Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.
1. **About you and your organisation**

Your name: Ed Owen  
Name of your organisation: Cystic Fibrosis Trust  
Your position in the organisation: Chief Executive  
**Brief description of the organisation:** We are the UK’s only national charity dealing with all aspects of cystic fibrosis. We fund research to improve cystic fibrosis care and treatment, and aim to ensure appropriate clinical care and support for people with cystic fibrosis.

The Trust has not received any funding from Vertex Pharmaceuticals for work related to issues relevant to this submission. All Cystic Fibrosis Trust funding received from pharmaceutical manufacturers are carefully considered to ensure they do not breach best practice guidance regarding commercial funding agreements.

2. **Living with the condition**

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Cystic fibrosis is a multi-system, progressive, debilitating and life-limiting disease. Cystic fibrosis kills. The median age at death is just 28. Many will die as teenagers or younger.

In October 2015, the Cystic Fibrosis Trust surveyed 1426 people whose lives are affected by cystic fibrosis: people with the condition (n=248), families, partners and friends.

Our findings confirmed that cystic fibrosis imposes significant and often devastating daily challenges from birth, which affect everyone connected to the person with cystic fibrosis, that get worse with age, and make it difficult to grow, develop and plan for the future.

Additionally, the Cystic Fibrosis Trust hosts and manages the UK CF Registry, which monitors health data from over 10,000 people with cystic fibrosis in the UK, representing over 99% of the patient population. Our submission draws on data from this resource.

Cystic fibrosis necessitates a heavy burden of formal and informal care that has a wide-ranging impact and progressively increases in line with health deterioration and additional complications, such as CF-related diabetes and osteoporosis.

46% of adults with the condition told us that, on average, they will spend more than 3 hours each day on their CF treatment regime (Fig. 1 in Appendix 6).

One person with cystic fibrosis told us: “It’s exhausting. I try to carry on working and want to do this for as long as possible, however my treatments are getting more and more and massively eat into my day. My wife works two jobs and then has to spend time doing my physio and help with antibiotics. We would like to have a family which means fertility treatment and I want to be there for any potential child, however the time I spend doing treatments or being very ill concerns me.”
When asked where cystic fibrosis had impacted on their lives in the past year, our respondents highlighted that family life (67%), social life (74%), planning ahead (69%), and holidays (67%) had all suffered (Fig. 2).

70% of responders to our survey who have cystic fibrosis or support someone with cystic fibrosis told us that the condition negatively affects their financial situation (Figs 3 & 4).

In explaining this situation, a typical response would highlight the impact of frequent and costly trips to specialist care centres, the cost of providing a healthy high-calorie diet, and, most significantly, reduced earnings through a reduced ability to secure full-time employment that is commensurate with qualifications and experience, due to periods of illness or care responsibilities. Both people with the condition and their support networks report extensive underemployment, necessitated by the demands of managing the condition.

One person with cystic fibrosis said: “I’m only able to work part time as, when working full-time, my health declined rapidly due to not having time to do my treatments properly, or to exercise before work. When working full time I was earning a good salary, but finding good quality part time work is incredibly difficult, and finding good part time work which will also further your career is next to impossible. This means I end up jumping from contract to contract, earning far less than I could otherwise. But I have to put my health first, so there is no option other than to accept any part time work I can find.”

Despite the myriad challenges that people with cystic fibrosis face in work and education, the UK CF Registry records that 70% of adults with cystic fibrosis are in full- or part-time work or a student.

The psychological and emotional impact of the disease was the second most frequently referenced topic – after the burden of care – that responders mentioned when we asked what it is like to live with the condition. Symptoms of stress, insecurity, anxiety and depression are elevated in both people with cystic fibrosis and parents, with a prevalence 2 to 3 times higher, compared with the rest of the population. (A Quittner et al: Thorax, Sep 2014)

The triggers and manifestations of these symptoms are highly complex and diverse. Psychological symptoms in both individuals with cystic fibrosis and parent caregivers have been associated with decreased lung function, lower body mass index, worse adherence, worse health-related quality of life, more frequent hospitalisations and increased healthcare costs. (A Quittner et al: Thorax, Oct 2015)

In the experience of one person with cystic fibrosis: “Every day is unpredictable which means living day by day. Hardly ever making plans for too far ahead. Also sleepless nights due to various CF related things and also mental health issues. Hate being a burden and often feel sad at relying on others to help with simple things. Also being in public and coughing. My worst nightmare.”

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most
important? If possible, please explain why.

Standard cystic fibrosis care, which until the advent of a new class of highly-innovative drugs that target improved functioning of the abnormal protein that causes the symptomatic expression of cystic fibrosis, had sought solely to manage and contain symptoms.

We asked what treatment outcome is most desired when looking to tackle a chest infection and the outcome with the largest support from both people with the condition and their families told us that an increase in lung function (measured as FEV1% predicted), followed by reduced breathlessness, increased energy, and reduced coughing symptoms (Figs. 5 & 6).

However, when asked about what factors influence choices about treatments, the same groups, collectively and separately, scored a treatment’s potential to protect future health and wellbeing marginally higher than a treatment with the potential to immediately reduce symptoms and make one feel better (Figs. 7 & 8).

What is your organisation’s experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Even with an optimal treatment regime, people with cystic fibrosis develop frequent chest infections and exacerbations that will often require intravenous antibiotic therapy (IV therapy) to treat infection, inflammation and to help prevent further damage to the lungs. In 2014, the UK CF Registry recorded that 47% of patients required IV therapy with a median length of treatment of 28 days. 38.5% of patients received inpatient IV therapy with a median length of treatment of 15 days.

In our survey, IV therapy was considered by nearly 30% of responders with the condition to be the CF treatment that had the greatest adverse effect on their lives, alongside physiotherapy (32%) and nebuliser therapy (20%) (Figs. 9 & 10). When asked to rate the importance of a series of care outcomes, fewer exacerbations (86%) and fewer courses of IVs (79%) were rated as ‘very important’, behind an increased life expectancy (90%) but ahead of reduced symptoms, daily treatment burden, socialising, education and work (Figs. 11 & 12).

IV therapy is typically seen as the most disruptive treatment option in respect of planning ahead, maintaining work and education opportunities, and socialising. Hospital inpatient therapy is generally regarded as a “last resort”, as the risk of cross-infection, the subsequent isolation, and the hospital setting carry an emotional and psychological burden for all involved.

One parent says: “Our daughter hates being admitted to hospital. It can be very lonely as patients cannot mix with each other because of cross-infection. Often family and friends do not visit as the hospital is far away from where we live. She feels isolated, bored and becomes depressed.”

4. **What do patients or carers consider to be the advantages of the treatment being appraised?**

| Benefits of a treatment might include its effect on: | }
Appendix G – patient/carer organisation submission template

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

We asked people directly what benefits they expected eligible patients to gain from the lumacaftor/ivacaftor therapy.

- Improved disease progression/life expectancy scored highest (96%), followed by improved physical symptoms (91.90%), Improved quality of life (91.70%), greater capacity to do daily tasks (78%), better psychological/mental health (68%), and greater convenience/ease of use (62%)

Clinical trials show lumacaftor/ivacaftor therapy significantly reduces chest infections. We asked what a reduction in chest infections leading to intravenous antibiotic therapy would mean to the carer or the person with cystic fibrosis. The data below are extrapolated from free text:

- Improved quality of life scored highest (50%); followed by increased opportunity for employment/education (48%); improved physical and mental well-being (23%); fewer symptoms and exacerbations (14%); ability to exercise more (11%); improved life expectancy (7%) and reduced treatment burden and weight stabilisation.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Lumacaftor/ivacaftor is a relatively low burden treatment that may reduce dependence on high burden treatments, such as IV therapy, and keep people with cystic fibrosis out of hospital.

Lumacaftor/ivacaftor therapy is a twice-daily, orally-administered tablet. Only 3% of survey respondents consider tablets the most burdensome treatment. (Figs. 9 & 10)

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

No comment.
5. **What do patients and/or carers consider to be the disadvantages of the treatment being appraised?**

<table>
<thead>
<tr>
<th>Disadvantages of a treatment might include:</th>
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</thead>
<tbody>
<tr>
<td>• aspects of the condition that the treatment cannot help with or might make worse</td>
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<tr>
<td>• difficulties in taking or using the treatment (for example, injection rather than tablets)</td>
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<tr>
<td>• side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)</td>
</tr>
<tr>
<td>• where the treatment has to be used (for example, in hospital rather than at home)</td>
</tr>
<tr>
<td>• impact on others (for example, family, friends and employers)</td>
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<tr>
<td>• financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)</td>
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<tr>
<td>• any other issues not listed above</td>
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Please list any concerns patients or carers have about current NHS treatments in England.

Please see Answer 3(b).

Please list any concerns patients or carers have about the treatment being appraised.

A strong theme emerged from our questions in this area: the benefits outweigh the disadvantages. Some said it depended on the side effects, others that side effects are inevitable. Below are some key statistics that reflect this:

**We asked people if they had any concerns about potential side-effects or disadvantages of the therapy.**

- 75% of respondents had concerns about potential side-effects
- 50% had concerns about aspects of their condition that this therapy cannot help or might make worse
- 21% had concerns about difficulty in taking or using the therapy

**We then asked if respondents consider these disadvantages to be an acceptable part of the treatment. 88% felt they would be acceptable.**

We then asked why potential disadvantages were an acceptable part of the treatment. Respondents typically suggested that side effects where acceptable if, on balance, the therapy delivered net benefit in preferred treatment outcomes, including: lung function, life expectancy and quality of life. Many responses highlighted that clinicians would be able to support them to make informed decisions on the relative benefit/disadvantage ratio of the therapy.

One respondent commented: “As an adult with CF, time is not on our side. Any new treatment is worth trying.”
If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No comment.

6. **Patient population**

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

No comment.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No comment.

7. **Research evidence on patient or carer views of the treatment**

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered ‘no’, please skip the rest of section 7 and move on to section 8.

Please comment on whether patients’ experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

No comment.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The pivotal Phase III clinical trials for the lumacaftor/ivacaftor combination therapy, TRAFFIC and TRANSPORT, captured important treatment outcomes for people with cystic fibrosis. The importance of FEV1 and pulmonary exacerbations as outcome measures have been discussed, and Body Mass Index (BMI) is associated with resilience to infection and health stability.

As discussed, improved quality of life rates highly as a desired treatment outcome, with 95% of adults with the condition saying they consider it an important factor in deciding which treatments they take (Fig. 13). The Phase III trials did seek to measure effect on quality of life by collecting data on patient-reported respiratory symptoms through the CF questionnaire-revised (CFQ-R) – a clinically validated instrument.
Appendix G – patient/carer organisation submission template

However, the Cystic Fibrosis Trust believes this measure generally does not accord with the way people with the condition and their families think about quality of life and will not be sensitive enough to understand the impact of the treatment and cannot be used in isolation to draw conclusions about the impact of the therapy on quality of life.

For people with cystic fibrosis and their loved ones, quality of life may mean: liberation from daily maintenance treatment, freedom from regular exacerbation, greater resilience, ability to plan for the future, better energy levels, sleeping better, and a more general sense of functional fitness.

These are basics of security and independence, and by measuring respiratory symptoms through the CFQ-R alone, they are significantly overlooked in valuing the impact of this therapy on quality of life. Further study that utilises a more sensitive and person-centred instrument is necessary to assess real impact on quality of life.

One person commented: “[The trial endpoints] are clinically important but, for patients, factors such as quality of life are more important e.g. I went to a comedy show and I was able to laugh without coughing. FEV1 won't measure this. It's the qualitative factors which matter most to people with CF.”

An additional significant limitation of the trial data, in the context of its mode of action and effect, is its relatively short-term nature. For a therapy with a protective effect on health status, much longer-term data are the only way to achieve a clearer picture of clinical benefit or to understand the impact on quality of life. The Trust’s views on this subject are discussed further in the section for issues for the Appraisal Committee to consider.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No comment.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes  ☐ No

If yes, please provide references to the relevant studies.

Please see appendices.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.
Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No comment.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No comment.

9. **Other issues**

Do you consider the treatment to be innovative?

X Yes □ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The technology is the first disease-modifying therapy available to this patient group, targeting the cause, not the symptoms, of the disease. In this respect, it must be considered a 'step-change' therapy, and as a new, original and advanced mechanism of therapy in cystic fibrosis must be classed as highly innovative.

The treatment’s health-related benefits are a result of partial correction of the specific dysfunctional protein that causes cystic fibrosis, as opposed to combating the abnormal symptomatic expression of the protein’s faulty functioning.

This constitutes a fundamental shift in approach for both patients and clinicians and has been described as the beginning of effective therapy for cystic fibrosis associated with the most common mutant form of CFTR (P Davis – NEJM, Jul 2015).

Are there any other issues that you would like the Appraisal Committee to consider?

The Cystic Fibrosis Trust recognises that this therapy is a typical rare disease product in that it targets a small population with significant unmet need, has an innovative mechanism of action, and has an immature body of data that naturally cannot describe the full-extent of the clinical potential of this novel and innovative therapy.

However, the product has sufficiently demonstrated safety and efficacy through well-powered and executed Phase III clinical trials. As such, the Cystic Fibrosis Trust
believes that clinicians should be given the opportunity to prescribe this treatment with minimum delay.

Given the opportunities that present themselves in cystic fibrosis care – a defined patient population, a high-quality patient data registry, and a well-established network of specialist care centres with well-established protocols and routines for data collection – it is imperative that the Appraisal Committee explore how these assets can be innovatively used, within the assessment process, by all parties, to support negotiated access to this safe and effective therapy and to facilitate improved understanding of the therapy.

10. **Key messages**

In no more than 5 bullet points, please summarise the key messages of your submission.

- The therapy is safe and effective, and targets clinical outcomes that are most associated with disease progression and early death.
- The therapy reduces the number of pulmonary exacerbations, which are causal events directly linked to treatments viewed by people with cystic fibrosis and carers as the most burdensome and disruptive to daily life.
- The UK CF Registry and network of specialist care providers is a unique environment for further drug efficacy evaluation and must be utilised.
- The therapy is highly-innovative and unique in this patient population as the first and only licensed disease-modifying therapy.
- Clinicians should be given the opportunity to prescribe this treatment with minimum delay.

Uploaded to ‘NICE Docs / Appraisals’, alongside this submission are the following appendices:

- **Appendix 1** – Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK, 2nd edition – December 2011
- **Appendix 2** – UK Cystic Fibrosis Registry 2014 Annual Data Report
- **Appendix 4** – CFF and ECFS consensus statements for screening and treating depression and anxiety (A Quittner et al: Thorax, Oct 2015)
- **Appendix 5** – Another Beginning for Cystic Fibrosis Therapy (P Davis: NEJM, Jul 2015)
- **Appendix 6** - Charts and figures from Oct 2015 survey
- **Appendix 7** – Full survey
- **Appendix 8** – What’s it like to live with cystic fibrosis - [https://vimeo.com/145843717](https://vimeo.com/145843717)

We ask that these appendices are made available to the Appraisal Committee.