K is found in approximately 7% of our CF population.

5. Place in Therapy

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

For pwCF who have at least one F508del allele, ETI is currently added to existing therapies. ETI would similarly be added to existing CF therapies for pwCF with a CFTR responsive mutation without a F508del allele. Published Standards of Care recommend that pwCF carrying non-F508del variant should be considered for CFTR modulator therapy if *in vitro* or clinical trial data support potential responsiveness to modulator therapy.

Studies are underway to evaluate the effect of decreasing the number or intensity of other CF therapies for pwCF taking ETI.

Furthermore, pwCF with a ETI CFTR responsive mutation without F508del allele should not require trying other CFTR modulator therapies such as ivacaftor, lumacaftor/ivacaftor or tezacaftor/ivacaftor before initiating treatment with elexacaftor/tezacaftor/ivacaftor + ivacaftor due to the superior clinical results with the triple therapy.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

At present time, the patients most suitable for ETI are CF patients ages 2 years and older who have a least one F508del mutation in the CFTR gene or a CFTR mutation that is responsive to therapy based on *in vitro* and/or clinical data. Mutations responsive to therapy could be identified *in vitro* via a process of theratyping or by clinical data.
Patients who do not have any CFTR mutations that respond to therapy would be least suitable for treatment, but this may change over time if other therapies are developed to correct the underlying disease and require a CFTR modulator to work synergistically.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

There are outcomes used in clinical practice that align with outcomes typically used in clinical trials that demonstrate positive treatment response including an improvement in pulmonary function tests, quality of life assessments, nutrition as measured by maintained or improved body mass index, reduction in pulmonary exacerbation frequency thus leading to

decreased hospitalizations, decreased oral and intravenous antibiotic use and an improvement in symptoms. Fortunately, since the introduction of this medication, we have learned that there is an increase in overall life expectancy and a decrease in the requirement for lung transplants in this patient populations.
Cystic Fibrosis patients who response to ETI are better able to perform activities of daily living. Patients have reported increased employment opportunities, less missed work and school days, better time spent with family.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Adverse effects that preclude the use of therapy including anaphylaxis or as per patient experience and goals.

The development of worsening liver disease may require stopping treatment.

Drug-drug interactions with ETI and another medication may require stopping treatment.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

We believe that this therapy should be prescribed by practitioners who specialize in CF care at specialized CF clinics.

6. Additional Information

1. https://doi.org/10.1183/13993003.00110-2023
2. https://doi.org/10.1016/j.rmcr.2023.101938
3. DOI: 10.1183/13993003.02774-2020
4. https://doi.org/10.1172/jci.insight.139983.
5. https://www.cff.org/sites/default/files/2022-02/Trikafta-Approved-Mutations.pdf
6. FDA Monograph: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212273s004lbl.pdf
7. https://doi.org/10.1016/j.jcf.2022.10.002

7. 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.

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

   No

7. 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

8. 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 who 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

Name: Winnie Leung, MD FRCPC
Position: Edmonton Adult Cystic Fibrosis Clinic Medical Director, Associate Clinical Professor, University of Alberta
Date: 17-03-2024

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex Pharmaceuticals	X			
Horizon Therapeutics Canada		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Ashten Langevin, RPh PharmD
Position: Clinical Pharmacist, Calgary Adult Cystic Fibrosis Clinic, Foothills Medical Centre/University of Calgary
Date: 18-03-2024

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex Pharmaceuticals	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: **SR0837-000**
Generic Drug Name (Brand Name): elexacaftor/tezacaftor/ivacaftor and ivacaftor **Cystic fibrosis, F508del or responsive CFTR mutation, 2 years and older** Name of Clinician Group:
CF Canada Health Care Advisory Council
Author of Submission: Dr Mark Chilvers, Chair.

1. About Your Clinician Group

Cystic Fibrosis (CF) Canada is a national not-for-profit corporation committed to improving and lengthening the lives of people living with cystic fibrosis. It is a leading organization with a central role engaging people living with cystic fibrosis, parents and caregivers, volunteers, researchers and healthcare professionals, government and donors to work together to change lives through treatments, research, information and support.

As part of this is the CF Canada Healthcare advisory council, a group composed of 10 Interprofessional healthcare providers and 2 lay members. These members are involved in the provision of care to children and adults with CF in Canada. The council supports CF Canada in developing CF care policy and guidelines to support the CF clinic directors and community.

2. Information Gathering

The information included in this submission was gathered in several ways:

1) Experience gained by working with and delivering medical services to people with cystic fibrosis.
2) Experience treating people with cystic fibrosis who received elexacaftor/tezacaftor/ivacaftor (elexa/teza/iva), ivacaftor, ivacaftor-lumacaftor, and ivacaftor-tezacaftor either during participation in clinical trials, through the Health Canada Special Access Program, and/or since the Health Canada marketing authorization for persons ages 2 years and older.
3) Review of the medical and scientific literature, including clinical trial results, real world experience and other jurisdiction approvals.
4) The Cystic Fibrosis Canada Canadian Cystic Fibrosis Registry, a collection of patient data and other information regarding CF care and outcomes.
5) The Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis (Feb 2024, 3rd edition) [1]

3. Current Treatments and Treatment Goals

Cystic fibrosis (CF) is a fatal, progressive genetic disease that affects approximately 4,500 Canadians, with an incidence of approximately 1/3,600 live births. In 2022 there were 80 new cases diagnosed in Canada, with 55 of those diagnosed through provincial newborn screening programs.[2] It is a lifelong, chronic, degenerative disease that affects multiple organ systems, most importantly the lungs and the digestive system. According to the Canadian Cystic Fibrosis Registry, 4,451 individuals live with CF, of whom 425 (10%) don't carry a copy of the F508del Cystic fibrosis transmembrane regulator (CFTR) variant but may be responsive to Elexakaftor/Tezakaftor/Ivakaftor (ELX-TEZ-IVA).[3]

In order to treat the underlying symptoms, people with CF (pwCF) are prescribed a multitude of treatments, including high-calorie high fat high protein diets, digestive medications, and airway clearance treatments.

Physiological manifestations of CF start very early in life, before many tests will show significant changes. Consequently, many of these treatments start at the time of diagnosis, usually in infancy, and continue every day throughout life. Medications commonly used in CF include; acute and chronic antibiotic therapies, mucolytics, bronchodilators, pancreatic enzymes, fat soluble vitamins, insulin for people with cystic fibrosis related diabetes, and ursodiol for liver disease. Chest physiotherapy treatment is prescribed several times a day. The average time for pwCF for to undertake therapy is >2 hours/day. As disease severity increases so does time commitment to treatment.

One transformational change was the introduction of newborn screening for CF. This is now standard practice across all of Canada. Children are now diagnosed within 1 month of life instead of a median 2-3 years.

Consequently, therapy is commenced within weeks of life and significantly alters the natural history of CF disease progression. One of the principles of screening is that there must be an accepted treatment for patients with recognized disease. With the introduction of ELX-TEZ-IVA there is now not just an accepted treatment but a highly effective one.

A second transformational change, was the introduction of CFTR modulators, a revolutionary treatment for CF care. Non-modulator treatments are aimed at targeting symptoms, treating exacerbations, and slowing the progression of what is a life-long, degenerative, and fatal disease. CFTR modulators are the first commercially available therapies that target the basic defect in CF by improving the production and function of the abnormal CFTR protein. Although none of the modulators are a “cure” for CF, the improvement in CFTR production and function, minimizes symptoms, improves clinical parameters such as lung function, body mass index, pulmonary exacerbations, and sweat chloride measurements. They have been shown to have a positive effect on quality of life in pwCF. The second-generation modulators had a modest but important clinical effect, but response to the third-generation modulator, ELX-TEZ-IVA is substantially greater and more comparable to the response of pwCF with eligible mutations to ivacaftor[5].

Ivacaftor is currently approved for pwCF ages 2 months and up who have one or two of a small number of CFTR mutations, representing 4% of Canadians with CF. Since ELX-TEZ-IVA received market authorization, access to the medication was initially limited by type of insurance and province of residence. However, it is now fully available for all patients with CF who have 1 copy of F508del aged 2 years and older. From the CF Canada registry (2024) 87% of CF patients are now eligible and have received ELX-TEZ-IVA. The Canadian Clinical Consensus Guideline for use of CFTR modulator therapies in pwCF, provides comprehensive recommendations for criteria for initiation, monitoring and response for all patients with CF[1]. Within this guideline, the recommendation is that all patients with ELX-TEZ-IVA CFTR responsive mutations and a diagnosis of CF should have the opportunity to be treated. This highlights that there is currently a shortfall in access to medication for a further 10% of patients who **MAY** have a response to ELX-TEZ-IVA[1].

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 2021 Cystic Fibrosis Registry report, Canadians with CF had over 17,000 clinic visits that year and logged 16,000 hospital days and 10,000 home IV treatment days[4]. In 2022, the report shows this to be trending down, with a 50% reduction in home IV days, 86% reduction in lung transplantation and reflects the impact of CFTR modulator therapy in those CF patients having access[2].

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 2021 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.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Most of the currently available treatments only treat the symptoms and complications of CF and attempt to slow down the eventual fatal progression of the disease. Most patients die from end stage respiratory failure.

While ivacaftor is a highly effective CFTR modulator, it is effective for only about 4% of Canadians with CF and is not effective for CF patients who are homozygous for F508del or who carry one F508del mutation and a mutation that is not treatable by ivacaftor. These patients make up approximately 86% of people with CF.

For pwCF ages 2 years and older, clinical studies and real-life clinical experience of ELX-TEZ-IVA in Canadian provincial CF Clinics has shown a positive therapeutic response. In the PROMISE study, subjects with mild CF lung disease showed significant improvements in ppFEV1, sweat chloride measurement, CFQ-R Respiratory domain score, and BMI. This is despite these patients being perceived to have milder disease[7].

Although, newborn screening has been shown to alter the natural history CF, it has been shown that these newly diagnosed patients still have evidence of lung disease and other manifestations of CF early in life. These changes are progressive, cumulative, and ultimately lead to death despite early initiation of standard treatment. Access to effective CFTR modulators has been show to significantly alter these early changes. As illustrated by the improvement in sweat chloride and lung clearance index in an open label study of children aged 2-5 receiving ELX-TEZ-IVA[7]. Similar findings were seen in children aged 2-11 years who are now receiving commercial drug in Canada and so it is likely these findings are transferable.

However, there exists a treatment gap in CF care on two levels. Firstly, those patients who have received a lung transplant. Participants who had undergone lung transplantation were excluded from the original pivotal RCTs, expansion of access for this group is rational. While those who have undergone lung transplantation will not receive lung function benefits, they may still benefit from CF modulator therapy. For example, sinus disease, which can be debilitating, is expected to improve with ELX-TEZ-IVA[8]. Improving sinus disease can diminish the risk of developing chronic rejection post-lung transplantation, so ELX-TEZ-IVA should be considered in those lung transplant recipients with significant sinus disease.

Secondly, 10% of Canadian patients with “Rare mutations”, who have CFTR variants responsive or potentially responsive to ELX-TEZ-IVA, do not have access as no clinical trials have been conducted. Benefit relies solely on reports of real world evidence, in-vitro data or individual trials of therapy.

Clinical trial data on modulator use in patients with variants other than F508del or gating and conductance mutations is lacking. At least one clinical trial has been conducted by Vertex for ELX-TEZ-IVA in individuals with no F508del variant but with at least one of a short list of other variants primarily identified in *in vitro* laboratory data to potentially be responsive. While at the time there were no Canadians with some of these mutations, others including A455E, D1152H, L206W and M1101K were represented in significant numbers (from 10-30+ for each variant) of Canadians. To date these results have not yet been published, however the manufacturer has stated that the cohort of the study had a 9.2 percentage point increase in ppFEV1; $P<0.0001$; 95% CI [7.2, 11.3][1].

While it is important to conduct well-designed, placebo controlled double-blinded clinical trials to assess modulator effectiveness where possible, in most cases such trials are not feasible given the small numbers of patients with each potentially responsive variant. Recognizing this, the FDA approved the use of Ivacaftor (Kalydeco™) for 23 different variants based on clinical trial data and also, *in vitro* laboratory data on drug response of mutant CFTR protein overexpressed in the Fischer Rat Thyroid (FRT) cell line[1]. Through subsequent *in vitro* testing, to date the US label has now been expanded for CF modulators with the following number of CFTR variants: ELX-TEZ-IVA (177 variants), and Ivakaftor (96 variants) [1]. This has increased patient access to modulator therapy based on safety data from F508del trials and *in vitro* laboratory data negating the need for clinical trials for each specific CFTR variant. Real world evidence (RWE) will ultimately support the use of highly effective modulators in patients with many of the mutations on the expanded label[1].

5. Place in Therapy

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

The development of a CFTR modifier such as ELX-TEZ-IVA fills a niche in CF care that is not currently occupied by any treatment. The fact that it is an oral medication will have a huge impact on adherence and started earlier in life will modify disease progression and prevent other therapies being required. In future CF care this will reduce the need for current CF therapies. The Canadian guidelines recommend that ELX-TEZ-IVA is added on to existing therapies for a duration of one year and response to therapy evaluated and recorded as part of the national CANimpact study. In addition, this study will evaluate the impact of ELX-TEZ-IVA in decreasing the number and intensity of other routine CF treatments[9].

Most patients with CF are pancreatic insufficient requiring the need to tale pancreatic enzymes to absorb food and grow. Data have reported the recovery of pancreatic function in some patients on CFTR modulators. Early introduction has been key. Similarly, preservation or stabilisation of pancreatic function has helped reduce the frequency of CF Related diabetes.

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 challenging with time.

Adherence to treatment and simplifying treatment burden is a major concern for people with CF and for CF clinicians. This is paramount in the 2-5 year old group where treatment is solely dependent on the parent or caregiver. Burden of care is high from the time of diagnosis 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[9]. 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% 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%) reported that their treatments get in the way of family relationships, relationship with a partner (69%), and relationships with friends (75%). An impact of treatments on socialising and on sports and hobbies was reported by 81% and 80%, respectively. Treatments need to be able to be easily integrated into daily life, to not form a barrier that limits participation in important activities during childhood, such as school, family life, peer relationships, sports, hobbies, and play.

Other treatments to treat the molecular basis of the disease, such as gene therapy, are currently under development and still within the pre-clinical stage. This has potential, but will likely target single organ CF dysfunction rather than systemically as seen in CFTR modulators.

The impact on lung transplantation in CF has been impressive. Since the introduction ELX-TEZ-IVA the need for lung transplantation within the community has fallen by 89%.[2]

A Canadian group used a microsimulation transition model to estimate the effect of the introduction of ELX-TEZ-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.[10]

Expanding access to those patients with other responsive CFTR variants will allow access to another 246 patients. This will have lifelong benefit, as mentioned previously, because the medication addresses the underlying disease process ie. decreased production and lack of function of the defective CFTR protein. Importantly, it will improve equitable access to those from marginalised communities in whom these rare mutations are often found.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The recent Canadian guidelines clearly define patients who should be treated with a CFTR modulator and recommend all patients with CF who have at least one ELX-TEZ-IVA responsive CFTR variant[1]. The Canadian Cystic Fibrosis clinic system is well established and covers almost all persons with CF in Canada. Patients likely to respond to this medication have been well described in the clinical studies and will be identified by their CF clinic based on genotype of their CFTR mutations. The criteria for diagnosing CF are well established and standardized, and the appropriate tests are available at CF clinics. Most patients are now being diagnosed through CF newborn screening programs. Early initiation of therapy is key to this patient group.

As we move into rare CFTR variants there is limited data to support the use of ELX-TEZ-IVA. As stated earlier this is based on limited clinical trials, Real world evidence and in-vitro data. The key to assess response is for individualised therapeutic trial of medication. The Canadian CF clinics are well positioned to measure response to therapy and discontinue medication if needed.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Spearheaded by the Health Advisory Group at Cystic Fibrosis Canada, a group of Canadian CF clinicians have developed standardized guidelines for all patients started on CFTR modulator treatment and for assessing response.[11] In addition to the regular clinic visits every three months, an additional visit has been recommended 1 month after starting therapy with ELX-TEZ-IVA to assess the initial response to therapy, to screen for side effects, and to address patient concerns. At follow up visits, outcomes measured include a history and physical exam, measurement of height/weight and calculation of BMI, laboratory tests to follow parameters associated with potential side effects (liver enzymes, creatine kinase), sputum microbiology, quality of life questionnaires and mental health screening, and a review of prescribed therapies. Fecal elastase and sweat chloride levels will be monitored at intervals. Regular follow up with a yearly ophthalmological examination is also recommended. These outcomes align with those identified in the clinical trials and with normal standard care of patients with CF.

Meaningful clinical responses to be monitored include[1]:

1. Improvement in lung function as measured by FEV1 or Lung Clearance Index (LCI) (where available) obtained at a time of clinical stability, for individuals over 6 years of age
2. Prevention and reduction in the number of pulmonary exacerbations
3. Stabilization in lung function over time (i.e. attenuation of the usual decline in lung function in CF)
4. Reduction or stabilization of respiratory symptoms
5. No decline, or an improvement in nutritional and growth status
6. Improvement in quality-of-life scores

7. Reduction in sweat chloride.

For children aged 2-5 years standard lung function is not reliable and is not performed and consequently is not valid as a response to therapy. The measurement of lung clearance index, as reported in the study, is not approved for clinical use in Canada and is only available in 3 Canadian centers as a research tool. CT scans require sedation and are therefore not recommended for routine surveillance. An outcome of particularly interest is recovery of pancreatic function. 95% of CF patients are pancreatic insufficient. Early treatment of patients receiving ivacaftor showed there was recovery of pancreatic function. Similarly, this has been described in real world experience.

The improvements that have been measured in most clinical trials include pulmonary function testing, pulmonary exacerbations and antibiotic use, 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, having less difficulty maintaining a healthy weight, missing less work or school due to hospitalization for pulmonary exacerbations, 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.

These treatment responses include some quantifiable measures (pulmonary function, BMI) that should not vary across physicians. Whether a pwCF is admitted to hospital or treated as an outpatient for a pulmonary exacerbation may be physician, centre, or location dependent and may also be affected by other factors.

However, the effect of the medication on disease stability should not vary greatly by physician. Quality of life measures and patient reported symptoms should also not be practitioner dependent.

Criteria for determining response or non-response to therapy has been clearly identified by the Canadian Guideline for patients aged 2 years and older, including recommendations for dose interruption and discontinuation.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

As with any treatment, discontinuation should be considered if there is lack of clinical response following a trial of therapy, a severe side effect, allergy, or other adverse event occurs. The Canadian guidelines provide recommendation for dose reduction or discontinuation and potential side effects[1].

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Almost all patients with cystic fibrosis in Canada are followed at accredited hospital based Cystic Fibrosis clinics, which are staffed by professionals who have the training and experience in diagnosing, treating, and monitoring people with CF. Experience is already gained with the medication in the population who have already receive it over the last 2 years.

5. Additional Information

References

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10. Canadian Observational Study Evaluating the Long-term IMPACT of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators on People With CF (Can-IMPACT CF) ***NCT05200429***

6. Conflict of Interest Declarations

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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.

   Unpublished Data form the CF Canada Registry

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 who 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

Name: Dr Mark Chilvers
Position: Chair, CF Canada Health Care Advisory Council

Date: 23-05-2023

☒**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.

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