NICE National Institute for Health and Care Excellence

Patient organisation submission

Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation [ID1661]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. To help you give your views, please use this questionnaire with our guide for patient submissions. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Dr Keith Brownlee**
2. Name of organisation	The Cystic Fibrosis Trust
3. Job title or position	Director of Policy, Programmes and Support
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Cystic Fibrosis Trust is the only UK-wide charity dedicated to fighting for a life unlimited by cystic fibrosis (CF) for everyone affected by the condition. We receive no funding from government and rely almost entirely on donations by the public. We fund ground-breaking research, facilitate and support the delivery of clinical trials, and provide vital information and direct financial and emotional support. We also promote the highest quality of clinical care and run the UK CF Registry.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?	Yes, we have received income from Vertex through the pharmacovigilance programme, whereby they pay us a contracted amount to provide analysed data from the Registry. We have also received funds through their "circle of care" grant giving programme.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Between March and April 2020, the Cystic Fibrosis Trust surveyed 746 people whose lives are affected by cystic fibrosis: people with the condition (n=315), families, partners, and friends, asking a range of questions on their treatment experiences, expectations and goals. The Cystic Fibrosis Trust hosts and manages the UK CF Registry, which monitors data from 99% of people with cystic fibrosis in the UK. This submission also draws on data from this resource. Results from a report produced by the Cystic Fibrosis Trust and CF Voices, which examined the social media content produced by the CF community in the UK, focussing on seven areas of interest related to impact of CF on families and carers and the impact of initiation on CFTR modulator therapy, were also drawn upon to inform this submission. A copy of the report is attached to this submission.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with cystic fibrosis is to live with physical and social restrictions, a rigorous medical regimen, concerns about illness and death, and uncertainties about the future. Cystic fibrosis is a progressive, life-shortening disease where respiratory symptoms of cough and shortness of breath become more severe and harder to manage with age. Over the last fifty years, new treatments and specialist care have transformed the outcomes for people with cystic fibrosis. The availability of Kalydeco, Orkambi, and Symkevi, the first CFTR modulators have led to significant improvement in wellbeing, quality of life and survival in some people with CF. In our analysis of social media, Social media posts relating to CFTR modulators are invariably positive, for a minority there is the occasional setback, however, most report a rapid and sustained improvement in health, symptoms, wellbeing, exercise tolerance and quality of life. Below is one story from April 2020: *"Just an update on the little man and how he's doing on Orkambi...! We weren't, truth be told, expecting to see many changes with [XX], who is in good overall health. Having been on it now for 3 months, we've noticed: - a big increased in energy!! No longer does [XX] ask for shoulder carries, this boy will now walk/run or bike for miles without getting tired. - far less tummy trouble, meaning better sleep at night - less snoring! [XX]'s always sounded a little congested at night, as if he's got a cold even when he's well. This has markedly decreased on Orkambi, which is incredible, it just shows what's going on in his little*

	body as his cells start to function more normally. - just before schools closed [XX] started with a runny nose, which lasted a good two weeks. Pre-Orkambi this would always have resulted in a cough, requiring 10-14 days of antibiotics. This time, [XX] cleared it with no cough, no antibiotics needed... amazing." Yet, cystic fibrosis remains a severe, progressive condition. Lung infection, damage, and reduced lung capacity make it difficult to breathe and move around. Shortness of breath can affect the simplest of everyday tasks like climbing a flight of stairs and walking around your home. For many people, breathlessness also leads to experiences of panic. Progressive lung damage causes respiratory failure in cystic fibrosis leading to death or necessitating lung transplant to prolong life. Cystic fibrosis is unpredictable, and symptoms and disease severity fluctuate. This unpredictability disrupts everyday life, making it difficult to plan anything in advance –from a day out to planning a career. Our survey of patients and carers also showed wider challenges in living with the condition: • The financial impact of cystic fibrosis is profound. 345 people with CF or carers (73% of those who responded to this question) that we surveyed stated that having CF has negatively impacted their financial situation and 368 (76%) said it negatively impacted their school or work. During an acute period of ill-health (an exacerbation) normal life including work and education must be put on hold immediately and everyday tasks become even more challenging. The limited ability for people with cystic fibrosis and their carers to work leads to reduced earnings and increased costs such as travel to specialist centres. When a deterioration in health forces people with cystic fibrosis to reduce their working hours (or stop working entirely), for many financial resilience depends entirely on benefit support, including Universal Credit and Personal Independence Payments. During changes to work circumstances, applying for a new benefit can contribute to a worsening state of mental health for a person with cystic fibrosis, often compounding an already rapid deterioration in physical health that placed them in this situation. • 299 (58% of those who responded to this question) survey respondents stated that having CF has had a negative impact on their relationships such as partners, families and friends 368 (73%) said it negatively impacted their leisure or social activities. Persistent coughing can cause sleep disruption which makes it difficult to do daily activities. People with cystic fibrosis also need to consider how to manage their time between socialising, work, education, and leisure against their treatment regime of medications, food and medication preparation, physiotherapy and appointments. Exercise is a vital aspect of cystic fibrosis management, but many do not feel comfortable exercising in public due to embarrassment, misunderstanding the condition, alongside the constant risk of transmissible bacterial infections and/or viruses that could cause an exacerbation. • Rational fear of bacterial infection, the need for constant vigilance and the persistent coughing/coughing up of mucus often leads to stress and anxiety in social and public situations. 302 people with CF or their carers (81% of those who responded to this question) that we surveyed stated that having CF has had a negative impact on their mental health.

Results from our social media analysis showed that individuals sought to communicate their experiences of being mistreated or misunderstood by others in relation to their condition. Experiences included treatment by doctors, the general public, family members and friends. Content in this theme was almost invariably negative in sentiment. For example, one tweet from December 2017 said:

"Someone at work once pulled me aside and said "I think you should go to a Dr; do you know you cough a lot? Everyone is talking about it." I was SO embarrassed but I let it go, in the past when I have told people they usually go "what's that then does your Mum have to hit you????" (meaning give me physiotherapy)

For many, cystic fibrosis casts a shadow across lives of patients, carers and families, disrupting lives and causes great suffering.

- Progressive damage also leads to comorbidities including diabetes, liver disease, and osteoporosis. In 2018, of the 10,509 people with cystic fibrosis in the UK on the UK CF Registry, 1,301 had liver disease, 1,476 had weaker bones (1,013 had osteopenia and 463 had osteoporosis), and 2,174 had CF related diabetes. The additional treatment burden of comorbidities is significant. For example, Cystic Fibrosis-related diabetes alone requires constant monitoring and care to ensure blood sugars remain stable. Experiencing hypo or hyperglycaemia makes people with cystic fibrosis feel suddenly unwell, tired, and unable to concentrate. CF-related diabetes leads to additional challenges such as managing weight loss (malnutrition), retinal damage, kidney disease, and nerve damage.

For those not eligible for modulators, people with cystic fibrosis and their carers emphasised in the survey that living with cystic fibrosis is burdensome. Treatment weighs heavily every day as a non-stop challenge. Yet despite this heavy burden of care, treatments are only minimally effective at alleviating symptoms. From our survey, only 140 respondents (29%) said that the treatments improved overall wellbeing. Further, carers living with this knowledge and having to explain it to a child and help them deal with both their physical and mental health is very difficult.

One respondent said: "Every day is a fight and for 40 years the underlying worry for my family has been tough. Now I am a parent I worry so much *more* about the future and how my health will affect our family life. People who care for someone with CF must learn to cope with the unpredictability of the disease. It can turn life on its head in an instance. Uncertainty, worry, and having to adapt around CF is something everyone who knows a CF patient must cope with. It's a drain and a strain on everyone."

This was also evidence in the report by the Cystic Fibrosis Trust and CF Voices which showed the wave of emotions people with CF and their carers experience when attending a CF appointment. Social media posts showed the anxiety experience when awaiting results from the CF team, or knowing a phone call from the CF team indicated negative news as can be seen in this excerpt from a Tweet from July 2019:

	"When I see my phone ringing and it's [XX]'s CF TEAM..... My heart sinks. It means only one thing! [XX] has grown staph again!?? When I told him, he cried. More antibiotics for him to start tomorrow." It is not only the burden of treatment that makes life with cystic fibrosis difficult but also the amount of time spent on medical appointments. People with cystic fibrosis are closely monitored by specialist cystic fibrosis centres through outpatient appointments and inpatient stays. According to the 2018 Cystic Fibrosis Registry report, people with cystic fibrosis spent on average 22 days as an inpatient and 11 days as an outpatient in the last year. The results from our survey showed that an outpatient appointment from leaving home to arriving home takes on average 5 hours. The impact of the condition is all encompassing when considering finding time to do treatments, the energy it takes to go to social activities, which can cause excess fatigue for days, and feeling safe leaving the house knowing the possibility of catching an infection which can cause irreversible lung damage. Lastly, it is the draining thought of 'How long will this pain/discomfort last?' As our respondents stated, CF can be emotionally, physically and mentally exhausting. It is scary and terrifying, not knowing what to expect in the future whether it is tomorrow, a month or a year from now as our respondents pointed out that they are always in worry, for example (1) whether they will experience an exacerbation and need to stay in hospital, or (2) even if they fully follow their daily medicine regime how quickly will their cystic fibrosis progresses.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	People with cystic fibrosis have a heavy burden of care consisting of physiotherapy, exercise, nebulisers and antibiotics, which takes hours each day. Current treatments to address the symptoms of cystic fibrosis are not adequate. They are, time-consuming, intrusive, and indiscrete. Administering standard maintenance treatments takes hours out of every day and is associated with unacceptable levels of hearing loss and kidney failure due to toxicity of antibiotics needed to treat lung infection toxicity. Few people with cystic fibrosis manage to complete every prescribed therapy with only 41% managing every prescribed therapy daily. It is unrealistic to expect people with cystic fibrosis to endure this high burden for their lifetime. The James Lind Alliance Priority Setting Partnership - a partnership that enables clinicians, patients and carers to work together to identify and prioritise evidence uncertainties in particular areas of health and care that could be answered by research - found means to alleviate the burden of care to be the most important research priority amongst people with cystic fibrosis. There are mixed reviews of the effectiveness in alleviating current treatments, as only 140 respondents (29% of those who responded to this question) said that the treatments improved overall wellbeing. More specifically, 126 respondents (26%) find treatments for upper respiratory symptoms to be effective, 165 respondents (34%) found treatments to improve

	breathing to be effective and 231 respondents (49%) found treatments to alleviate gastrointestinal symptoms to be effective. As such, there is a clear need to access treatments that target the root cause of the disease (such as CFTR modulators) to reduce the burden of care but to also minimise the need to use these other treatments. Social media analysis showed that content is primarily focus on conversations about routines, and exasperation at the pressures inherent in such routines and manifestations of this. People report exhaustion, stress, anxiety, and depression. *"It is so hard to fit in all the treatments for twins; a minimum of two lots of physio a day, totalling one hour, the physio vest, medication and cramming in the calories. The latter is no mean feat with two three-year old boys, who don't want to sit at the table for ages, but sadly it's another of their treatments. Without high calories, they are more prone to getting ill."* *"My body has given up! my son is down for a nap and I'm under a blanket on my sofa just taking a moment to myself! I'm so tired today so I've done my morning physio and now I'm treating my body to a rest. I tried putting a wash on, but my body said 'nahhh'"* Social media posts in general were mixed with positives and negatives – feelings of success when routines ("being on top of the condition") but then also, the stress, anxiety, and exhaustion as routines take their toll on both patients and carers Day-to-day management is illustrated constantly, but as a background image to other significant events. One area that was particularly prominent in this theme was that of illness. Illness experienced by patients often is expressed as a change or escalation in routine, for example an infection detected at or after clinic visits is lamented due to the increased intensity of the care routine required to deal with it. The burden of self-care, or care of a dependent, comes into sharp focus when exacerbated by acute illness. We found that modulator therapy was generally shown to result in positive changes in daily routine as some of the limiting effects of CF are reduced. This further emphasises that current treatments to target the symptoms aren't enough in helping people with CF live fulfilling lives, whereas CFTR modulators have had a significant impact on the treatment and symptoms of CF.
8. Is there an unmet need for patients with this condition?	Since the UK now has access to Kalydeco, Orkambi and Symkevi, there are two separate groups within the CF community – those ineligibles for modulator therapy and those on them. Kalydeco, Orkambi and Symkevi only cover approximately 50% of the CF community. Meanwhile, the remaining 50% of the CF population are still relying solely on treatments which manage the symptoms. Elexacaftor, tezacaftor, and ivacaftor targets the dysfunctional protein that causes cystic fibrosis. Results from the pivotal phase III clinical trials have shown potential to restore lung function, decrease hospitalisation, and address the multisystem

	nature of the disease. People with two copies of the F508del mutation had a 10 percent increase in lung function compared to treatment with the modulator tezacaftor/ivacaftor (Symkevi), and people with one copy of F508del had more than a 14 percent increase in lung function compared to placebo. In people with one copy of the F508del mutation, elexacaftor, tezacaftor, and ivacaftor was also associated with significant improvements in sweat chloride, pulmonary exacerbations and quality of life. This treatment will also reduce the burden of care whilst helping people with cystic fibrosis stay well for longer resulting in a reduction of medication use, such as corticosteroids which have a long-term negative impact on the patient and reduce use of NHS resources (clinicians, appointments, other medications). This in the long-run may also help reduce the prevalence of cystic fibrosis-related comorbidities. These improvements over time also suggest that this treatment has the potential to be transformational in its effect of the health and quality and length of life for not only patients' lives but the lives of all those who support them: partners, families, friends, and carers. Improvement in overall health will also allow people with cystic fibrosis to work full time and for longer therefore contributing to society. However, the potential transformative effect of this treatment also introduces uncertainty about the relevant pathway of care for people with CF once receiving elexacaftor-tezacaftor-ivacaftor. This expected transformational effect is such that it is unclear and uncertain how this treatment will affect standard clinical management including current treatment pathway and sequences for all or for specific groups of patients. These uncertainties are explained further in the attached information on CF STORM, an innovative trial will explore whether this treatment will lead to simplifications of the treatment burden for cystic fibrosis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	All respondents we surveyed strongly believe the treatment will enable massive improvements in their lives due to the promising clinical trial results and anecdotal feedback from those already on the treatment, where some say they feel like they no longer even have cystic fibrosis. When asked for further clarity on what the CF community expect will happen when on this treatment, everyone reiterated this will completely transform their lives as they won't need to have this constant resilience and feel like they are actually enjoying their lives rather than focusing on staying well. For example, one respondent said: "I never thought that drugs like this would exist in my lifetime as an adult with CF. The thought that future generations of people with CF, and parents of children with CF, won't have to go through what previous generations have is so important in getting access to these!" Another respondent said that: "This treatment will mean my daughter can live the life she so deserves as she's not eligible for the other CFTR modulators on the market."

	Our survey also showed that people with CF believe that the treatment will slow disease progression and increase life expectancy (98%), improve their physical symptoms (93%) and improve their quality of life such as happiness, lifestyle, work and social life (93%). Further advantages identified were around mental health (84%) and feeling more positive about the future (87%). Many also believe they will have a better ability to do daily tasks (84%) and improve their relationship with loved ones and the lives of their loved ones (72%). This is mainly attributed with the idea that access to the triple therapy will simplify their treatment regime (87%). Overall, the CF community see this treatment as close to a cure as possible and expect it will allow them to live a normal, full life. Given the significant burden of treatment that they undergo and the delays to accessing the CFTR modulators in the past, the CF community are eager to access this treatment as soon as possible. This is the true 'game changer'.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The CF community are aware that any new treatment can have negative side effects. Given how long people with cystic fibrosis have waited for such a highly effective treatment the CF community believe the benefits far outweigh any disadvantage of the treatment. In our survey, we found that only 10% of people with cystic fibrosis and their carers, are concerned about any potential negative side effects with 96% feeling that these concerns were an acceptable part of taking a new treatment. Further, our survey showed that the respondents were not concerned about taking more medication and adding to the treatment, neither were they concerned about difficulties in using the new therapy. The CF community have been struggling to maintain their daily medicine regime, that the advantages for this treatment significantly outweigh the disadvantages and make it worth the risk.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others?	None
Equality	
12. Are there any potential equality issues that should be taken into	Variation around the ability of people with cystic fibrosis to access modulator therapies has equality implications.

account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Overall, the cystic fibrosis community are anxious about facing any unnecessary delays to accessing this treatment. This is the most promising drug in an innovative pipeline that addresses the underlying cause of CF symptoms and is therefore an essential step-change in our progression towards a cure for the condition. The results cannot be disputed as not only has it shown to have a tremendous impact on a person with cystic fibrosis' overall health, but it may have wider financial benefits to the NHS such as reduced inpatient treatment and to the Government through maintenance of employment by people with cystic fibrosis. One respondent who is already on the therapy has called the treatment a 'game changer'. Another respondent who is on the therapy said the following: "Trikafta changed my life. Since I started taking it in November 2019 my Pulmonary Function Tests have improved by more than 40%. I can exercise at the gym 5 times weekly, do daily activities with more energy and efficiency than ever before, and I'm about to finish a university degree. I have hope for the future, for the first time I dream about what it's like to live to be middle aged, I can breathe like I have never been able to in my life. Every cystic fibrosis patient deserves to know what it feels like to take a deep breath."
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • This is the first highly effective therapy that is effective in up to 90% of the cystic fibrosis population and for over half of this 90% will be the first modulator therapy they can benefit from. • Efficacy in clinical trials show unprecedented results for a cystic fibrosis therapy. • Clinical data leads a heightened anticipation from both patient and clinical communities, that this therapy can not only save and extend lives but improve a host of symptoms linked to this multi-system disease. According to the 2019 CF Registry report, the median age of the 137 people who died in 2018 was 32. Median age of death is based on the people with CF who died in any given year • This is the final drug in an innovative pipeline that addresses the underlying cause of cystic fibrosis symptoms and is therefore an essential step-change in our progression towards a cure for the condition. • Responsible monitoring of real-world effects of high-cost medicines is well established in cystic fibrosis and the infrastructure to collect and report this data is in place to apply this new therapy.	

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