CADTH

CADTH REIMBURSEMENT REVIEW

Patient Input

ELEXACAFTOR/TEZACAFTOR/IVACAFTOR AND IVACAFTOR (TBC)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Triple Combination Therapy (elexacaftor/tezacaftor/ivacaftor and ivacaftor) tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

CADTH received patient input from:

Canadian Cystic Fibrosis Treatment Society

CF Get Loud

Cystic Fibrosis Canada

February 12, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Elexacaftor/tezacaftor/ivacaftor and ivacaftor for the treatment of Cystic fibrosis, F508del CFTR mutation**
Name of thePatient Group	**Canadian Cystic Fibrosis Treatment Society**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Canadian Cystic Fibrosis Treatment Society was incorporated as Not For Profit Organization in 2014. Its singular mandate is to advocate for individuals with cystic fibrosis (CF) that require access to medications and medical procedures that save and improve lives.

In carrying out this mandate we challenge, where necessary, private insurance companies, pharmaceutical companies, government and its agencies or quasi-judicial agencies, health charities and hospitals and the health care system. Our challenge to each of these entities is to rise to the occasion and ensure that no one with cystic fibrosis is left without the medical treatment that they require and that their physician has prescribed for them.

We carry out this advocacy in the boardroom and have, when necessary, also worked with patients and law firms to advance a patient's interest in the court room.

The organization is founded by Chris MacLeod who has cystic fibrosis and was in need of the life sustaining medication Kalydeco in 2012. He was on 4 litres of oxygen a minute and had spent weeks on end at St. Michaels Hospital in Toronto with limited to no meaningful response to intravenous antibiotic treatment. He was recommended for Kalydeco by his treating physician. Kalydeco had not yet been submitted to Health Canada. He was permitted compassionate-use by the manufacturer but the medication was not allowed in through the Special Access Program.

He realized that there was no one who advocated for individuals with CF in situations such as the one he found himself in. He pulled together a team and secured access for himself to Kalydeco. However, it was clear that an organization needed to be established to advocate for individuals with CF when they needed treatment and access to such treatment was denied. The Canadian CF Treatment Society is housed at his law firm, Cambridge LLP. It is through the support of his firm, his law partners and the volunteer members of the Board of Directors that the work of the Treatment Society can proceed.

Our website is www.cfadvocacynow.com

2. Information Gathering

The information in this submission has been gathered through one-on-one and group discussions with individuals with cystic fibrosis as well as parents, caregivers and treating physicians. In addition to speaking with hundreds of Canadian patients and caregivers, the CF Treatment Society spoke with more than 20 out of the 150 Canadians who have accessed Trikafta through Health Canada's Special Access Program / compassionate use program of the manufacturer. Hundreds of Canadian patients, CF parents and caregivers have reached out to me proactively to learn more about the CF Treatment Society and what we do.

3. Disease Experience

CF is insidious in that the individual from birth is in a constant battle with lung infections. The infection doesn't rest. It attacks the lungs relentlessly until the patient simply cannot get sufficient oxygen to sustain life. The damage to the lungs is too great to recover and either a lung transplant is required or they expire.

While this is a multi-system, multi-organ condition, the lungs and the mischief that a given infection causes is ultimately what kills an individual. A central challenge for the patient in the fight of his/her life is summoning the constant daily energy to fend off the infections. To do so requires energy that without gene modulators like Trikafta is simply not possible. It becomes an insidious cycle. You don't have the physical resources because you can't digest the food to fight infection and the infection is constantly and continuously attacking the lungs.

CF is a daily challenge: a constant. A 24/7 battle. Infections don't rest as we see from COVID-19. The experience with the disease today is one that has important rays of hope. A patient with CF born in 1969, life expectancy was just six years. The founder of the CF Treatment Society is now 5 51, and though his health and daily life challenges have been incredibly difficult at times – a feeling like you are drowning – there is now a feeling of hope that the progression can be stopped and even reversed in some cases.

4. Experiences With Currently Available Treatments

Currently-available treatments now include four gene modulator therapies. These drugs normalize the genetic defect in cystic fibrosis. Each drug addresses a different gene type. For example, the founder of the CF Treatment Society has the Delta 551 gene type. Kalydeco addresses the challenges posed by this gene type and the approximately seven other gene mutations that are remedied by Kalydeco. It is nothing short of life changing. This committee will recall it gave approval to Kalydeco in 2012. Gene modulators normalize the genetic defect and there appear to be virtually no side effects.

In the case of CF Treatment Society's founder, experience with Kalydeco for the past eight years has facilitated weight gain to normal levels, providing resources to fight infection and preserve and gain lung function. Lung function has doubled, and people close to him have remarked: "Chris, while you used to cough continuously, you no longer cough." The financial cost of this medication was successfully negotiated by the provincial and federal governments, and now the price is being re-negotiated along with a subsequent gene modulator, Orkambi. One of the biggest challenges patients with CF face is securing publicly-funded access to these life-saving treatments, and this experience has been extremely traumatic, difficult and unnecessary, because in the end, deals are struck that ensure affordability and patients access life-saving medicines. Too many Canadians with CF have lost their lives while waiting for government agencies to make key evaluations and decision, and it is this trauma that has marked much of our collective experience with current treatments.

5. Improved Outcomes

It is critical that the decision, whether or not a medication is provided, be between a doctor and their patient. A treating physician and the patient must ultimately decide the treatment regime for a given patient.

The issue is not necessarily how much lung function you will gain because for all those older individuals, lungs have already been damaged. The first priority is that there be no more decline in lung function and that we can finally have a base line that we do not fall below. From there the patient can work on increasing lung capacity.

Improved outcomes in this context means retaining lung function and, in many cases, increased lung function.

These clinical benefits have massive and positive impacts on patients and families that cannot be overstated. There is generally a feeling of wellness and well-being once a patient commences gene modulators.

There are also economic benefits. In the case of the founder of the CF Treatment Society, the size of his law firm doubled since beginning on Kalydeco. That has meant, the creation of many new high-paying significant jobs. Cambridge LLP also provides a phenomenal group benefit plan to all employees and their families, which is paid for by the firm, therefore, taking people off the government drug programs.

It is vital that we get as many people back on to the ice and playing in the game of life.

To do so, when the private sector cannot cover an individual, the state should step in. The state will only step in and negotiate prices if there is a positive CADTH review.

6. Experience With Drug Under Review

Canadian CF patients who have spoken with the society have described Trikafta as nothing short of game-changing and revolutionary. It is the difference between living a full life, creating jobs, assisting society and improving the life and outcomes of others. As people engage again in life, they work and create wealth and then pay taxes. They also engage in the business of life which is helping the least fortunate amongst us.

7. Companion Diagnostic Test

N/A

8. Anything Else?

It is imperative that this committee understand the full import and significance of this medication. In many ways, your decision on Trikafta will be a referendum on CADTH itself. This drug has had, by all accounts, game-changing, life-saving effects without exception across individuals with cystic fibrosis around the world.

Canada is firmly in last place in looking to publicly reimburse this medication. Sadly, it was a Canadian doctor and researcher at Sick Kids Hospital that was the first to discover the gene for cystic fibrosis at in 1989.

Thirty-one years later, we are now firmly the last to reap the benefits of that discovery.

The founder of the CF Treatment Society can personally attest that as a result of gene modulating therapy (Kalydeco) he has:

- Been healthy enough to act as an articling principal for many law students who wished to enter the legal profession
- Been able to employ young lawyers, mentor and help them with their career
- Worked relentlessly on the protection of Canadian citizens abroad, helping Canadian citizens whose human rights have been violated

None of these activities that help hundreds of others would have been possible without access to life-saving medication.

We all owe it to our fellow citizens to give them this same chance to live a better and longer life and make a difference in their families and society.

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. This submission was completed by myself, CRM.

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. We did not.

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of$50,000
n/a				

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: Chris MacLeod
Position: President/National Chair
Patient Group: Canadian Cystic Fibrosis Treatment Society
Date: Feb 12/2021

CF GET LOUD

CADTH Reimbursement Review
Patient Input

CADTH Reimbursement Review
Patient Input

Name of the Drug and Indication: Triple Combination Therapy/Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor for the treatment of Cystic fibrosis)

Name of the Patient Group: CF Get Loud

Author of the Submission: [redacted]

Name of the Primary Contact for this Submission: [redacted]

Email: [redacted]

Telephone Number: [redacted]

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About CF Get Loud

We are Canadian CF patients and caregivers fighting for CF patients.

CF Get Loud is Canada's largest CF grassroots movement. We were founded and are led by three CF patients and one CF mom. We have grown to represent a community of over 4,000 patients, families and allies across Canada who have gotten LOUD, with the goal of bringing hope, in the form of new life-saving medicines, to our community. Our origin story is a direct response to the barriers to access Trikafta, and we have grown into a mighty advocacy group focused on empowering our community and allies to make change and help overcome the challenges the CF community faces in Canada. Understanding the constantly evolving political landscape and regulatory barriers that restrict and delay access to life-saving medications has been our driving force. Additionally, we strive to look beyond this one issue and aim to serve our community wherever the need arises. We engage with Canadian CF families, and help elevate the voices of those individuals and caregivers with a unified message.

We have felt the hearts of our community through a multitude of conversations, engagements and virtual events. We have learned about the journeys and lived experiences of many CF families; difficulties, triumphs, joys and sorrows that have taken us from laughter to tears and back.

Information Gathering (process)

Our patient advocacy group reaches from coast to coast across Canada. Most of our members are CF patients and caregivers. Since our inception, we have run a number of campaigns for Canadians with CF to share their stories, including their experience with the disease, experience with currently available treatments and the improved outcomes they expect from the drug, as well as experiences with the drug under review.

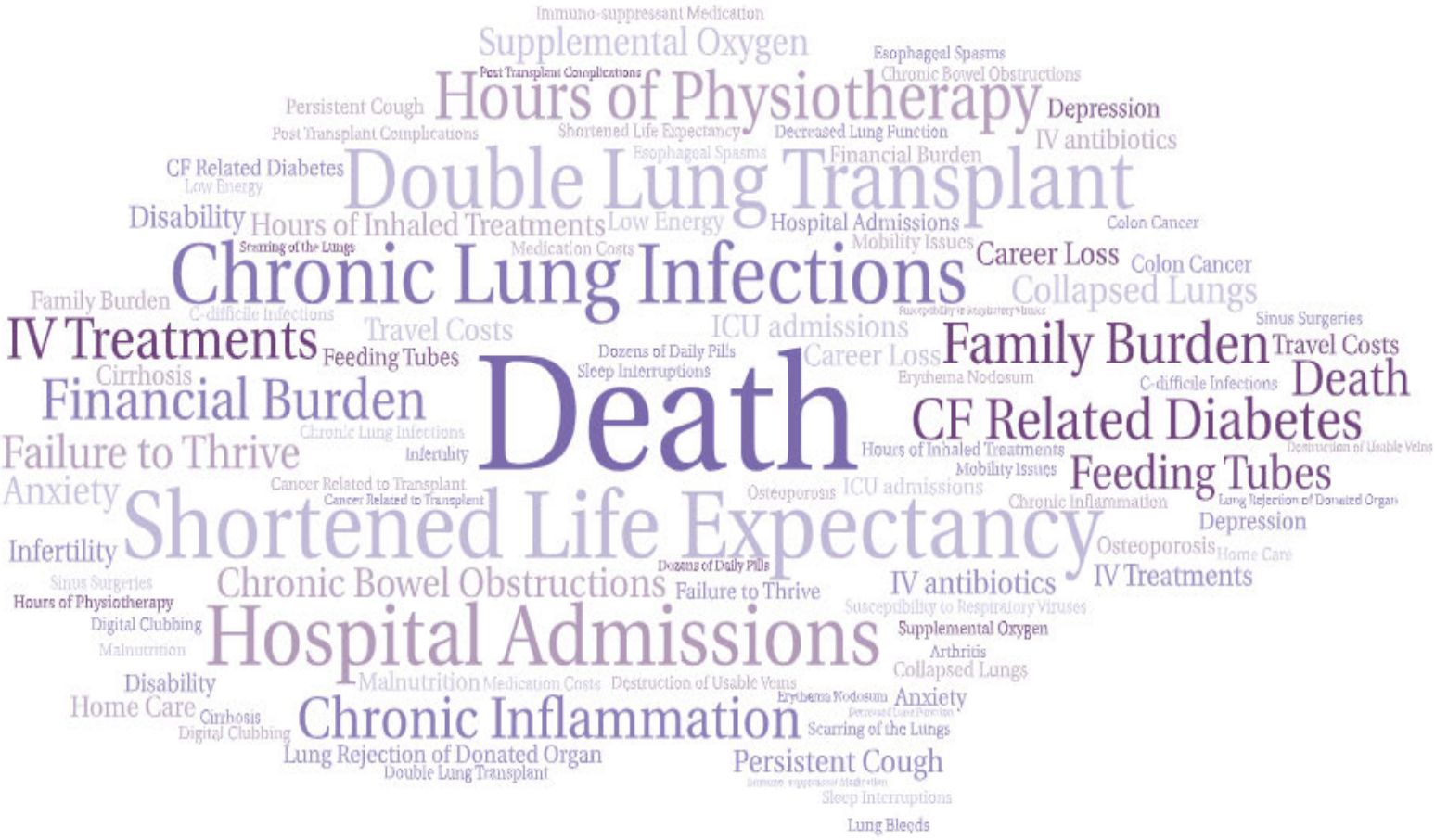
One of our education projects last year was our Letter for Lives initiative (July 2020), in which we received copies of 11,364 letters from Canadians speaking to the unique impact Trikafta has or will have on Canadian lives. We have also hosted a CF community town hall (May 2020), where we heard from experts and leaders in our own community about the ground-breaking nature of Trikafta and what it means for CF families across Canada. Furthermore, we heard from more than 20 Canadians who are currently receiving Trikafta as part of the Compassionate Care program from Vertex administered through the Special Access Program (SAP). Many of these individuals have endured the physically and mentally exhausting journey of undergoing tests and evaluation required to qualify for a double lung transplant, with the hopes of receiving a second chance at life. Due to this life-saving medication, these patients have a unique story to tell in Canada since they have experienced firsthand the dichotomy between staring death in the face and regaining their ability to thrive and be a productive member of society, without having to undergo transplant surgery. This metamorphosis from slowly dying to active living is evident in every single individual we have spoken to and is representative not just of the physical effects of Trikafta, but also the mental and emotional impact that access to this drug will have on Canadian families.

These initiatives and projects have provided CF Get Loud with a diverse and rich data set with a unique and comprehensive perspective of the Canadian CF community and that data has helped to inform this submission.

Disease Experience

CF is a progressive disease that affects primarily the lungs and digestive system, but other organs and systems can be impacted as well. It is a complex and devastating disease. CF results in premature death 100% of the time. However, this no longer needs to be the reality for Canadians with CF, and this evaluation that CADTH conducts can be instrumental in changing that.

The following word cloud visualizes the dozens of feelings, interventions, concerns and issues that Canadians with CF experience. The descriptions have been selected after analyzing over 11,000 letters that were submitted last year, as noted above, and reflect real-world experience from the perspectives of patients and caregivers. These concerns, emotions and impacts on quality of life are further explored and evident in Appendices B & C, which include personal testimonials and photos of Canadians with CF before and after they received Trikafta.



In this context, the goal of a CF patient and their loved ones is to hold the line against irreversible damage to our bodies as steadfastly as possible, for as long as possible. As noted above, CF ends in a painful death, often at a very young age, despite every effort to maintain health for as long as possible.

People living with CF are unable to build enough body mass to fight off infections because our digestive system is compromised, often requiring a feeding tube for supplemental nutrition. Our livers can be damaged and often bear the burden of necessary and frequent antibiotic treatments to keep recurring lung infections at bay. A damaged liver leads some to require a liver transplant and this is unfortunately considered maintenance of the disease if our lungs are capable of carrying on. When these organs manage to remain functional, there are various additional complications that will arise.

In addition to the decline of our bodies, many suffer from the unseen effects of CF. These include, but are not limited to, depression, anxiety and hopelessness. The mental anguish caused by the ever-present awareness of one's mortality cannot be expressed in words and are often not quantified in these analyses.

Experience with Currently Available Treatments

As illustrated above, CF affects many organs and different systems in the body. Treatment for one symptom can create additional negative side effects, exacerbate organ damage and/or other unpleasant symptoms. Available treatments are reactionary in nature and are designed to address the symptoms of the disease. While these treatments can slow the progression of the disease, they ultimately fail. Until the development of CFTR modulators, all available treatments were maintenance medications; therapeutics to manage and react to new symptoms and lung infections as they occur.

The development of CF related diabetes often exacerbates an already complicated balance between specialized nutritional needs and an overwhelming regiment of daily medications. A CF patient will take an average of 70 pills per day and complete approximately three hours of daily inhaled treatments and respiratory physiotherapy. CF patients end up building our lives around treatments and medications rather than have medications and treatments that allow us to live improved lives.

Ruptured veins from repeated intravenous antibiotics often result in PICC (peripherally inserted central catheter) lines and central IV ports which carry their own inherent risks. In addition, drug allergies and the development of bacterial drug resistance often begin eliminating antibiotic treatment options one by one. Despite these numerous medical interventions, the battle against CF is lost, little by little. Lung function gradually (sometimes rapidly) declines to the point that we arrive at the final "currently available treatment" intervention: a double lung transplant.

In short, the currently available treatments involve a rigorous and time-consuming schedule that fills much of our day. Over time, they are hard on all systems of the body and can further the decline of already compromised organs.

Improved Outcomes

Let's be clear: Trikafta is a life-changing and life-saving medication. It will dramatically change much of the current trajectory and burden of this disease provided it is accessible before permanent lung and other organ damage has occurred.

Families who have newborns diagnosed with CF and individuals whose disease progression has been mild or who have not experienced a period of rapid decline will benefit not only from improved health in the short term but also slowed disease progression in the long term. The expected outcome is that CF evolves from being a swift and efficient killer to a disease that is more predictable and can be managed with close monitoring. It is an exciting time to be a CF patient! We now live in a time when a disease caused by a genetic defect can be potentially neutralized and corrected through precision medicine in the form of gene modulators. Months of hospital admissions, many invasive medical procedures and countless minor treatments and appointments will not be required in the same way. The daily burden of disease management will be lifted as some of those treatments either become redundant or more effective and less time-consuming.

For the young adult who is fighting with all their strength to stay alive and slow the deterioration of their health, Trikafta means:

These are not hypothetical outcomes. They represent a consistent account of what life after just a few weeks or months on this life-saving medication looks like. We have experienced this firsthand and have received anecdotal accounts from community members (see Appendix B) who receive Trikafta via the SAP (Special Access Program).

Experience with Drug Under Review

As shown in the section above, there are many positive impacts experienced by those who take the drug under review. However, there are two clinical outcomes that may be the most important and have the most impact on CF patients.

- Deferred lung transplant
- Negative CF diagnostic sweat test (sweat chloride levels below 60 millimoles per liter)

As stated earlier, two of our executive team members at CF Get Loud have firsthand experience with the outcomes presented. Due to their extremely poor health, they were granted access to Trikafta through the SAP (Special Access Program). They have both been able to postpone a double lung transplant that was fast approaching, are revitalized and have gained back their lives in ways that words cannot truly capture.

The primary diagnostic test to confirm a CF diagnosis is a sweat chloride test. Months after starting Trikafta, they both completed a sweat chloride test and the results came back in the normal range, that is, negative for CF. From a diagnostic perspective, their defective genes have been corrected to the point that they no longer test positive for CF which indicates their bodies are working as they should. However, the drug under review cannot reverse years of pre-existing damage, and that is the reason it should be made available not only as a last resort, but also to those who have not declined and sustained permanent damage to their organs that would result in a lower quality of life.

Through our lived experience with the drug under review, and through several comprehensive interviews with other Canadians that have also gained access to it through the SAP, it is important to note that the improved outcomes listed in the previous section are the reality that individuals with CF are experiencing now and have communicated to CF Get Loud.

Visible physical improvements and the decrease of clinical symptoms are one way to view and quantify the positive impacts the drug under review has. In addition to that, and as important, are the unseen symptoms described earlier, the mental and emotional impacts of a medication that changes the trajectory of our disease. These positive impacts, though difficult to quantify, must not be discounted or forgotten.

Hope has been injected into our nightmare. The solution for our losing battle has given us the ability to plan for the future and allowed light to shine into the darkness. The ripple effect permeates all areas of life as personal growth prospects rise, and the doom and gloom start to dissipate. The prospect of family planning and a life beyond the immediate disease management routine starts to become reality. The ability to pursue professional aspirations is rekindled and the prospect of again being a contributing member of society is invigorating and exciting. The societal benefits of the drug under review extend

beyond the scope of our immediate circles and grow exponentially as it gives patients and their caregivers renewed health, purpose, independence and vitality.

Companion Diagnostic Test

There is no companion diagnostic test for this therapy.

Gene modulating therapy works for individuals with specific genetic mutations that respond to the medicine.

Eligibility criteria for the drug under review should be based on genetic mutation only (F508 plus 1) as the US FDA has indicated. If further study determines individuals without a F508 genetic mutation could benefit, they should be eligible as well. Canadians born with CF should have access to every therapy that their genetic mutations respond to if it is approved as safe for their age group.

There must not be restrictions or performance measures attached to the recommendation for this therapy and all those that can benefit from it should be able to access it based on consultation with their CF physician.

The drug under review will have profound impacts on CF patients and their caregivers in Canada provided it is used as intended, as a standard preventative therapy that will prevent and limit damage to our bodies and correct defective cell functions. It should not be a limited therapy to prescribe after currently available medications have failed.

Each individual with CF experiences and are physically/mentally impacted by the disease in unique ways. CF is a complex disease and manifests in various ways depending on the individual so use of performance metrics outside of genetic mutation is an inappropriate and flawed measure. CF Get Loud endeavours to ensure that no CF patient who could benefit is left behind, as miracles of modern medicine become available after a lifetime of research.

Anything Else

Three other CFTR modulators have received Notices of Compliance from Health Canada over the past eight years. Unfortunately, they remain widely inaccessible for most Canadians with CF, with the exception of one drug that most, but not all, who benefit from it are able to access in several provinces. Canada has fallen behind in access for CFTR modulators, including the drug under review. The United States, the EU and the UK have approved use of this drug and their CF patients are benefiting from it as the Canadian CF community waits and deteriorates as our disease progresses. CF can't wait any longer and should not have to as a truly life-saving therapy is suspended out of reach.

On average, we will lose one Canadian with CF per week, with a median age of 30.

Canadians with CF have watched with excitement (as well as some envy) as patients in the US, Europe and the UK share their transformations on social media, accomplishing goals that prior to accessing Trikafta would not have been possible. Some received their second chance over one year ago, before a respiratory pandemic made our lives even more complicated and vulnerable. Please treat this therapy with the **urgency** it deserves so that the health of CF patients in Canada is preserved and more resilient in the face of the COVID-19 pandemic.

Appendix A: Patient Group Conflict of Interest Declaration

Our group has compiled data from advocacy initiatives held since January 2020 that the Canadian CF community participated in. No additional help outside our patient group was received to complete this submission. Our group did not receive any help to collect or analyze the data used in this submission. Our group has not had any financial payment from any company or organization since our inception. We are a patient and family volunteer group.

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: Jacob Jaramillo

Position: Director

Patient Group: CF Get Loud

Date: February 12, 2021

Appendix B: Testimonials

Stephanie Stavros
Greenwood, Ontario

My name is Stephanie Stavros and I am a 37-year-old patient living with Cystic Fibrosis.
Without Trikafta, 2020 would have looked very different. I would either have been recovering from a double lung transplant (if lucky) or my 5-year-old son and my husband would have been grieving my death.

In 2019, I was in end-stage lung disease and my digestive system was failing me. I had lost everything. I lost my career, my independence and my ability to be an active parent. I was tethered to an oxygen tank and an IV pole. My body was worn down from the steroids and ICU-grade antibiotics running through my small body 10 hours a day. My intestines developed a c-difficle infection, my bone density decreased, and my energy was depleted. Walking became unsteady and at times impossible. Simple tasks like bathing and speaking became difficult.

I was being evaluated for a double lung transplant and pain management became a critical part of my health regime. My lungs were scarred, my ribs cracked easily, and lung bleeds increased. One evening a large bleed landed me in the ICU. My family feared the worst.

When Trikafta was approved in the US, I was shocked that it wasn't on its way to Canada. I didn't have time to wait. Thankfully, because I was dangerously close to losing my battle with CF, the manufacturer granted me Compassionate Care for Trikafta.

On Jan 23rd, 2020, my life was saved and dramatically changed when I took my first dose of Trikafta.

I was asked by my care team to make goals for my Trikafta journey. My goals were to independently bathe myself, laugh without a coughing fit and dance with my son.

Within hours of taking it, my body began to transform.

Within 10 days, I reached each goal with ease. Within 7 days I gained back years of lost lung function. Within 6 months I gained back a decade of lost lung function. My lung function when from 28% to 41%. For 36 years, my body was malnourished. I didn't have fat on my body to protect and nourish me. Within 3 months on Trikafta, I gained 30 pounds. For the first time as an adult I have normal liver levels. My sense of smell and taste returned,

and brightness came back to my skin tone. The most unbelievable part is that I now test NEGATIVE for CF as long as I am taking Trikafta.

I find myself for the first time in my adult life taking deep, full breaths. My body has relaxed. It is no longer in a war with itself and I can finally get a full night's sleep. At home, I used to go to bed with tears streaming down my face, worried that I wouldn't wake up in the morning. I would position my lungs in a way that I could find a stream of air amongst the thick fluid while I slept. I would pray that my shallow source of air wouldn't fail me while I slept. Many times, my limited lung capacity would fill with large volumes of blood and we would have to rush to the hospital in the middle of the night.

While in the hospital, falling asleep would cause alarm bells to sound as my oxygen dropped and my heart rate spiked. I had my best friend sleep next to me to hold me through panic attacks while I searched for air. My husband would take shifts being by my side and when I drifted off to sleep, he would have to wake me up and yell "BREATHE Stephanie!" as alarm bells rang on all the screens connected to me. My then 4-year-old son would visit me in the hospital and even talking to him would take more energy than I had.

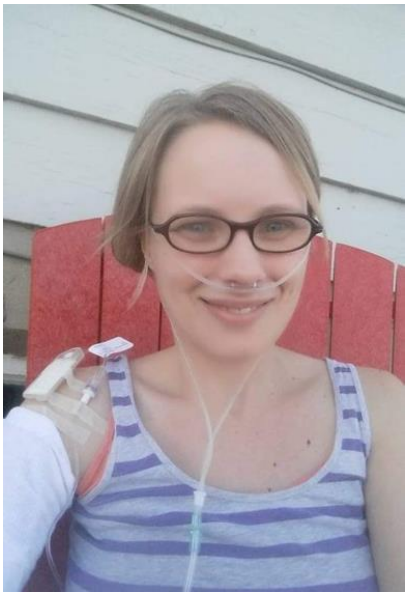
Taking Trikafta has allowed my husband to complete a full day of work. It's allowed my parents to relax after 37 years of being CF caregivers. These 3 simple pills taken every day brought me back to my son. I am now the present and active mother that I dreamed of being. My chronic pain has disappeared, and I am stronger than I have been in more than a decade. I've transformed from a 36-year-old that needed to be supported to use the washroom to a 37-year-old that for the first time in life, has gone running.

My season of life was coming to an end. My doctor said to me during an appointment, "Stephanie, women with CF in their mid-30s don't do well with CF. And by don't do well, I mean die." I started preparing paperwork. For the first time in life I saw each person close to me cry out of fear. We were losing hope… until Trikafta changed it all. I am now VIBRANT. I am a new person. Even my skin colour changed from pale-grey to a pink, oxygen rich tone.

Since starting this medication, I have witnessed my family's fearful tears transform into tears of joy and reprieve. They are witnessing my second chance at life and I am thriving. I'm writing this with 98% oxygenated blood while breathing room air. For a CF patient that was facing transplant, this still feels unreal. This is truly been a miracle for my health. I can only hope that all Canadians with CF can realize the power of this medicine.

Amanda Bartels
Calgary, Alberta

Thank you for the opportunity to provide a testimony from a patient's perspective on the benefits of Trikafta.



I am a 38-year-old wife and mom. Due to the excellent group benefits plan my husband has, I was fortunate to have access to the first and second-generation CFTR modulators. First, Orkambi in 2016 and then I switched to Symdeko in 2018. I accessed both drugs within only a couple months of Health Canada approval. After a steep decline in 2015, these drugs provided a stabilizing effect on my declining lung function and corrected my BMI with needed weight gain. Sadly, by 2019 even these drugs, which were partially correcting my defective genes, could not hold back the ravages of cystic fibrosis on my lungs. The result was increased exacerbations, bacterial lung infections and complications that required repeated hospital admissions, particularly in 2019.

2019 was the hardest year of my life. I had already been on continuous oxygen for a few years and spent nearly six months on intravenous medications and in the hospital for treatment of my CF exacerbations and lung collapse. I continued to decline, and after spending nearly 4 months in the hospital, my physician submitted an application for Special Access for Trikafta in the last quarter of 2019. Three months later in the beginning of 2020 that application was denied, and I was devastated. I was not sick enough yet, which was very difficult to comprehend after the year I had endured. My mental health is typically quite good, which is not true for many with a fatal disease like CF, but this crushed me. Knowing a drug existed that could save my life but was just out of my reach was incredibly difficult to deal with. At that time, I was undergoing tests to qualify for a double lung transplant and Trikafta was my last chance to avoid or postpone that process.

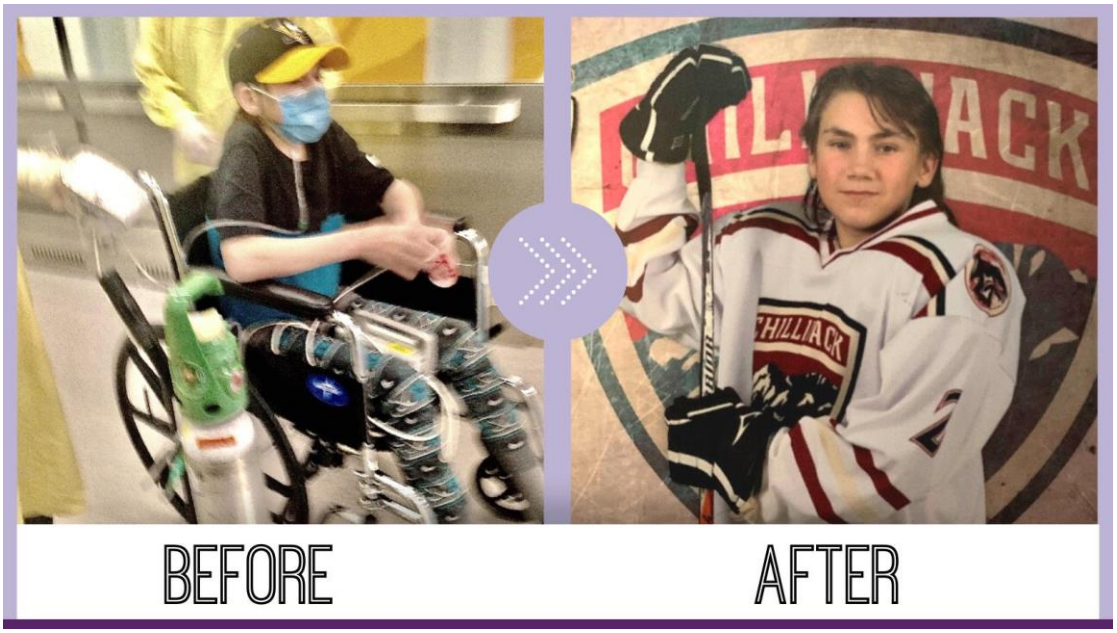
In spring 2020, after another hospitalization as COVID19 infections exploded across the country, a second application was made, and I was deemed sick enough to receive Trikafta through the special access program. Both I and my family were elated at this second chance! I did not want to raise my expectations too high and took things a day at a time as we waited for the first shipment of pills to arrive. Since then, life on Trikafta has exceeded every expectation and I could feel it working within hours of taking my first dose. The thick, sticky mucous that has lined my lungs for my entire life was mostly purged over the first few weeks. I have had zero CF exacerbations. I have had a nearly 10% increase in lung function and no need for IV antibiotics or hospital admissions. My daily airway clearing treatments and therapy no longer exhaust me and are more effective than they have been for many years. Plans to possibly move forward with listing for new lungs has been put on hold indefinitely. I put away my oxygen tanks within a couple of months, can take deep breaths and can exercise and am living life like a 38-year-old mother should be.

My daughter just turned 10 and my hope when she was born had been to be here for her through puberty because no girl should be without her mom in that time of her life. That hope slipped away as my health declined drastically and I revised my 'goal' to age 10. Because of Trikafta I was here for her 10th birthday with my own, original lungs. In addition to that, I am currently more active and feel healthier than I have been since she was 6 months old when I developed pneumonia that robbed me of nearly 25% of my lung function. This is not supposed to happen for CF patients, particularly without having a lung transplant, as CF is a progressive disease. You just don't get better and improve, until now with Trikafta. The joy and relief this brought to my family is tangible and now I am blessed to plan a future with my husband and daughter that I will be a part of, hopefully for many years to come.

I did not know it in spring 2020, but I had forgotten what if felt like to truly breathe. Within a couple weeks of starting Trikafta my lungs cleared, and I could take a deep breath and walk across my front yard without oxygen and without having to stop to catch my breath. By the end of summer, I biked nearly 50 kilometers in an afternoon and the last time I could maybe do that was over 15 years ago. After nearly a year since my last hospitalization, I am now starting to forget the pain and impact of countless medical interventions, IVs, appointments, breathlessness and exhaustion and it is liberating.

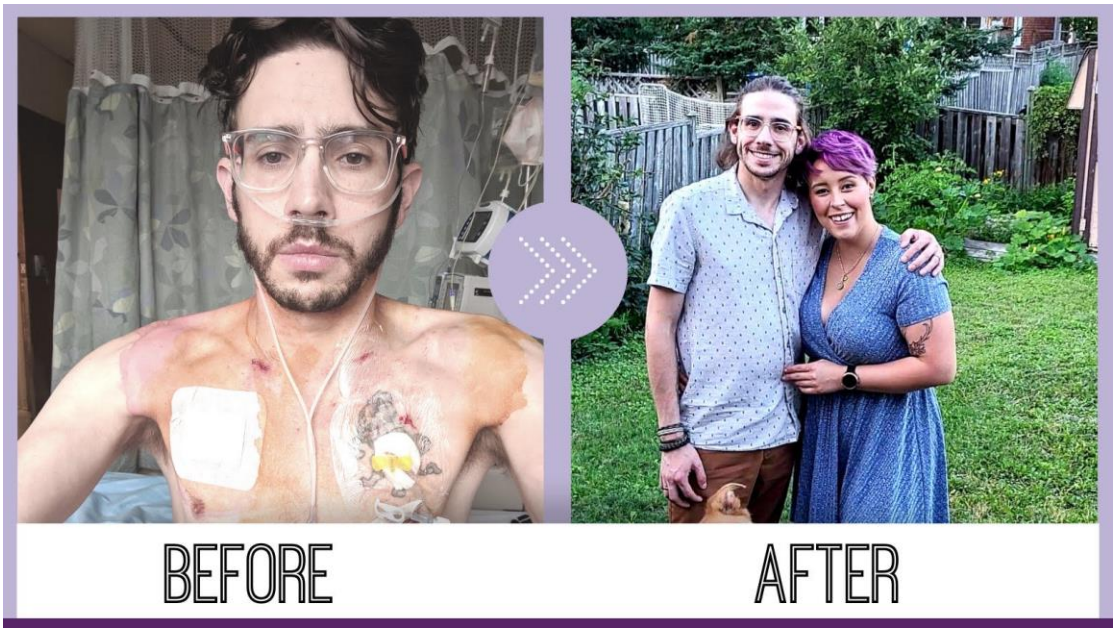
The only thing I am left wondering is how my life would have been different if Trikafta had been available to me as a 12-year-old, when I had nearly full lung function. Would cystic fibrosis, a deadly, unpredictable and devastating disease have been tamed and would my lungs have been spared the irreversible damage and extreme scarring I now have? I can only imagine how much my care has cost the health care system in Canada for the past 38 years, particularly the last decade, which would have continued to grow with the costs of additional hospitalizations and a potential lung transplant if Trikafta was not available for me. I am so hopeful for the future for all Canadians with cystic fibrosis who will benefit from this medication. It cannot come soon enough and needs to be provided for everyone, before irreversible damage occurs, so that children with CF may not have to go through what I have.

Appendix C: Before and After

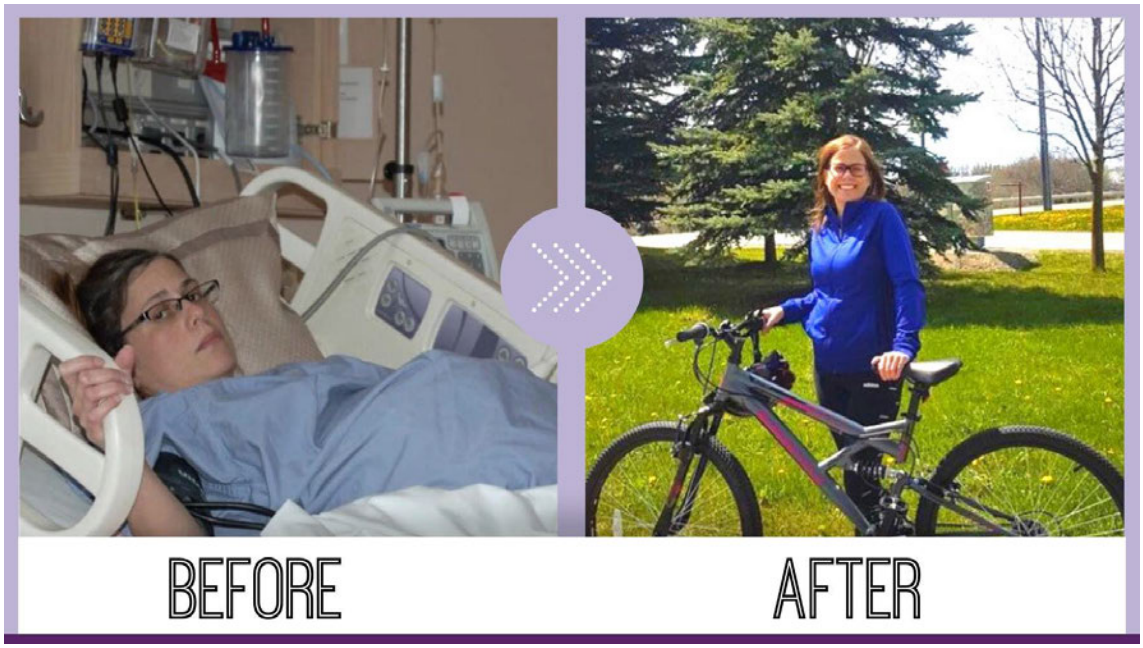


Steven James, 17

Ashley Roy, 27



Kyle Laplante, 38



Sue Alonzi, 49

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

Reimbursement Review of lexacaftor/tezacaftor/ivacaftor

[redacted]

February 12, 2021

1. About Your Patient Group

Cystic Fibrosis Canada has dramatically changed the cystic fibrosis story. We have advanced research and care that has more than doubled life expectancy. 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 work together to change lives through treatments, research, information and support. Despite our remarkable progress together, we are not yet done. Not when half of the people with cystic fibrosis who died over the past three years were younger than 34. Not when a child born with cystic fibrosis still has only a 50% chance of living to 54. We will keep pushing, keep going further until all people with cystic fibrosis can and do experience everything life has to offer — 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-two 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 and clinical communities allows us to better understand 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 42 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 DSMBs, 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.[1] 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 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 250 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.

2. Information Gathering

Cystic Fibrosis Canada gathered information for this submission through a cross-Canada survey of patients and caregivers. We reference Cystic Fibrosis Canada's publications, including the 2019 Canadian CF Registry Annual Data Report. We cite the scientific literature and clinical trial data and other

[1] Canadian Cystic Fibrosis Registry 2019 Data Report, https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf

published studies on elexacaftor/tezacaftor/ivacaftor and ivacaftor (hereinafter called Trikafta) and its impacts, as well as a Cystic Fibrosis Canada funded study published in the fall of 2020[2] 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 recently submitted CADTH submissions.

We surveyed our community from January 18 until January 25, 2021. Patients and caregivers were invited to participate through postings at cystic fibrosis clinics, through direct email, Facebook, and other social media channels. 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.

Of the 422 adults with cystic fibrosis who responded 12% are currently taking Trikafta through the Special Access Programme (SAP), 7% received it through a clinical trial and all but one adult is still accessing it, 6% tried to access Trikafta through the SAP but were unsuccessful, and 63% have not tried to access Trikafta but are indicated for it. One is a US citizen living who is working in Canada and who accesses Trikafta through their cystic fibrosis clinic in the USA. Four percent were none of the above and were excluded from further analyses.

3. Disease Experience

Cystic fibrosis is the most common fatal genetic disease affecting children and young adults in Canada. There is no cure. Cystic fibrosis 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 progressive loss of lung function will eventually lead to death in most people with cystic fibrosis. Respiratory failure causes eighty-five percent of cystic fibrosis fatalities.

Cystic fibrosis is the most common fatal genetic disease affecting children and young adults in Canada. There is no cure. 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 frequent pulmonary exacerbations (PEx) requiring weeks of hospitalization and I.V. antibiotics. PEx cause rapid decline of lung function and more rapid disease progression and are

[2] 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).

[3] Canadian Cystic Fibrosis Registry 2019 Data Report, https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf

associated with a greater risk of death (Stanford, G. E., Dave, K. & Simmonds, N. J., 2021)[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.

Cystic fibrosis is a complex disease caused by mutations in the gene for the Cystic Fibrosis Trans-membrane 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.

Thanks to significant progress in treatment and care, the majority of children with cystic fibrosis will reach adulthood. The estimated median survival of Canadians with cystic fibrosis in 2019 was 54.3 years of age.[5] Half of the Canadians who died from cystic fibrosis in 2019 were under 42 years, compared to 33 years in 2018 and 28 years in 2000.

As the disease advances, even 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.*
>
> *– CF grandparent*

From Cystic Fibrosis Canada's Patient-Submission to CADTH 15March2018:

> *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*

[4] Stanford, G. E., Dave, K. & Simmonds, N. J. Pulmonary Exacerbations in Adults With Cystic Fibrosis: A Grown-up Issue in a Changing Cystic Fibrosis Landscape. *Chest* **159,** 93–102 (2021).

[5] Canadian Cystic Fibrosis Registry 2019 Data Report, https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf

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. – CF parent

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. – CF parent

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.

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. – CF parent

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. 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.

> *The benefit of living a longer healthier more productive life is worth quite a lot of side effects. CF already comes with burdensome, painful symptoms, as do existing CF drugs. I often have severe reactions when I must take IV antibiotics, the last line of defence for me currently before transplant, and they barely work to slow the disease progression at all anymore. My inhaled therapies similarly don't work well, and cause bleeding, inflammation, hearing loss and more. Oral infection treatments also cause hearing loss, build up resistance, and damage my liver and digestive system. I would do anything if it meant I got to live. – Adult with cystic fibrosis*

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.

In terms of time, money and overall health, the burden of care of cystic fibrosis is tremendous, on those who live with cystic fibrosis, their caregivers and society. 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.[6]

Long-term use of powerful antibiotics to fight chronic, persistent infection ultimately leads to anti-microbial resistance. As in the quotes above and below 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*

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.[7]

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[6] Cystic Fibrosis Trust https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/physiotherapy/physiotherapy-faqs#howmuchairwayclearance January 31, 2021

[7] Canadian Cystic Fibrosis Registry 2019 Data Report, https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf

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).*[8]

<u>Availability of CFTR modulators:</u>

Trikafta is the third generation of CFTR modulators. All modulators are tailored for specific CFTR mutations. Only the first-generation modulator, Kalydeco, is broadly available in Canada. 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, but neither is available through public payers in Canada, excepting Quebec which provides access only to those who meet the strict eligibility requirements of the 'patient d'exception' program.

Clinical benefits gained from Kalydeco are more modest than those from the newest, third generation modulator, Trikafta. Although the patient populations served are distinct, patients on Kalydeco with a F508del mutation are likely to benefit from Trikafta. On average, clinical benefits 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.

> *Orkambi had side effects I couldn't tolerate. Trikafta is my one and only hope. - – Adult with cystic fibrosis*

> *I am on Orkambi now. It's working great. Trikafta is a better modulator than Orkambi. … I am trying to conceive because I'm healthy enough from Orkambi. – Adult with cystic fibrosis*

[8] Source material: https://marikasmotorcyclediaries.wordpress.com/2014/02/19/typical-day-at-home/

Caregiver Impact: Current Therapies

Spouses or caregivers of an adult living with cystic fibrosis accounted for 34% of caregiver respondents, 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, 87% have not sought access to Trikafta. Five percent care for children who tried to access Trikafta through the Special Access Programme but were unsuccessful, and 2% care for children who had access through a clinical trial but no longer do.

One hundred nineteen caregivers of adults with at least one F508del mutation responded. Most, 66%, have not sought to access to Trikafta. Two percent care for adults who participated in a trial but no longer have access and 15% tried unsuccessfully to access Trikafta through the Special Access Programme.

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. Virtually all current therapies treat individual symptoms or individual organs.

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. 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 as a result of their disease.

> *We have kids. Because the one parent has CF, kids would not be possible without immense additional caregiving over and above the normal work involved with raising children.*
>
> *– CF spouse*

> *My wife is still capable of her own basic care, but we've decided I will be responsible for household income to facilitate her ability to invest time in her health. Of course partners are also always partly responsible for support of mental health and well being of the other. Often someone suffering from a fatal and debilitating disease will require more than average support in this area. – CF spouse*

> *Our daughter has her own apt now but we help out weekly with meal prep, grocery shopping, housework, Rx pick ups, rides to Dr appts when she is not able physically to do these tasks because of feeling unwell and tired due to her CF. – parent of a CF adult*

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.

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 multipled. It should come as no surprise when one parent of multi-patient households typically leaves the work force to care for the children.

With respect to employment, 60%, of reporting caregivers for adults with cystic fibrosis have had to take time off work to meet their caregiving requirements of their loved one; 6% said that they had to quit their jobs altogether, 6% had to reduce from full-time to part-time work and 4% had to take time off school or leave school altogether. 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, and 13% had to quit work altogether and 2% had to take time off school or leave school altogether.

> *For many years, I gave up working full-time to be available for the unpredictability of CF in our family's life. – CF spouse*
>
> *As the mom of two teens with CF the amount of time and stress in regards to living with cystic fibrosis is unpredictable. Because of the unpredictable and cruel nature of this disease I had lost my registered nurse license due to a lack of enough nursing hours. It was impossible to commit to any kind of position in my field when I had to do multiple treatments with my children every day which included doing chest physio on both children. Due to hospital admissions, procedures, doctor appointments and the kids getting sick on a regular basis caring for them has been a full-time job which has always left us with just my husband being able to work full time. – CF parent*
>
> *My husband and I both had to quit our jobs and relocate back to Canada, as we had been working abroad. We had to move our family of 5 from their home. While my husband had to search for work back in Ontario, I have not been able to return to work due to daily therapies, frequent hospitalizations, and other health concerns. – CF parent*
>
> *I am a registered nurse and have never been able to take any kind of full time position due to so many appointments, treatments, sickness and hospital admissions. – CF parent*
>
> *My husband and I work alternating shifts [he works nights, I work days]. – CF parent*

Significantly more caregivers for adults with cystic fibrosis (44%) said caregiving had a negative impact on their physical health than said it had a positive impact (17%). 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 just been fired from 10 years of employment with no notice or severance as my performance suffered too much due to caregiver burn out. – CF parent*
>
> *I have had mental health problems watching my child fall ill. – CF parent*

I worry constantly. Knowing medication may be available that could better her life but she may not be able to access it is very stressful. – CF spouse

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

She would be totally independent, free to plan her life without all the physical, and medical regime restrictions she has to endure at present, because her health status would improve greatly on the drug. She would finally be able to breathe easy, to be happy and hopeful for a long enriching life. – CF parent

My son would be able to pursue his studies as an Engineer without the health decline that comes with CF. He could work, chase his dreams like anyone else. – CF parent

I wouldn't have to think about becoming a widow before age 40. – CF spouse

It would have a positive impact all around not only for them, but also on the rest of the family- especially their mental health. – CF parent

5. Improved Outcomes

Trikafta is the third generation of CFTR modulators with the potential to treat up to 90% of Canadians with cystic fibrosis. It represents 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. The Washington Post named it number one of nineteen good things that happened in 2019.[9]

Canadian research[10] 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. Understandably, expectations amongst the cystic fibrosis community are high, but also down to earth. Patients often simply want, and hope for, 'normalcy'.

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

I have simple hopes for Trikafta - to not have a coughing fit while laughing, to be able to go on walks with friends, to be able to sleep, to stabilize my disease progression, to be able to take a

[9]Opinion: 19 good things that happened in 2019. Editorial.The Washington Post. https://www.washingtonpost.com/opinions/19-good-things-that-happened-in-2019/2019/12/17/719f50d6-2025-11ea-86f3-3b5019d451db_story.html February 2, 2021

[10] 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).

deep breath. These simple things would completely change my world and mental health in addition to the physical health benefits. – Adult with cystic fibrosis

Patients also long for the ability to breathe unencumbered, to live without fear that normal activities will cause further damage.

My hope is that getting access to this drug would improve my quality of life and allow me to breathe and function in a way I never have before. My hope is that my quality of life will be improved and that my body will be capable of doing things without so much struggle to breathe. – Adult with cystic fibrosis

I am 43 years old and I was always told that my life expectancy is a certain age. I want to be the woman that lives to be an old lady and I want to beat this disease. I want to be able to go for a walk and not be out of breath and coughing my head off. I would love to never fear about getting sick and if I do get a cold I can fight it off. Just giving us this chance to try this new drug would be my dream come true. So please give us a chance to take this drug and live our life being able to breathe. – Adult with cystic fibrosis

Trikafta is a big life raft for many of us living with CF. We know it's not a cure but we have seen almost miracle improvements in those lucky enough to be able to take it. If i had access to it and it worked for me it would radically change my life. As it stands my day consists of taking care of my CF, hours of therapies, trying to eat enough, trying to manage everyday life to not make things worse for my health. I can't even imagine what life could be like if I didn't have to worry about that all the time. – Adult with cystic fibrosis

They also want to be able to contribute to society. Parents and caregivers hope for unencumbered lives for their loved ones.

Overall benefits by improving the underlying issues, if it helps keep me alive and productive longer, I can contribute to society and help absorb the cost of my care. – Adult with cystic fibrosis

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. – CF parent

…I have not been able to work in over a year and that has been the most depressing thing. All I want to do is work, I want to be a active member of society. I want to buy a house, I want to have kids and I believe Trikafta will help me achieve all those things. I have been hospitalized for over 78% of this past year and it has put a major damper on my life. I have become depressed and Trikafta has given me hope. – Adult with cystic fibrosis

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.

Trikafta would clear the mucus in my lungs and stop me from feeling like I am suffocating. Both my brother and I have CF double delta f508, and it would save my brother's life. – Adult with cystic fibrosis

I am really hoping it would help with GI issues such as DIOS. Also not sure what you need to qualify but if it's as life changing as others discribe I don't want to have to wait till I am a lower lung function. I would like to have a better quality of life sooner than later. My lung function remains pretty good but GI issues are a larger problem. – Adult with cystic fibrosis

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.

I have spent most of my adult life never being over 100 pounds and I have seen so many people on Trikafta saying they've gained so much weight and that alone would improve my overall health so much. I have also seen a lot of CF women get pregnant after taking it and that is also my dream that is currently affecting my emotional and mental health. – Adult with cystic fibrosis

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 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

My hope is that Trikafta would at minimum slow my health regression or at best improve my health so that I can make longer lasting health improvements that would ultimately lead to a longer lifespan. – 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

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

The anticipation for this drug is so high as to have one disturbing, unanticipated impact, that of patients hoping to get sicker, to be sick enough to qualify for compassionate access. This appears to be tied to the very strong improvements some patients have seen with the drug and the belief that the loss of an additional few percentage points of lung function would be more than compensated for by the gains made by accessing the drug.

I was declined because I am not sick enough yet? I look forward to the day when I will take Trikafta daily and able to breathe and live a long healthy life. – Adult with cystic fibrosis

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

I am running out of options due to antibiotic resistance & low lung functions, … I hope it 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 exist – Adult with cystic fibrosis.

Not sick enough with pft 30-40% to have DR apply for SAP. – Caregiver of an adult

6. Experience with Drug Under Review

A total of 57 respondent patients have experience with the drug under review. Sixteen were part of a clinical trial on Trikafta and continue to access Trikafta, whereas forty-one have received access to Trikafta through the Special Access Programme. 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: 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.

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

Most respondents that have taken Trikafta noted that the burden of care associated with cystic fibrosis lessens with Trikafta. After taking Trikafta, adults with cystic fibrosis spent a median of 10 hours of week on disease management, whereas their caregivers spent a median of 4 hours. Still, respondents noted that even greater benefits could have resulted had they had access to Trikafta sooner.

My life post Trikafta is not even comparable to before. I haven't been hospitalized or on antibiotics in over two years. I can work and contribute to society like a normal human. – Adult with CF

Eighty four percent of adults found that Trikafta improves lung function better than other therapies, 80% noted that it results in fewer pulmonary exacerbations, and 68% found that it improves nutritional status better than other therapies.

I have more energy and I am not so fatigued all the time. I barely cough or spit up mucous. I am able to do more activities and not run out of breath so quickly. My appetite has gone up and weight gain has been way easier. – Adult with CF

I did lung transplant work up. I got Trikafta under compassionate care. My lung function increased by 13%. I no longer cough, have gained 25 pounds and have a new quality of life. Put it this way I wasn't able to walk up a flight of stairs pre-Trikafta I am now bike riding.
– Adult with CF

Seventy nine percent of parents of children with cystic fibrosis who are 12 years of age or older said that their child's experience with Trikafta was very positive, and 21% said it was positive. When compared to other therapies, adult caregivers of children with cystic fibrosis noted that Trikafta better manages improvements in lung function (93%), improvements in nutritional status (64%), and reductions in rate of pulmonary exacerbations (57%).

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.
– CF parent

Lung function has increased by over 10%. No side effects have been experienced.
– CF parent

Coughing in cystic fibrosis is chronic to the point of severely impacting quality of life. It impedes sleep, interferes with normal everyday activities like laughing and when coughing bouts strike shortly after meals can easily cause vomiting. It is anecdotally one of the first effects of a modulator on patients and appears frequently in the responses. In both the adult and child populations, a number of respondents noted improved sleep and better mental health.

My mental health was at an all time low, I accepted death and wanted it over soon. Now I have a new insight on life, I am excited to plan a future with a family and have begun a new career.
– Adult with cystic fibrosis

I have been on it for just over nine months. Life changing. I have gained twenty pounds. I don't cough all night long all the time. I barely cough at all. My sputum went from being thick and yellow-green to thin clear sputum. I have energy and walk 6.5 kilometres a day. I have a renewed lease on life. I have not had a cold or any exacerbation for over 10 months. I love what Trikafta has done for me. – Adult with cystic fibrosis

Side Effects: Patients on Trikafta

Almost 30% of children who are taking Trikafta experienced side-effects: headache (25%), high liver enzymes in the blood (50%), and having a rash (25%).

About 50% of adults noted that they had experienced side-effects, including but not limited to: headache (38%), abdominal pain (29%), rash (21%), diarrhea (17%) nasal congestion (17%), and runny nose (17%), and high liver enzymes in the blood (13%).

In terms of side-effects, adult respondents found all of the side-effects associated with Trikafta to be acceptable. Cataracts were the least acceptable, with only 2% of respondents finding them to be acceptable.

> *The benefit of living a longer healthier more productive life is worth quite a lot of side effects. CF already comes with burdensome, painful symptoms, as do existing CF drugs. I often have severe reactions when I must take IV antibiotics, the last line of defence for me currently before transplant, and they barely work to slow the disease progression at all anymore. My inhaled therapies similarly don't work well, and cause bleeding, inflammation, hearing loss and more. Oral infection treatments also cause hearing loss, build up resistance, and damage my liver and digestive system. I would do anything if it meant I got to live. – Adult with CF*

> *Those symptoms are all superficial compared to not being able to breathe. the only deal breaker would be if the medication destroyed my liver faster than CF would destroy my lungs. – Adult with CF*

> *The alternative is worse. CF kills 100% of the time. – Adult with CF*

Adult caregivers of children with cystic fibrosis felt that all side effects are acceptable except cataracts. Side effects such as headache (64%), nasal congestion (64%), runny nose (55%) and rash (55%) were more tolerable than others.

Ease of Use

Almost 80% of adults reported Trikafta to be easier to take than other medications. For the most part, adults noted that it was easier to take because it is just three pills twice a day. Likewise, 92% of caregivers of children with cystic fibrosis noted that Trikafta was easier to take than other therapies for the same reason.

> *All other medications treat the symptoms associated with CF. It's a struggle to have my child take them 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. – CF parent*

> *You just take your pills and that is it. Nothing else. No other med has accomplished this result before. It's quick and effective. – Adult with CF*

> *What's a couple more pills a day, on top of the dozens I already take? No contraindications/interactions with other meds/most foods, taken twice a day. Adult with CF*

Health Outcomes

In terms of health outcomes, adults reported that Trikafta has resulted in positive changes to their health. Specifically, it helped them gain weight (87%), increased their lung function (85%), slowed or stopped progression of symptoms (83%), resulted in fewer hospitalizations (83%), improved their energy (83%), improved mucus clearance (81%), and improved mental health (64%) among others.

Increased energy, dramatic improvement in his mental health. – CF spouse

I was so sick my doctors had nothing else to offer me, I was enjoying family time because I did not have much longer to live, I now feel amazing without any barriers.
– Adult with CF

It [Trikafta] saved my life. I was being evaluated for a double lung transplant and was able to postpone it and doubled my lung function. – Adult 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 [Trikafta] 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%. – Adult with CF

I was sick with an infection for 2 years. I missed school for 2 years and became reliant on a wheelchair and stayed in hospital for most of the year. I was told I was going to die and soon after Trikafta got in my hands. I was discharged a month after and can exercise and go to school now. I'm also no longer on antibiotics. – Adult 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!
– CF parent

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

Impact on Other Medications

The survey also found that 60% of adult respondents who are taking Trikafta noted the drug has helped them reduce the number of medications they take, including but not limited to inhaled antibiotics (63%), chest therapies (48%), anti-inflammatories (30%), antifungals (26%), and antivirals (22%).

Oral antibiotics, since I have not gotten sick in the 2.5 years I have been on Trikafta. – Adult with CF

Vast reduction in need for antibiotics during Phase 1. Also increased appetite and some height and weight gain (but not conclusively attributable to Trikafta). – CF parent

Since starting on Trikafta almost 10 months ago, I spend every day feeling like I don't even have cystic fibrosis. My breathing is remarkably normal. My exercise tolerance is much improved (I can even baby wear my 1-year-old and walk around the neighborhood). Incredibly, my FEV1 has gone up to 35% so far and I have put on 6kg so easily. I have cut out some of my inhaled symptom management drugs as well. – Adult with CF

This was also the case with children with cystic fibrosis who have taken Trikafta: 25% of respondents said that their child has reduced the number of medications they take since starting Trikafta. This includes but is not limited to reductions in use of inhaled antibiotics (67%), chest therapies (33%), and antivirals (33%).

Hopes and Dreams

Among adults with cystic fibrosis who have not had access to Trikafta, 96% believe that Trikafta could improve their health and well-being. In particular, 95% of adults thought that Trikafta could increase their lung function (95%), 93% said they hoped it would help them live a healthier life, 93% hoped it would help them live a longer life, 90% said that hoped that their symptoms will slow or stop.

Almost 100% of caregivers of children with cystic fibrosis that have not accessed Trikafta believe the drug would improve their child's health and well-being. When caregivers considered how they hope Trikafta could help their children, 96% hoped for their child to have a longer life, 94% hope for a healthier life for their child, 93% want the drug to slow or stop the symptoms, and 85% hope for improved lung function for their child.

Trikafta could improve quality of life overall for the child with CF and the family unit as a whole, such as better and more integrated into time with family, friendship and social time outings since this drug can improve turn around health so much so we likely wouldn't be so worried about managing health and symptoms and having so many fears of decreased health due to contact with viruses that are so prevalent in society that contribute to decreased health and lung function without these modulators drugs. – CF parent

Gaps and Unmet Needs

Almost 80% of adult respondents not on Trikafta said that there is a gap or unmet need in current therapies that Trikafta could alleviate. In particular, it would give some adult respondents a more efficacious option than other modulators (61%), it could be of benefit to those who could fail on another modulator (37%), it can treat some mutations that other modulators don't (35%), and it would give some choice among modulators (35%).

Twenty other countries are funding it except Canada. I personally deserve the right to try. Canada deserves better. It needs to be funded. – Adult with CF

Because of access barriers, I have not been able to even try the earlier modulators. I am hopeful that, because Trikafta has such incredible results, that publicly funded drug plans will actually cover Trikafta. – Adult with CF

One of the biggest complaints from the patient side is requiring us to be "sick enough" to qualify for a drug. Preventive medicine is important ... – Adult with CF

Seventy-nine percent of caregivers of children that have not accessed Trikafta believe that Trikafta can address a gap or unmet need in therapy. Specifically, 63% identified a gap in efficacy, saying it is more efficacious than other modulators. Others identified a gap in the mutations that modulators treat, 46% said Trikafta can treat their mutation, whereas the other modulators cannot, and 41% said it would give their child another choice among modulators.

> *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. – CF parent*

Impact on Caregivers: Addition of Trikafta

The number of hours caregivers of adults spend per week on caregiving activities changed following access to Trikafta. The number of caregivers spending 10 hours or less went from 40% to 55%, the number spending between 11-20 hours went from 33% to 24% and the number spending more than 20 hours per week went from 27% to 20%. Note that nearly twice as many adults with advanced disease and the heaviest burden of care gained access to Trikafta through the Special Access Program on compassionate grounds than patients with mild or moderate disease got access to Trikafta through clinical trial or other means. Caregivers of adults on clinical trials reported a median of four caregiving hours per week after the adult they care for started Trikafta.

> *Trikafta has saved the person I care for! I have far less stress thinking about day to day living. They are independent and do not depend on antibiotics to get through each day. They no longer require as much assistance with day to day activities. – CF Spouse*

The change in burden on caregivers of children was less significant. Of the 12 caregivers of children who gained access to Trikafta, 11 indicated that they spend 21 hours or more weekly on disease management post-access to Trikafta. This is in fact not surprising. As noted above, children generally have milder disease than adults, and even children who appear healthy and have normal FEV1 are subjected to an aggressive treatment regimen under SOC, and the burden falls almost exclusively on the caregivers.

Nonetheless, 27% reported that Trikafta had a *very positive* impact on their caregiving requirements, and 45% reported that it was *positive*. Specifically, Trikafta helped 22% of respondents reduce the number of caregiving requirements they have, and 22% said they reduced the amount of time they spend on caregiving duties, among other things. In addition, the impact on the mental health of cystic fibrosis parents whose children start Trikafta was significant. As respondents noted:

> *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 son's 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. 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.*
> *– CF parent*

7. Companion Diagnostic Test

Since the discovery in Toronto of the gene responsible for cystic fibrosis 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 2,090 mutations in the gene responsible for cystic fibrosis have been identified. One thousand of these mutations are ultra-rare, found in five patients or fewer world-wide.

Medical diagnostic laboratories typically conduct panel screens for the most common mutations in Canada. Such tests detect the mutations in approximately 98% of the Canadian cystic fibrosis population. If medically indicated, complete exome sequencing will identify virtually all cystic fibrosis mutations, and in fact the falling costs of such tests make it even more economical to sequence than to screen panels of mutations. Both the coverage and the availability of genetic testing vary across Canada.

Trikafta is the first CFTR modulator therapy available to treat patients with a at least one copy of the most common cystic fibrosis mutation, F508del.

According to the Registry genetic mutations have been identified in 99% of all patients who were seen in a cystic fibrosis clinic in 2019. The vast majority of individuals for whom Trikafta is indicated, are known by their clinic or can be queried by their clinic using the 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).

As described above, the clinical progression of the disease is highly variable, even for patients with the same mutations, and studies supported by Cystic Fibrosis Canada and others have identified a number of genetic loci (called modifier genes) that appear to impact disease progression. Not surprisingly, evidence from the clinical trials also reveals a wide range of short-term responses to the drug, with changes in FEV1 ranging from little to no change, to as high as 40% improvement in FEV1 over baseline. Improvements in other symptoms, such as BMI and especially a significant reduction in PEx may also vary. In the ensemble however, all patients seem to benefit. Importantly, the efficacy of CFTR modulators appears to be maintained over time.

While it is not currently possible to determine who will benefit from Trikafta in advance of administering the drug, Cystic Fibrosis Canada has partnered with SickKids Hospital and Genome Canada on a precision medicine project to develop predictive tools that will help clinicians determine the right medicine for the right patient. The research team is examining how genetic factors, which can be assessed from a non-invasive blood test, can help predict individual treatment responses. They also examine if drug testing on patient-derived tissue samples can be used to inform the potential clinical response to drugs by each patient. The team is working with academic and industry partners, and patient organizations to promote the tools, once they have been shown to be effective, to Ministries of Health to integrate into patient care. In addition, trials are underway in Europe to use rectal organoids to test *in vitro* a patient's response to drugs[11]

[11]HIT-CF Europe https://www.hitcf.org, February 10, 2021.

In summary, the entire Canadian population of patients eligible for Trikafta are already identified for the clinicians that will ultimately prescribe the drug. 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?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Perhaps the most important potential benefit from Trikafta is a reduced rate of decline in disease progression, that, if treatment is started early enough, may prevent much of the organ damage observed in patients with advanced disease from ever occurring. This is also an extraordinarily difficult change for an individual patient to observe or evaluate with any degree of confidence. A 2019 publication (Volkova, N. *et al.* , 2019)[12] presents data that supports the conclusions of previous studies and the evidence that a CFTR modulator modifies the course of disease in patients with cystic fibrosis, and a recent publication by Stanojevic et.al. (2020) projects significantly better overall outcomes for the Canadian cystic fibrosis population should Trikafta be made available in 2021. Evidence of a change in decline is difficult to prove at least in part because true control cohorts would be unethical and are not possible. In cystic fibrosis we nonetheless have an extraordinary resource in the Registry that will allow us to track and evaluate the impact of all modulators over time. Indeed, Cystic Fibrosis Canada-funded studies are ongoing to evaluate the long-term impact of the first- and second-generation modulators in the Canadian context.

> *Current treatments for CF are all reactive - treatment of disease progression. I am excited for there to be an option for halting/ slowing disease progression. Better overall health, less time in hospital, longer more productive life! – CF adult*

The announcement in November of 2019 that Trikafta had received approval from the FDA, and six months ahead of schedule caught a number of groups off-guard. The response of the cystic fibrosis community in Canada was immediate, and visceral. Canadians have contributed generously to the global advances in cystic fibrosis treatment and care, investing, through Cystic Fibrosis Canada more than $261 million in research and care. CFTR modulators exist today because the gene was cloned in Toronto, by Canadian scientists, funded by the generosity of Canadians and the Canadian cystic fibrosis community. Canadian scientists helped decipher the structure and function of CFTR, the gene product, that laid the foundation for the drug discovery. Canadians felt let-down and left behind and our collective mental health was impacted. The impact on mental health of "being left behind" is evident elsewhere in the cystic fibrosis community. Five percent of Canadians only have mutations (nonsense mutations and others) that cannot be corrected by CFTR modulators, and that community's mental health suffers precisely because they have no such options and feel left behind.

Trikafta was fast-tracked for access by the U.S Federal Drug Agency (FDA) and granted a priority review by the European Medicines Agency (EMA). Trikafta has received regulatory approval in 32 countries, 27

[12] Volkova, N. *et al.* Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *J. Cyst. Fibros.* **19,** 68–79 (2019).

within the EMA centralized regulatory approval in addition to receiving approval in the United States, United Kingdom, Norway, Iceland and Liechtenstein. Trikafta has received public reimbursement in the United States, United Kingdom, Ireland, Austria, Denmark, Germany, and Slovenia. We believe that the collective mental health of the Canadian cystic fibrosis population would suffer serious negative consequences from a negative HTA recommendation. It is unclear if, or how, that impact, or the impact on the mental healthcare system might be considered in the evaluation, but the negative consequences to the community would be real.

> *So many other countries have this available to them. All we are asking for is a chance for them to just be children. Canada used to be one of the front runners for CF treatments. Now it seems like we are finally behind many other countries who already have this available to their CF community. Very sad – Adult with CF*
>
> *It's the difference between living a life lockdown and being able to be free again. – Adult with CF*
>
> *Trikafta gives me hope. – Adult with CF*
>
> *The evidence shows how is could save/better ones life. Physically, Mentally, Emotionally. If something is available that can save your life or help maintain a healthier lifestyle where you can work, raise a family, have less hospitalization, how could you deny that access? Anyone would want to have access to this and it's crazy that I am writing and advocating for this to be available. This is the right direction but I know there are people in the CF community who need access to this right away and each day they don't have it, the worse they get. Thank you – Adult with CF*
>
> *Just knowing there is something out there that could improve his quality of life as he ages instead of him getting progressively worse is encouraging. We just hope to have access to it sooner rather than waiting until he is older and becomes too sick. – CF parent*

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, we prepared this submission in house. No.

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, we collected and analyzed the data ourselves. No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. All funds received were for unrestricted programming.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
CREON				x
Horizon Pharmaceuticals – Head Office				x
Mylan Pharmaceuticals				x
Vertex Pharmaceuticals (Canada) Main Account				x
Abbvie			x	
AstraZeneca Canada Inc.	x			
Bayer Canada	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: February 12, 2021

Scientific literature cited:

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