Patient Group Input: Canadian Agency for Drugs and Technologies in Health

Reimbursement Review: elexacaftor/tezacaftor/ivacaftor for 6 years and older

Dr. John Wallenburg, Chief Scientific Officer

December 16, 2021

Name of Drug: lexacaftor/tezacaftor/ivacaftor (hereinafter “Trikafta”)
Indication: For the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Name of Patient Group: Cystic Fibrosis Canada
Author of Submission: Dr. John Wallenburg, 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. Half of the people with cystic fibrosis who died over the past three years were younger than 34. A child born with cystic fibrosis in 2019 has only a 50% chance of living to 54. We will keep pushing, keep going further until all people with cystic fibrosis experience — and enjoy everything life has to offer.

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-one 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 $261M in research and clinical care support. The close relationships with the research, clinical and patient communities gives us an excellent understanding the disease. 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. We launched in 2018 the Cystic Fibrosis Canada Accelerating Clinical Trials (CF CanACT) network that now includes 10 of the 41 cystic fibrosis clinics serving over 60% of Canadians with cystic fibrosis. 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 on 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.

We work closely with our patient community to advocate to improve their health and well-being. In 2020, Cystic Fibrosis Canada’s National Advocacy Network consisted of over 200 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 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 Trikafta for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. We appreciate the consideration CADTH gave to our submission on the 12+ population and to our response and our clinicians and researchers' responses to the draft criteria. CF clinicians and researchers share this sentiment. Collectively, we look forward to providing CADTH with a suite of submissions for the 6+ population in Canada to help guide CDEC’s deliberations to ensure the broadest access possible for this life-changing therapy.

2. Information Gathering

Cystic Fibrosis Canada gathered information for this submission through many channels, including a cross-Canada survey of patients and caregivers in January 2021. We reference Cystic Fibrosis Canada's publications, including the 2019 Canadian CF Registry Annual Data Report, press releases, news stories, government submissions, as well as information gathered through social media campaigns, posts from individuals and traditional media sources.

We cite scientific literature, clinical trial data and other published studies on Trikafta and its impact on health outcomes, as well as a Cystic Fibrosis Canada funded study published in the fall of 2020[1] that projects the impact on the Canadian cystic fibrosis population of access to Trikafta. Where appropriate (in descriptions of the general impact of cystic fibrosis on life for example) we have used information gathered for our recently submitted CADTH and INESSS submissions, as well as those from the submissions of CF clinicians and researchers.

We reference findings that were recently presented at the 2021 North American Cystic Fibrosis Conference[2].

Patients and caregivers were invited through postings at cystic fibrosis clinics, through direct email, Facebook, and other social media channels, to participate in a survey conducted from January 18 until January 25, 2021. In total,1,455 people responded to our survey. According to their residence, all respondents live in Canada. The percentages provided below refer to the percentage of individuals who responded to a given question in the survey.

Thirty-one percent of all respondents were adults living with cystic fibrosis, 17% a spouse or caregiver of an adult living with cystic fibrosis, 12% parents of one or more children with cystic fibrosis between the ages of 12-17 years, and 20% were parents of one or more children with cystic fibrosis aged 11 years or younger. Twenty percent of the respondents did not belong to any of these categories and were excluded from further analyses.

At the time of the survey, of the 422 adults with cystic fibrosis who responded, 12% were taking Trikafta through Health Canada's Special Access Program (SAP), 7% received it through a clinical trial and all but one adult was still accessing it.

As reported by responding caregivers, 5% of children 11 years of age or younger accessed Trikafta as part of a clinical trial, fewer than one percent received the drug through the Special Access Program, and 3.5% of respondents in this age group tried to access Trikafta through the SAP but were unsuccessful. Of the remaining participants, the caregivers of 79% of those 11 years of age or younger noted that their children were indicated for Trikafta, while 5% of caregivers for this cohort stated that their children were not indicated for Trikafta.

3. Disease Experience

Cystic fibrosis is the most common fatal genetic disease affecting children and young adults in Canada. There is no cure. It is a complex disease caused by mutations in the gene for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). There are over 2,090 known mutations. Cystic fibrosis has a tremendous impact on the people who live with it, their loved ones, and on society. Every week in Canada, two people are diagnosed with cystic fibrosis, one of them through newborn screening. Every week in Canada, one person with cystic fibrosis will die.

Cystic fibrosis causes various effects on the body, but mainly affects the digestive system and lungs. The clinical progression of cystic fibrosis can vary greatly from person to person, even with the same mutations. The most significant clinical impact is in the lungs, where patients have difficulty in clearing secretions, which in combination, with aberrant inflammation leads to persistent infections with cycles of inflammation that are ineffective in clearing infections. This leads to progressive scarring of the airways and a progressive and sometimes rapid decline in lung function. Pulmonary/ infection/ cardiovascular complications cause eighty percent of cystic fibrosis fatalities.[3]

Patients may suffer from pulmonary exacerbations (PEx, flares of lung disease) requiring weeks of treatment with antibiotics and often requiring hospitalization and I.V. antibiotics. PEx cause rapid decline of lung function and more rapid disease progression and are associated with a greater risk of death[4]. Other consequences of having cystic fibrosis include malnutrition and very low BMI, and cystic fibrosis-related comorbidities like cystic fibrosis-related diabetes (CFRD) and cystic fibrosis-related liver disease.

Thanks to significant progress in treatment and care, most children with cystic fibrosis will reach adulthood. The estimated median survival of Canadians with cystic fibrosis in 2019 was 54.3 years of age.[3] There were no deaths amongst 6-11 year olds in 2019.

As the disease advances more time and effort are needed to manage the progressive and debilitating symptoms. Children with cystic fibrosis may need to quit school or go part-time, adults with cystic fibrosis may need to leave the work force or undertake part-time work, as may caregivers of children and adults with cystic fibrosis.

> *Our four year old grandson has missed out in so much of his life that he deserves more childhood instead of all the time the medications and therapies take away. – Grandparent of a child with CF*

> *Growing up, I spent a lot of my life trying to show everyone that I was tough and that I could handle CF because I didn't want their worry or their pity. I have to live my life knowing that it's most likely going to be shorter than my parents' lives. Shorter than my younger brother's life. No one should have to live like that. Now that I'm an adult living with CF, the realities of the disease are catching up to me. My health is worse than it's ever been before. Not having enough breath to do the things I want to do on a daily basis is incredibly frustrating. I want to have enough breath to run up the stairs. To hike down to the dock and go fishing with my dad. To clean the house. CF is slowly stealing my life from me. I have dreams. I want to get married and not break my husband's heart when CF stops mine. – Adult with CF*

> *I have experienced many health crises related to cystic fibrosis leaving me with no other option but to consider a double-lung transplant. In 2011 my lung function reached an all-time low sitting at 26 percent and my family and I were faced with the difficult reality of having to make a decision. At this point I was so exhausted I couldn't even perform basic tasks. – Adult with CF*

> *I struggled to keep up with work and university and had to spend up to 2 hours a day on exhausting, never ending, treatments. For 20 years I had about 3 hospital admissions a year. This meant I had over 60 hospital admissions, equaling more than 3 years of my life in hospital. – Adult with CF*

> *When two of my children were first diagnosed, the doctor told me I'd never go back to work again. It is a full-time job keeping my children healthy. From helping with their physio to clear mucus, frequent CF clinic visits, hospital stays, and on top of that ensuring our third child does not feel left out as a healthy child. – Parent of a child with CF*

> *My 11 year old daughter spends in excess of 26 hours a week trying to stay healthy. The fight against CF is all encompassing for the family. It requires giving up 2 to 7 hours every day for her therapies. The physical therapies take a toll on my and my wife's bodies. We both have repetitive strain injuries and arthritis in our hands, wrists and shoulder. This commitment requires scheduling all meals and everyone's activities around her therapies. We restrict our social activities to prevent passing on colds and flus. Each day that a control for cystic fibrosis is not available to her is a day that her lungs are deteriorating. All the treatments that she has access to only try to mitigate her existing health problems, none address the root cause. Without the availability of drugs that fix the basic defect in cystic fibrosis, our daughter and others like her will lose their valiant fight as they pass away while gasping for air. – Parent of a child with CF*

> *I lost three friends in three months, while they waited for a lung transplant. It's not right to bury your friends all under the age of 25. I've been to more funerals than weddings in my life. – Adult with cystic fibrosis*

Moreover, research has shown that patients with chronic diseases (defined as a condition that persists for longer than three months) can often have anxiety and depression. It is estimated that up to one third of individuals with a serious medical condition will experience depression. Depression is one of the most common complications of chronic illness like cystic fibrosis, and it also affects caregivers[5].

> *On April 1st, 2011 my son and daughter were both diagnosed with Cystic Fibrosis. It remains the most devastating news I have ever received. My 9-year-old son has already spend in total over 6 months of his life in the hospital. Each time he is away from school, his friends, his extra-curricular activities, his bed, his family. He is stuck in a hospital room attached to cords and tubes. He's not allowed to leave his room due to infection control. It's complete isolation. Being away from home for 2 weeks at a time affects the whole family. My daughter has developed separation anxiety. – Parent of a child with CF*

She had a really rough first four or five years. Constantly sick, in and out of the hospital, had trouble gaining weight … it's a lot of she just 'can't breathe.' She can't breathe in, and she can't breathe out a full amount of breath. In the last two years, she's become a different person because of this disease. In March, she tried to take her life because she said, living with cystic fibrosis is not living it's surviving the life she doesn't want to live. – Parent of a child with CF

4. Experiences With Currently Available Treatments

There are hundreds of therapies that aid in symptom management of cystic fibrosis 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. 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. Patients frequently have periods of infection and acute inflammation called exacerbations that require a hospital stay of at least two weeks and that frequently last four weeks. The steroids that are used to reduce the inflammation and help patients recover from the exacerbation ultimately damage organs in the long run, contributing to the development of cystic fibrosis related diabetes (CFRD) in 35.2% 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. Since therapy starts at the age of diagnosis, this process begins at an early age for many, often two to three weeks old thanks to newborn screening for cystic fibrosis, now provided right across Canada. Newborn screening was put in place so that treatment can begin as early as possible, to help slow the progression of the symptoms of the disease.

Right now my child cannot access any modulators, and preventative therapies currently are not taking away the progression of her disease. Quality of life is hugely impacted and lessened, having no modulator to improve her overall health and help her body be protected from other illnesses. – Parent of a child with CF

Hospitalizations interfere with school, and jobs, for both adult patients and the parents of children with cystic fibrosis. In 2019, there were 1,952 hospitalizations recorded which added up to almost 25,246 days spent in hospital (nearly 70 years total). This does not include visits to the out-patient cystic fibrosis clinics. A total of 4,316 (99.4%) individuals with cystic fibrosis visited a cystic fibrosis clinic at least once in 2019 with 3,367 (77.5%) having three or more clinic visits. Twenty-one percent of cystic fibrosis patients travel more than 250 km one-way to their cystic fibrosis clinic to receive routine care, with the concomitant interruptions on day-to-day life. At home, individuals with cystic fibrosis had 842 courses of home IV therapy adding up to over 15,530 days on home IV antibiotics[3].

In terms of time, money and overall health, the burden of care on those who live with cystic fibrosis, their caregivers and society is tremendous. Over the course of a year, people with cystic fibrosis can take tens of thousands of symptom management medicines and supplements. Together inhaled and physio chest therapies can take between 2-4 hours a day, every day of the year.

Long-term use of powerful antibiotics to fight chronic, persistent infection ultimately leads to anti-microbial resistance. Patients describe the fear of running out of options.

I am running out of options due to antibiotic resistance & low lung functions, so this is a possible treatment when without it, I have no other option. – Adult with cystic fibrosis

I am running out of options due to antibiotic resistance … I hope [Trikafta] comes quickly, as I am sick but not sick enough for SAP, which is very hard to cope mentally that I am suffering with no options, And my health is deteriorating, but I'm not dying enough to get it yet, so I am concerned about the damage to my lungs while I wait that could have been avoided when Trikafta exists. – Adult with cystic fibrosis.

Eventually the ongoing cycles of infection and inflammation destroy the lungs. Lung transplantation is the last recourse for people with end-stage cystic fibrosis. Between 1988 and 2019 eight hundred and eighty-four individuals with cystic fibrosis had received one or more lung transplants, with three hundred eighty-five post-transplant reported deaths, or 499 survivors. Fifty percent of today's lung transplant recipients are expected to live over 10 years[3].

A summary of the day in the life of one cystic fibrosis patient with advanced disease, during the evaluation period pre-transplant:

> *A typical day at home: 6:00-7:30 AM: intravenous (IV) antibiotics (2x40 mins). They connect with my picc-line. It's rather tedious because of the many steps of the procedure: disinfect, flush with saline, connect the antibiotic, wait 40 minutes, flush with saline again, connect the next antibiotic, wait 40 minutes... etc. Very often, my Mum, Dad or sister will do this for me while I sleep in, so I can catch a bit more sleep. 8:00-9:00 AM: wake-up routine; asthma meds, inhaled antibiotics and enzymes, pep-mask physiotherapy, wash all the nebulizers, prep any meds that need to be reconstituted. 9:00-10:00 AM: breakfast; meal routine: check blood sugar, take insulin, have breakfast, morning pills (the usuals + check calendar for the ones on a variable schedule), Scandishake, after-breakfast meds, if any (check calendar). 1:00-2:00 PM: lunch; repeat meal routine; 2:00-4:00 PM: IV antibiotics (3x40 mins), (concurrent) 3:00-3:10 PM: inhaled antibiotics. 4:00-5:00 PM: exercise. 6:00-7:00 PM: supper; repeat meal routine. 8:00-9:00 PM: clapping physiotherapy. 9:00-9:30 PM: bedtime routine; asthma meds, inhaled antibiotic, bedtime meds (check calendar). 10:00-11:30 PM: IV medications (2x40 mins) Fairly often, my Mum, Dad or sister will do this one for me too so I can go to bed a bit earlier. Juggling the timing of everything is a bit of a headache, mostly because I need to space out eating with physiotherapy (doing physio or exercise tends to give me coughing fits, which makes me throw up if I've eaten too recently). On most days I've also got a limited amount of energy, so I've got to manage my activities to make sure I don't crash before the end of the day. Other regular tasks include: keeping medical appointments (1/week or more); preparing pills in advance (it saves time at meals); speaking with my pharmacist 2-3 x a week to order meds, arrange delivery...and…staying on top of insurance reimbursements (3-4 hours / month or so). – Adult with cystic fibrosis*[6]

Experience with currently available CFTR modulators

Trikafta is the first, third generation CFTR modulator. All modulators are tailored for specific CFTR mutations. The first generation modulator, Kalydeco, is now broadly available in Canada, but it took years for it to be so. Kalydeco treats about 4 percent of people living with cystic fibrosis. Orkambi and Symdeko are both second-generation modulators and could benefit as many as 50% of Canadians with cystic fibrosis. Orkambi recently became available in several Canadian jurisdictions, but access is extremely limited. Symdeko is only available through some private drug plans. The drug has not been reviewed by CADTH.

Clinical benefits gained from Kalydeco are similar but more modest than those from Trikafta. Although the patient populations served are distinct, patients on Kalydeco with a F508del mutation are likely to benefit from Trikafta. On average, clinical benefit gained from Orkambi or Symdeko are substantially more modest than those from Trikafta and more patients reported intolerable side effects with Orkambi in particular, however individual responses were highly variable, and some patients report having benefited greatly from one, or another of the earlier modulators. Any Canadian on or eligible for, Orkambi or Symdeko is likely to benefit substantially from Trikafta.

> *[Trikafta is] clinically shown to work better than Orkambi- which my child is on. - Parent of a child with CF*

> *Being on Orkambi increased my energy and overall improved my symptoms and it was great. I am thankful that I got to take Orkambi and stabilize my health. It was able to stabilize my health and I felt great. But it did not alleviate as many symptoms as Trikafta. When I started Trikafta it was life changing. It not only alleviated 99% of all mucus in my lungs. It increased my lung function significantly. Being on trikafta gave me a chance at living a life without an imminent need for a lung transplant. It has allowed me to put my cystic fibrosis on the back burner and it not be the only focus in my life. My cf is more of an inconvenience than a death sentence now that j am taking Trikafta. For me the obvious choice is that Trikafta works significantly better than Orkambi for my body. – Person living with CF*

This individual provided a detailed description of their experience on Orkambi, then Symdeko and finally with Trikafta. Their experience with Trikafta is presented in section 6.

I had the privilege of accessing Orkambi in 2016, Symdeko in 2018 and, as a recipient of compassionate access, Trikafta in 2020. … I began taking Orkambi in 2016 and shortly thereafter my declining health stabilized. My lung function (FEV1) remained stable for 1.5 years, I had significantly more energy and I gained a much needed 25 lbs in 4 months, which helped me finally reach a more normal, healthy weight class for my height and age. Orkambi slowed my rapid decline but I was still seeing losses and I knew that there was a next generation medication in the pipeline called Symdeko, as I had participated in a 30-day study for that one years before. When Symdeko was approved by Health Canada I was able to again access it within only a few months on my group benefit plan. Symdeko increased my FEV1 slightly for a time and the side effect of severe acid reflux I experienced while on Orkambi was resolved with Symdeko. Unfortunately, my CF lung disease, though progression was slowed, was severe at this point and I had several complications in 2019 which led to testing to initiate the lung transplant process. - Person living with CF

Together, all prior generation CFTR modulators could only help up to 54% of Canadians with cystic fibrosis based purely on genetic background. It comes as no surprise that in our January 2021 survey, 79% of respondents answered “yes” when asked if they think that there is a gap, or unmet need, in current therapies that they believe Trikafta will alleviate. Trikafta alone could help up to 90% of Canadians with cystic fibrosis.

Unmet needs include the fact that right now my child cannot access any modulators, and preventative therapies currently are not taking away the progression of her disease. Quality of life is hugely impacted and lessened, having no modulator to improve her overall health and help her body be protected from other illnesses. – Parent of a child with CF

Trikafta targets the root cause of cystic fibrosis and helps break the cycle of infection and deteriorating lung function. Our son calls this drug a 'dream come true.' We are forever grateful to the CF community for their efforts in making this day a reality. While this is an exciting day, we look forward to the day when every Canadian who needs Trikafta can access it. – Parent of a child with CF

[Trikafta is] proactive rather than reactive - preserve lung function and health. – Parent of a child with CF

[Trikafta] would be a preferred modulator, as others may have adverse side effects. – Parent of a child with CF

Caregiver Impact: Current Therapies

Spouses or caregivers of an adult living with cystic fibrosis accounted for 34% of caregiver respondents to our January 2021 survey, 25% were parents of one or more children with cystic fibrosis between the ages of 12-17 years, and 41% were parents of one or more children with cystic fibrosis aged 11 years or younger.

Of the 384 caregivers who responded and care for children with at least one F508del mutation, at the time of our January survey, 87% had not sought access to Trikafta. Five percent care for children who tried to access Trikafta through the Special Access Program but were unsuccessful, and 2% care for children who had access through a clinical trial but no longer do.

All of these people care for Canadians following current standard of care (SOC).

Current standard of care focuses on maintaining health and preventing progression. This is why children, who appear healthy and may have over 100% predicted FEV1 are nonetheless subjected to an aggressive regimen of physiotherapy and antibiotic treatments in addition to special diets and frequent (quarterly or more) clinic visits. Despite this aggressive early treatment, all patients will ultimately progress. This also explains why it is so vital to start children on Trikafta as soon as possible: to slow the progression of the disease and the irreversible damage it does to the body.

People with cystic fibrosis may take over a hundred different pills a day, along with an hour more of chest physiotherapy, and preparation and inhalation of aerosolized drugs, and injection of others, like insulin or i.v. antibiotics. Virtually all currently accessible therapies treat individual symptoms or individual organs. All people with cystic fibrosis take these symptom management drugs to survive. Their caregivers help them manage these medicines as well as their chest physiotherapy, not to mention countless other things that many Canadians with cystic fibrosis can’t do because of their disease.

Our survey findings indicate that the burden on caregivers of individuals with cystic fibrosis on SOC in terms of time and energy is significant. Of the caregivers of adults, 40% spend 10 hours or less per week on caregiving activities, but 33% spend between 11-20 hours per week and another 27% spend more than 20 hours per week on caregiving activities. Of the caregivers of children only 17% spend less than 10 hours per week, 53% spend 11-20 hours, 17% spend 21-30 hours and another 12% spend over 30 hours weekly on disease management.

While it might seem counter-intuitive that caregivers spend more time caring for children who are in general far healthier than adults, the reality is that care is complex and parents carry the full burden of caregiving, whereas patients typically transition gradually to adult care by increasingly adopting responsibility for their own care. While access to Trikafta will not eliminate standard of care, it can reduce the time and energy required in delivering SOC.

The combined total burden of care on both patients and caregivers to simply follow SOC to stabilize health as much as possible is that of at least a part-time job for most families, and for some families, equivalent to a full-time job, for each patient. For multi-patient households, the burden is multiplied. It should come as no surprise when one parent of multi-patient households typically leaves the work force to care for the children.

Amongst caregivers of children with cystic fibrosis, 60% of reporting caregivers had to take time off work, 12% had to leave full-time work for part-time work, 13% had to quit work altogether and 2% had to take time off school or leave school altogether.

> *I have had to quit my job and go on social assistance when I was a single mother. Now I am married but I still miss work due to my child's condition. – Parent of a child with CF*
>
> *My husband has missed work, I've missed opportunities for work, hospitalization and treatments make it impossible to plan and meet obligations sometimes. – Parent of a child with CF*
>
> *My wife quit her job and became a stay-at-home Mom when our daughter was born – Parent of a child with CF*
>
> *I am a single mother, I can't quit my full-time job - if I could, I would to care for my daughter. Instead I juggle hospital stays and remote working while she is in hospital or off sick. – Parent of a child with CF*
>
> *I have just been fired from 10 years of employment with no notice or severance as my performance suffered too much due to caregiver burn out. – Parent of a child with CF*

More than two thirds (72%) of reporting caregivers said that caregiving had a negative impact on their mental health while 11% felt that it had a positive effect. Parents and caregivers have an overwhelming desire to do something to help their loved ones. The observation of one parent suggests that caregiving may help counter the negative impact the diagnosis has on mental health. Just over half – 55% – of caregivers said caregiving had a positive impact on their relationship with the recipient. Seventeen percent felt it had a negative impact.

> *I have had mental health problems watching my child fall ill. – Parent of a child with CF*

When asked about what their child taking Trikafta could mean for them personally, caregivers said:

> *If my child received this drug, I believe it could improve her health so much so that we would feel comfortable having our lives return to a more normal social state. Such as in having her enroll in school and outside activities and travel, and allow my return to my career. Our family life and social life would greatly improve and benefit in our overall mental health. The stress of having to protect her health has completely altered our lifestyle, it keeps us from living a full life, we live an isolated life in protecting our childs health without any modulators, a decline in health is very real concern and it affects us greatly in our quality of life. – Parent of a child with CF*
>
> *I hope that my child would experience the benefits of a better mental health, better physical health. It would bring relief to us as parents, however it is about the emotional experience my child has to go through living with this disease. – Parent of a child with CF*

We hope for access to Trikafta...no matter the age or current health status. I truly believe by accessing Trikafta, not only will my childs health be greatly improved both physically and mentally. But it would allow our child and our family to become happier and much more fulfilled in life and much better contributing members of society. Our child would benefit by having a much more carefree childhood and experience all the fun things a child should instead of being held back and isolated from doing things due to her health, so her overall wellness would be an amazing improvement. We could more easily see a future and a healthy long life for our child like her peers instead of fearing the fatal disease that cripples our family. Our caregiving duties and stress would be greatly reduced to much more manageable levels without the constant fear and worry of the future of our childs health. Our mental health overall would benefit from this as well. I as the full-time caregiver, could return to my career that I had to leave when our child was diagnosed. Not only that, but by accessing these drugs, the health care system wouldn't be so burdened by the constant need for medical intervention and hospital stays to help and deal with the progression of the disease. – Parent of a child with CF

5. Improved Outcomes

Trikafta is the first, third-generation CFTR modulator. It has the potential to treat up to 90% of Canadians with cystic fibrosis and represents the single biggest advancement in treating cystic fibrosis in the history of the disease. It's 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. The Washington Post named it number one of nineteen good things that happened in 2019[7]. In 2021, almost 500 media stories were written about the drug in Canada, as was outlined in CF Canada's October 26 submission to INESSS regarding the access criteria it recommended for Trikafta.

Canadian research released in August 2020 predicts that rapid access to Trikafta could result in extraordinary health benefits by 2030, including 15% fewer deaths, 60% fewer people living with severe lung disease and an increased estimated median age of survival for a child born with cystic fibrosis of 9.2 years[1]. Understandably, expectations amongst the cystic fibrosis community are high, but also down to earth. Patients often simply want, and hope for, 'normalcy', and now that more people in Canada can access Trikafta, that sense of normalcy feels within reach for many.

My hope is that with access to Tikafta, my child will gain weight and lung function. Hopefully, he might be able to 'live' as other 10 year olds do- including partaking in activities that other 10 year olds do. Currently, he is a prisoner to his disease as he is restricted around his daily therapies which take time, knowledge and dedication. He is very embarrassed and aware that he requires extra support/therapy that other kids do not- even something as simple as taking enzymes at lunch time. He is very self conscious of this and he has voiced that he tries not to cough and refrain from going to the bathroom as he doesn't like to draw attention to himself in the classroom. As a mother, I only want the best for my child and to see him live a happy and healthy life. My hope is that Trikafta will be able to take him one step closer to that dream and maybe one day, his CF will be a controlled condition- not something he fights on a daily basis. – Parent of a child with CF

I am a 29 year old male living with cystic fibrosis, I truly believe this drug will finally change me to the point where I can finally think of myself as "normal" or "healthy" i've never known what its like to feel like a normal healthy person. I feel alienated in my own body. Living with Cystic Fibrosis is not easy. Growing up as a young boy in elementary school I went to school every day thinking I was different than every other kid there, and not different in a good way. I truly believe this drug can help me have a sense of normalcy. – Adult with cystic fibrosis

From popping pills and puffing in salt water to lunch breaks spent forcing myself to cough and strategically planning my grocery shopping trips... Living with cystic fibrosis means constantly trying to balance being normal and being chronically ill. It's more than just taking medication. I have to make choices all day, every day to make my health a priority, while still finding time to enjoy an evening out and taking snapchat selfies.
Unless you or a loved one has lived with it, what most people don't realize about cystic fibrosis, or any chronic illness, is that there's much more to it than just taking medications. Being sick is practically a full-time job and affects nearly every aspect of your life. Everything from simple tasks like grocery shopping, to making huge life decisions like what career field I wanted to go into have been influenced by my health.

Every day for me is a "sick day" because every day comes with an hour and a half to two hours' worth of inhaled medications and airway clearance, five hours of being hooked up to a feeding tube, over two dozen pills and vitamins, another two dozen digestive enzymes and over 50 units of insulin. But the truth is... that's a "good" sick day.

Some days I have more than that because as I like to call it, I'm "sick sick". When I'm fighting a virus or infection, which I was during this day, I spend at least 4 hours a day actively hooked up to IV therapy through a mediport that's permanently embedded in my chest wall. I double my respiratory therapy and I add in various other medicines as needed like nasal sprays/rinses, pain and nausea management medications. Or I get put on steroids, which mean doubling my hydration to avoid my digestive system from developing an obstruction. Those weeks are when CF rears its ugly side and wreak havoc on my daily life.

All in all though, I'm fortunate enough to be able to keep an active, normal lifestyle on top of managing my health. That hasn't always been true, I've struggled more in the past and it won't always be true in the future. Cystic fibrosis is a progressive disease and it will get worse as I get older. There's no way to sugar coat that. But there is a way to be thankful for the beautiful life I have now and live each day to the fullest, being the best person, patient and advocate for cystic fibrosis that I can be!

Please note, not every person living with cystic fibrosis will take these same medications or make these same decisions. Each person, even each day, can look different. But this is my story and I hope you all enjoy hearing it! - Adult with CF

I am overcome with the personal stories and clinical improvements in lung function that people have on trikafta. My daughter is 8, her last PFTs came in at 55%. I truly believe that trikafta would give us time between illnesses, time to work and be a part of our community, time to enjoy life and get breaks for mental health stability. Every time she gets a cold now, without a modulator, she requires increased medications and therapies. Trikafta will reduce the amount of time she is isolated (and me!). No other modulators will help her, she has 1 D508 and a class 1 mutation 711+1G>T. This is our hope. – Parent of a child with CF

Patients long for the ability to breathe unencumbered, to live without fear that normal activities will cause further damage. They also want to be able to contribute to society. Parents and caregivers hope for better, healthier lives for their loved ones.

Access to Trikafta would change our world completely, my son would be able to achieve and pursue his goals and dreams, countless medical appointments and other medications would be reduced, family productivity now and in the future with go up exponentially, all of a sudden you would have thousands of individuals and their families who could focus on careers, businesses the overall long-term economic benefit would be tremendous. – Parent of a child with CF

My daughter would have fewer hospitalizations, more time being a kid. She would live a MUCH longer life. Have hopes and dreams. Less stress and less worry about dying. Be a normal 11 year old. Go to school, play with friends. I would get to be a mom. I wouldn't have to be a nurse and doctor and advocate. I could be the mom I always wanted to be. – Parent of a child with CF

As described above, cystic fibrosis is a highly heterogeneous disease, with many possible symptoms. Clinical progress is highly variable, even amongst individuals with the same CFTR mutations. Individual patients may be more dramatically impacted by different symptoms, all of which can have a negative impact on survival.

Even though my daughter is far below the minimum age at this time, to have the promise of Trikafta to look forward to would be an amazing thing- knowing that she would have the chance to save her health from the earliest possible time and live as normal a life as her sisters. To not have to worry about the likelihood of multiple hospitalizations every year, or having to wait for and endure a lung transplant, or develop further CF-related complications would be an incredible relief. – Parent of a child with CF

Many patients struggle with maintaining their weight, (a concern given that a low body mass index (BMI) correlates with poor post-transplant outcomes and correlates negatively with survival in general) and believe Trikafta will help achieve a healthier BMI. – CF clinician

Cystic fibrosis is a relentlessly progressive disease. Young patients with mild disease may live nearly normal lives because the progressive damage that is occurring to their organs has not yet manifested in ways that can be seen without clinical measures. Many patients and their clinicians see Trikafta's potential to slow the progression of the disease or prevent co-morbidities from developing in the first place as the most important potential benefit.

> *Having access to Trikafta would give me the opportunity to strive toward my goal of becoming a doctor and helping others the way I have been helped throughout my life. I would be able to have children and live a relatively normal life without having the extreme physical and mental challenges that cystic fibrosis causes. [Without] Trikafta, there is no guarantee I will live past 25 years old as it is very unpredictable. Currently, my lung function is high but Trikafta is a medicine that works best in preventing damage. I need to have access to it before the damage becomes irreversible. – Adult with cystic fibrosis*

> *I hope it will slow the progression of my disease so that I have the ability to live more comfortably in the moment without being in constant state of distress over what my future holds.– Adult with cystic fibrosis*

> *My daughter is 3. Access to Trikafta at a young age could mean fewer hospitalizations, fewer medications, less lung deterioration or slower deterioration. It literally could mean that she could get pregnant when older, have a family, work full time and have a future that includes planning for retirement not early death. LIFE CHANGING both physically and mentally for us all. – Parent of a child with CF*

Even individuals currently on a CFTR modulator anticipate seeing a benefit from switching to Trikafta.

> *I am currently on Orkambi and although it has helped me greatly, I believe Trikafta will help me more now that I am beginning to plateau on Orkambi. – Adult with cystic fibrosis*

Prior to its approval by Health Canada the anticipation for this drug was exceptionally high.

> *I grew up hoping for something like this. It is a daily struggle right now to live, especially knowing that there is medicine that could help me. It is a special kind of hell. – Adult with cystic fibrosis*

6. Experience With Drug Under Review

Some public programs in Canada started reimbursing Trikafta as soon as September 2021. As of November 2021, some private drug and all public programs in Canada had committed to covering Trikafta for those who meet the eligibility criteria. Unfortunately, eligibility criteria are not uniform across payers or jurisdictions, in part because CADTH's recommendation for coverage for those 12 years old and over placed a controversial upper limit on lung function. With one exception, no other jurisdiction worldwide has placed such a restriction on access. The Health Canada indication is currently limited to those who are 12 years of age or older who have at least one copy of the F508del mutation.

As a result of the relatively recent public reimbursement of Trikafta, most patients with experience with the drug accessed it through either clinical trials or through the Special Access Program (SAP). Fifty-seven respondents to our January 2021 survey had experience with Trikafta. Sixteen were part of a clinical trial on Trikafta and continued to access Trikafta, whereas forty-one received access to Trikafta through the SAP. These are two distinct populations. The clinical trials recruited patients with mild to moderate disease (FEV1 between 40%-90% predicted normal), whereas the SAP grants compassionate access to patients with advanced disease, (FEV1 is invariably below 40%. We are unaware of a lower limit). Fifty-three of the above respondents offered descriptions of their experience with Trikafta[8]: forty-six (87%) found their experience with Trikafta to be very positive, six (11%) found it to be positive. One respondent (2%) indicated a neutral experience. There were no negative or very negative experiences reported.

Of the 57 total respondents with experience with Trikafta 53 offered detailed descriptions of their experience. Figure 1 shows the percentage of the 53 respondents who felt Trikafta improved various clinical parameters, but importantly also reveals the impressions of patients beyond what was measured clinically. For example, 72% believe that Trikafta decreased the rate of progression of symptoms. Three other subjective parameters support the very positive impact that Trikafta had on quality of life: 75% of respondents felt they had more energy, secretion clearance improved for 67% and just over 50% believe Trikafta improved both sleep (51%), and mental health (52%).

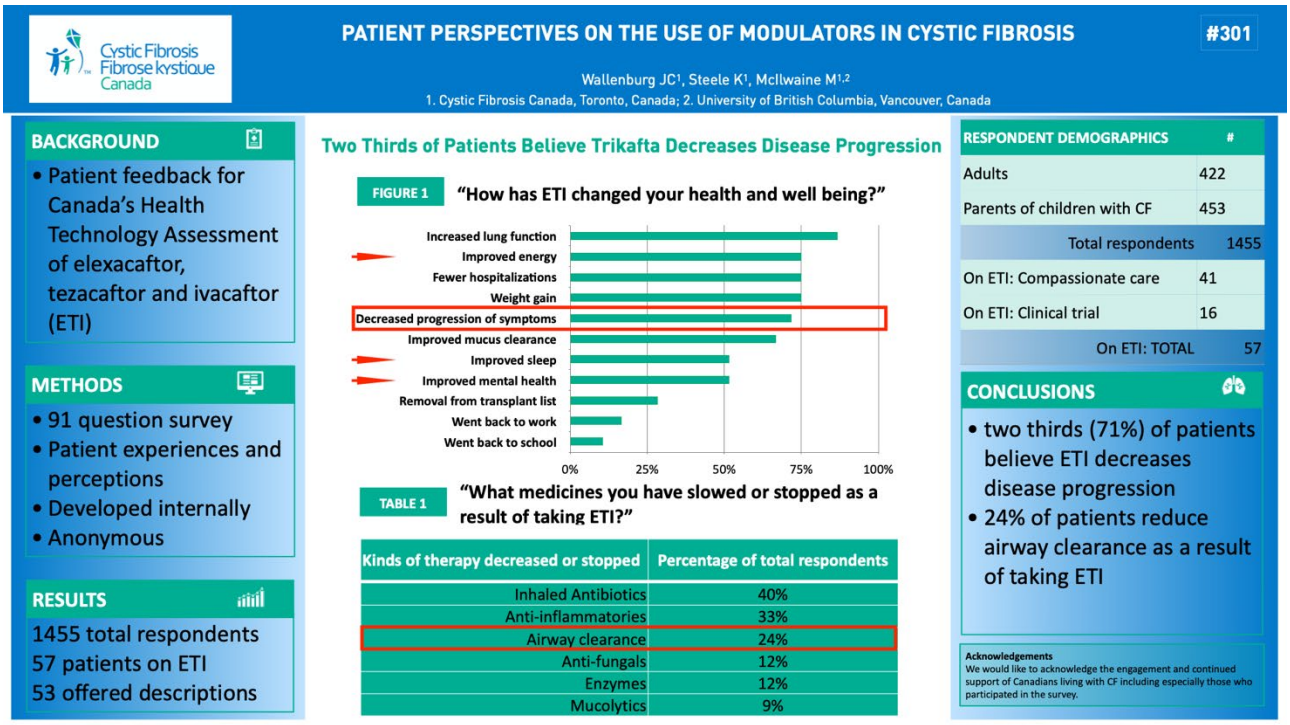
Lung function has increased by over 10%. No side effects have been experienced. - Parent of a child with CF

My son has had a 180 degree turn around in his health. We are so very blessed. - Parent of child with CF

Amazing improvements in weight, energy and lung function – Parent of child with CF

Total game changer. Weight gain, hasn't been sick at all since starting trikafta about a year ago – Parent of a child with CF

Figure 1: Poster: Patient Perspectives On The Use Of Modulators In Cystic Fibrosis



Of the clinically measurable parameters, patients reported that Trikafta improved lung function better than other therapies for 84% of the respondents, and improved nutrition for 68%. Eighty percent noted fewer pulmonary exacerbations (PEx). **Nine adults under evaluation for transplants were removed from the list.** Side effects were reported in 51% of respondents and included headache (22%), rash (12%), upper respiratory tract symptoms (URTI) (9%), elevated liver enzymes (6%), abdominal pain (10%) and nausea (3%). Respondents also reported on the acceptability of side effects. Headache, URTI and rash were deemed acceptable whereas elevated liver enzymes, abdominal pain and nausea were not.

People with cystic fibrosis have a very heavy treatment burden. To what extent does the improvement in quality of life that Trikafta brings lead to changes in the treatment burden? Significantly, 60% of respondents described slowing or stopping therapies as a result of taking Trikafta (Table 1 in Figure 1). Five of the six therapies listed in Table 1 (see Figure 1) could reasonably be reduced because of improved clinical symptoms. For example, a reduction in infections and /or PEx could readily lead to a reduction in antibiotic use or anti-inflammatories, and similar arguments can be made for anti-fungals, pancreatic enzymes and mucolytics. This is consistent with the results of the clinical trials, and in time should be confirmed with Registry data for the population at large. However, there is no reason for reducing airway clearance therapy, except personal choice, and 24% of respondents admitted to slowing or stopping airway clearance therapy. Standard of care calls for all patients, including children with healthy appearing lungs and non-productive coughs, to performance airway clearance therapy at least twice daily. Adult patients typically have positive feedback that coughing is productive – they produce and expel contaminated sputum. It might seem reasonable to patients whose sputum production is significantly reduced after starting on Trikafta, to also reduce airway clearance. This is not recommended but may be a natural outcome from dramatically improved quality of life after a very heavy life-long treatment burden.

See section 4 for the detailed description of this individual's experience on Orkambi, then Symdeko. Here, their experience with Trikafta is presented.

> *I had the privilege of accessing Orkambi in 2016, Symdeko in 2018 … Unfortunately, my CF lung disease, though progression was slowed, was severe at this point and I had several complications in 2019 which led to testing to initiate the lung transplant process.*
>
> *Fortunately, before that process was complete, I was approved for compassionate access to Trikafta in summer 2020. I did not have too high of expectations as I knew how my body did and did not respond to both Orkambi and Symdeko. My expectations were far too low! Trikafta began working within hours of my first dose and the mucous that lined my lungs was purged. Within a couple weeks, I did not need full-time supplemental oxygen, except for cardio exercise and my energy levels were higher than they have been in 10-15 years. I could take a deep breath and laugh without a coughing fit, something I had been unable to do for nearly a decade! I was finally able to participate in my life again instead of watching my family from the sidelines, something I truly believed would not be possible unless I received the gift of life, a double lung transplant. I still have severe CF lung disease as Trikafta cannot repair my scarred lungs and this is why it is so important that this medication be accessible before permanent irreversible damage has occurred so that Canadian children may not have to bear the burden of disease and trauma I have experienced. I can only imagine what my life would be like right now if Trikafta had been available to me when I was a young child. Since summer 2020, my lung function (FEV1) has increased by over 10 points and continues to slowly increase even 18 months later, which is not supposed to happen with a progressive disease like CF, but does because of Trikafta. In addition to that, before Trikafta, I typically was hospitalized every ±120 days for a minimum of three weeks at a time, for IV antibiotics and therapies to combat the chronic bacteria that live in my lungs. This need for acute care remained the case for much of my time on the previous modulators, Orkambi and Symdeko although my quality of life did improve and my lung function remained stable. I had been taking Trikafta for over 550 days before I needed a two-week hospital admission and this is a huge demonstrable improvement in need for acute care. However, looking beyond the numbers, I now have hope for the future for myself and our family. I am no longer wholly dependent on my spouse for my daily needs and I have confidence that I can carry out my daily tasks and not require days to recover from the exertion of completing them. I can tackle my basic needs like my airway clearing physio, household chores, groceries and still have energy for activities with my family and these are things I am forever grateful for. – Adult living with CF*
>
> *For the past 30 years, my parents have prayed and hoped for a drug that could cure CF. Trikafta is the closest thing we have ever seen. It is, truly, a miracle drug. I am one of the incredibly lucky few chosen to take part in the drug trial while it was being tested. My health improved dramatically, and almost overnight. When I began the trial, my CF lung function indicator, FEV, was around 75%. It had been decreasing 1-2% every year for the last 10 years. Within 2 weeks my FEV was back up to 89%. Two weeks later I was at 94%. My mother cried when I told her. Those were numbers I hadn't seen in more than a decade. In addition to measurable FEV numbers, my stamina was way higher. I am an avid mountain hunter and I didn't get winded nearly as quickly as usual. My digestive system became less volatile. My energy levels were up, my appetite increased dramatically. And, perhaps the most shocking thing of all, I gained weight! From when I started the drug to today, I am up 20 pounds. That is mind-blowing. My doctors actually had to tell me to decrease the amount of high fat foods I was eating. Those were words I never thought I would hear in my wildest imagination. – Adult with cystic fibrosis*

Twenty percent of respondents to our January 2021 survey were parents of one or more children with cystic fibrosis aged 11 years or younger. As reported by responding caregivers, 5.8% of children 11 years of age or younger accessed Trikafta as part of a clinical trial, and none received the drug through the Special Access Program. Given that Trikafta is not yet available for sale in Canada, the 11 children with cystic fibrosis aged 6-11 years who gained access through clinical trials are the only group with lived experience with the drug for whom we have data. Their experience is included above. Of the 11 children who participated in trials and whose parents responded to the survey, nine felt the experience was very positive, and two that it was positive. There were no neutral, negative or very negative responses. When asked to explain their responses, they described the following changes in their child's health:

> *My son has had a 180 degree turn around in his health. We are so very blessed. – Parent of a child with CF*

My son has never enjoyed better health than he has since accessing this drug. His chronic intestinal issues have cleared up (within days) and he had the longest period in his life without antibiotics. He's gained weight and height at a rapid rate. He looks healthy. – Parent of a child with CF

My son very healthy – Parent of a child with CF

Amazing improvements in weight, energy and lung function – Parent of a child with CF

We have seen some improvement in PFTs – Parent of a child with CF

Total game changer. Weight gain, hasn't been sick at all since starting trikafta about a year ago – Parent of a child with CF

Their growth and health has been excellent. – Parent of a child with CF

Lung function has increased by over 10%. No side effects have been experienced. – Parent of a child with CF

It's like she doesn't have CF anymore. She doesn't cough, she doesn't produce mucous, she is full of energy, she has an appetite and gains weight normally, she sleeps better, the list goes on! – Parent of a child with CF

Most parents felt that headache or nasal congestion were acceptable side-effects, whereas high liver enzymes and cataracts were not. Not surprisingly all parents felt Trikafta was easier to take than other CF medications, especially when compared to nebulized symptom management medications. In addition, as one parent described it: "i*t's a struggle to have my child take [other medications] as he saw no benefit. With Trikafta he saw the benefit immediately and since then I have never had to fight or force him to take any of his medications*." Table 1 shows the responses when parents were asked "How has Trikafta changed your child's health and well-being?". The question allowed parents to choose all answers that apply.

Table 1: How has Trikafta changed your child's health and well-being?

Answer Choices	Responses	
Increased lung function	83.33%	10
Weight gain	75.00%	9
Improved energy	58.33%	7
Slowing or stopping progression of symptoms	50.00%	6
Fewer hospitalizations	50.00%	6
Improved mucus clearance	41.67%	5
Improved mental health	25.00%	3
Went back to school	25.00%	3
Improved sleep	16.67%	2

This group of patients is of importance because cystic fibrosis is a progressive disease and this age group is generally in better health than older cohorts. This is reflected in data available for this category in the Registry. Of the individuals with spirometry records in the Registry (99% of individuals with CF over 12 yrs have a documented ppFEV1, 91% of individuals aged 6-11 have at least one documented ppFEV1) 73% of children aged 6-11 have a ppFEV1 >90% predicted, whereas only 27% of patients 12 and older test at >90% predicted (Stephanie Cheng, Director, Registry, Cystic Fibrosis Canada, personal communication). Disease progression is evident when looking at the median ppFEV1 vs. age of individuals with cystic fibrosis. There is a steady, rapid decline in lung function from the earliest recorded spirometry measures through a patients' early twenties (figure 17[3]).

There are few published studies that have looked at the 6-11 year old cohort specifically, however Zemanick et.al. evaluated the safety and efficacy of Trikafta in younger patients in a 24-week phase 3 open-label study in children 6 through 11 years of age with cystic fibrosis and at least one F508del CFTR allele. Their results show that the safety and efficacy of Trikafta in the children studied are consistent with those reported in adults and adolescents with cystic fibrosis, supporting the use of Trikafta in this younger patient population. Their results demonstrate that "the safety and efficacy of ELX/TEZ/IVA in these children are consistent with those reported in adults and adolescents with cystic fibrosis, supporting use of ELX/TEZ/IVA in this younger patient population."[9]

Reflective of the generally better health of the 6-11 yr old cohort, subjects in Zemanick et.al. study had substantially higher baseline ppFEV1 (~89%) than seen in the phase 3 studies in the 12 yr and older cohort (~62%). Baseline quality of life as measured by CFQ-R respiratory domain scores were also substantially higher. Despite the higher baselines, treatment with Trikafta led to significant improvements in both ppFEV1 (10.2%) and CFQ-R respiratory domain scores (7 points), consistent with results from other CFTR modulator studies.

The recently published interim results from the Phase 3 open-label extension of the above trial confirmed the initials observations that Trikafta was generally safe and well tolerated. In addition, the "clinically meaningful improvements in lung function, respiratory symptoms, systemic CFTR activity, and nutritional parameters observed in the pivotal study were maintained through week 24 of the OLE study"[2] confirming that Trikafta provides durable benefit in 6-11 year old subjects**.**

Importantly, the mean ppFEV1 baseline score for 6-11 year olds was 88.3%, very close to the upper limit of the inclusion criteria for the pivotal phase 3 study of Trikafta in patients 12+. CADTH's controversial recommendation to limit access to Trikafta to patients whose baseline ppFEV1 is ≤90% seems anchored in the suggestion that no evidence exists to support its benefit to patients whose baseline ppFEV1 90%. It is clear from the data of the Zemanick et.al. and Ratjen et.al. publications cited above, that Trikafta provides significant clinical benefit to all patients regardless of initial status.

This is also reflected in the feedback from caregivers.

> *There are no words to describe the improvement in my mental health. My anxiety attacks have stopped. I can sleep through the night. I actually have time for myself. Watching my sons health improve and seeing him be able to function and have the potential to become a productive member of society rather than live a bed ridden sick life has been the miracle I had always prayed for. – Parent of a child with CF*
>
> *His own outlook has dramatically improved and he looks forward to waking up, going to school and going to work. He has a second chance at life that he does not take for granted! Trikafta has blessed our family in so many ways and we are forever grateful – Parent of a child with CF*
>
> *This medication is a life changer. I feel so fortunate that my son has access but I worry about when the trial is over. We need this medicine in Canada. – Parent of a child with CF*
>
> *I'm hopeful that Trikafta will have a long term positive results for my daughter's health.– Parent of a child with CF*

Benefits to healthier patients with baseline spirometry greater than 90% was also confirmed in the findings of the PROMISE study, a post-approval, real-world, observational study to understand the effects of Trikafta in clinical use in the USA[10]. Nichols et.al. found substantial improvements across a range of clinical outcomes, including for a large subset of 196 patients whose baseline ppFEV1 was at or above 90% that saw a clinically significant mean improvement of 6.5% as well as improvements in CFQ-R of over 15 points, and an increase in mean BMI of +0.82.

The lived experiences of Canadians who have recently gained access to Trikafta or have a prolonged experience with it are consistent with the results observed in the clinical trials, the open-label extension studies and the post-approval real-world observational studies. In all cases, and regardless of baseline spirometry measures, patients see significant benefits.

> *I no longer want to celebrate the day that I was born. The day I truly want to celebrate is my Trikafta birthday. This is the first day that I have a sense of a future. Blowing out the candles on my cake on my first anniversary of Trikafta was so incredible, and I had the breath to blow out every single candle. My real birthday was counting down until death, and my Trikafta birthday is about counting up. And it's about life. – Adult with CF*

> *My son has never enjoyed better health than he has since accessing this drug. His chronic intestinal issues have cleared up (within days) and he had the longest period in his life without antibiotics. He's gained weight and height at a rapid rate. He looks healthy. – Parent of a child with CF*

> *It's like she doesn't have CF anymore. She doesn't cough, she doesn't produce mucous, she is full of energy, she has an appetite and gains weight normally, she sleeps better, the list goes on! – Parent of a child with CF*

7. Companion Diagnostic Test

Trikafta is currently indicated only for patients having at least one F508del mutation. As of December 2021, there are over 2100 known mutations of the CFTR gene, according to the Cystic Fibrosis Mutation Database (CFTR1). Fortunately, in Canada, genetic mutations have been identified and recorded in the Registry for 99% of all living Canadians with cystic fibrosis who were seen in a cystic fibrosis clinic in 2019 so patients eligible for Trikafta are readily identifiable.

Mutations of CFTR are generally classified according to structural functional defects into one of more mutation classes, ranging from I to VI[11]. F508del is classically considered a class II mutation as are many other, often rare, mutations and the possibility that Trikafta may be effective for other mutations is an area of active investigation. Preclinical model systems played a critical role in the development of CFTR modulators and have the potential to support the use of modulator therapies in new populations[12]. The US Food and Drug Administration (FDA) has in fact accepted the concept that positive drug responses in a laboratory system using Fisher Rat Thyroid (FRT) cells may be used as a surrogate for clinical efficacy and has used *in-vitro* data derived from that system to extend the label of Kalydeko, Symdeko and Trikafta to include multiple rare mutations[13].

While it is not currently possible to determine who will benefit from Trikafta in advance of administering the drug, a number of studies are underway to identify *in-vitro* assays with the potential to predict clinical response to CFTR modulators at an individual level[14]. Cystic Fibrosis Canada has partnered with the Hospital for Sick Children and Genome Canada on a project to develop predictive tools that will help clinicians determine the right medicine for the right patient[15]. In addition, trials are underway in Europe to use rectal organoids to test in vitro a patient's response to drugs[16].

In summary, the entire Canadian population of patients eligible for Trikafta are already identified for the clinicians that will ultimately prescribe the drug. Canada's CF clinicians have the Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis in place to help them manage access to modulators, including Trikafta. The Canadian Cystic Fibrosis Registry will continue to track all patients on the drug allowing for post-approval analyses of Trikafta's benefits and limitations and laboratory tools that will predict whether a patient is expected to benefit from a drug are under development and should be available soon.

8. Anything Else?

CADTH's recommendation with respect to the use of Trikafta for Canadians aged 12 and over living with cystic fibrosis was largely sound but included an ill-advised ceiling on eligibility limiting access to patients with a baseline ppFEV1 of ≤90%. This decision was based not on evidence but on the absence of it. As cited above, ample evidence now exists supporting the use of Trikafta in all populations approved by Health Canada.

Furthermore, Cystic Fibrosis Canada's key recommendations are that:

- CADTH recommend that Canada's public drug programs fund Trikafta for those who are 6+ without any upper limit on lung function start criteria.
- CADTH work with Canada's public drug programs to empower CF clinicians to guide prescribing and renewal activities, as governed by the Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis.
- CADTH recommend that *in-vitro* testing be accepted by Canada's public payers as effective tools for identifying rare mutations that will benefit from CFTR modulators as soon as correlation with clinical outcomes have been confirmed.

Appendix: Patient Group Conflict of Interest Declaration

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

   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.

   No.

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.

   Please see next page.

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie				x
Horizon Pharmaceuticals			x	
Mylan Pharmaceuticals ULC				x
Vertex Pharmaceuticals Canada				x
AstraZeneca Canada Inc	x			
Bayer Canada Inc	x			
Gilead Sciences Inc				x
Merck Frost Canada Inc			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. John Wallenburg

Position: Chief Scientific Officer

Patient Group: Cystic Fibrosis Canada

Date: December 16, 2021

References

1. Stanojevic, S. *et al.* Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. *J. Cyst. Fibros.* 109, 1521 (2020).

2. Ratjen, F. *et al.* 562: Elexacaftor/tezacaftor/ivacaftor in children aged 6 and older with cystic fibrosis and at least 1 F508del allele: Interim results from a Phase 3 open-label extension study. *J Cyst Fibros* 20, S265 (2021).

3. *The 2019 Annual Data Report of the Canadian Cystic Fibrosis Registry*. https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf (2020).

4. Stanford, G. E., Dave, K. & Simmonds, N. J. Pulmonary exacerbations in adults with cystic fibrosis - a grown-up issue in a changing CF landscape. *Chest* 159, 93–102 (2021).

5. Quittner, A. L. *et al.* International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and …. *Thorax* (2016).

6. Wallenburg, M. Typical day at home. *Typical day at home* https://marikasmotorcyclediaries.wordpress.com/2014/02/19/typical-day-at-home/ (2014).

7. Editorial Board. Opinion: 19 good things that happened in 2019. *Washington Post* (2017).

8. Wallenburg, J., Steele, K. & McIlwaine., M. 301: Patient perspectives on the use of modulators in cystic fibrosis. *J. Cyst. Fibros.* 20, S145 (2021).

9. Zemanick, E. T. *et al.* A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. *Am. J. Resp. Crit. Care* 203, 1522–1532 (2021).

10. Nichols, D. P. *et al.* Clinical Effectiveness of Elexacaftor/Tezacftor/Ivacaftor in People with Cystic Fibrosis. *Am. J. Resp. Crit. Care* (2021) doi:10.1164/rccm.202108-1986oc.

11. Veit, G. *et al.* From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Molecular biology of the cell* 27, 424–433 (2016).

12. Clancy, J. P. *et al.* CFTR modulator theratyping: Current status, gaps and future directions. *J Cyst Fibros* 18, 22–34 (2019).

13. Goor, F. V., Yu, H., Burton, B. & Hoffman, B. J. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. *J. Cyst. Fibros.* 13, 29–36 (2014).

14. Dumas, M.-P., Xia, S., Bear, C. E. & Ratjen, F. Perspectives on the translation of in-vitro studies to precision medicine in Cystic Fibrosis. *Ebiomedicine* 73, 103660 (2021).

15. Eckford, P. D. W. *et al.* The CF Canada-Sick Kids Program in individual CF therapy: A resource for the advancement of personalized medicine in CF. *J. Cyst. Fibros.* 18, 35–43 (2019).

16. Mourik, P. van *et al.* Rationale and design of the HIT-CF organoid study: stratifying cystic fibrosis patients based on intestinal organoid response to different CFTR-modulators. *Transl. Medicine Commun.* 5, 9 (2020).