**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

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

**Consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees. All comments were considered when finalising the scope.[a]

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] |
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| Appropriateness | Association of Chartered Physiotherapists in Cystic Fibrosis | It is appropriate to refer this topic to NICE for appraisal. |
| | British Thoracic Society | This is felt to be a highly relevant consultation for NICE. The current CF modulator drugs are highly effective and triple combinations show even more promise, AND cover around 90% of the CF population with regard to eligible genotype – which gives wider access compared with Symkevi and Orkambi |
| | Cochrane | Yes, it is appropriate for this topic to be appraised by NICE. |
| | Cystic Fibrosis Trust | Providing national guidance on the use of this technology would be beneficial for the CF clinical and service-user communities. |

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| Section | Consultee/ Commentator | Comments [sic] |
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| | CF Voices | Yes |
| | UK Cystic Fibrosis Pharmacists Group | Yes – would be very valuable to have definitive guidance on this technology which has the potential to have a significant benefit on the health of people with Cystic Fibrosis<br>We hope that putting this technology through this process using comparators that have been commissioned but not been assessed through a NICE TA will not adversely affect the availability of this or any other treatment for people with CF. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | Definitely – Three CFTR modulators are now available for CF patients who fall under the correct criteria for each medication, and this fourth modulator should cover the majority of CF patients not already covered for treatment with the three available modulators. |
| | UK Cystic Fibrosis Medical Association | Yes. This drug offers a major advance in CF care and would also be suitable for a wider number of patients with the appropriate genotype compared to current available CFTR modulators. |
| | Vertex | Yes, it is appropriate to refer this topic to NICE. |
| Wording | Association of Chartered Physiotherapists in Cystic Fibrosis | No alternative wording is required |
| | British Thoracic Society | The Title of the appraisal is NOT accurate :-<br>Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation<br>Should read |

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| | | Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with at least one copy of F508del mutation<br><br>With regards cost effectiveness – these drugs are additive to “standard care” and are likely to increase long term survival, and thus will increase cost of care compared with standard care. However the benefits on lung function , pulmonary exacerbations are highly significant. |
| | Cochrane | The current wording is appropriate and no alternative wording is required. |
| | Cystic Fibrosis Trust | The wording is clear and accurate. |
| | CF Voices | Yes.<br><br>However as two of the three active components (tezacaftor and ivacaftor, as Symkevi) are already routinely commissioned, it may be appropriate to appraise elexacaftor as a separate technology to be used in addition to the currently commissioned Symkevi/ivacaftor.<br><br>Please replace the word ‘mutation’ with ‘variant’ throughout the draft scope. As per adopted guidelines from the Association for Clinical Genomic Science, the use of ‘variant’ removes the negative connotation sometimes associated with the use of ‘mutation’. |
| | UK Cystic Fibrosis Pharmacists Group | Yes |
| | UK Clinical Pharmacy Assocation (UKCPA) | Yes |

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|---|---|---|
| | Respiratory Group | |
| | UK Cystic Fibrosis Medical Association | We suggest:<br>Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with at least one copy of F508del mutation |
| | Vertex | The wording of the remit should read:<br><br>'To appraise the clinical and cost effectiveness of VX-445 (elexacaftor), tezacaftor and ivacaftor for the treatment of cystic fibrosis in patients aged 12 and older with at least one F508del mutation in the CFTR gene.' |
| Timing Issues | Association of Chartered Physiotherapists in Cystic Fibrosis | We would consider that there is a matter of urgency required. People with Cystic Fibrosis carrying at least 1 copy of the F508del mutation currently being cared for in the NHS would benefit from this as for some there are no other treatment options currently available. |
| | British Thoracic Society | Urgent need for review |
| | Cochrane | We consider that there is a matter of urgency with regards to this appraisal. People with cystic fibrosis (CF) with at least 1 copy of the F508del mutation who are currently under the care of the NHS would benefit from this. For some of these patients there are no other treatment options currently available. |
| | Cystic Fibrosis Trust | Providing guidance that would facilitate routine access to this treatment is of critical urgency to all individuals who could benefit. The scale of benefit demonstrated by the Phase III trials |

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| | | suggests that the technology could address significant unmet need in all eligible individuals, who are not already able to benefit from the highly effective modulator therapy Kalydeco (ivacaftor).<br><br>Case reports already suggest that elexacaftor, tezacaftor and ivacaftor combination therapy can substantially improve the health and quality of life of people experiencing end-stage CF disease. This acute benefit, demonstrated in a relatively healthier population in the Phase III trials, is in addition to the reduction in health events linked to disease progression observed in the trials. Cystic fibrosis is a progressive condition and the protection of health is a priority of people with cystic fibrosis and their families.<br><br>This is a step change therapy across all populations above comparator combination treatments (ivacaftor-lumacaftor, ivacaftor-tezacaftor), while showing comparable levels of efficacy to ivacaftor monotherapy for a much greater eligible population. |
| | CF Voices | The highest urgency. Approximately 50% of people with Cystic Fibrosis are currently untreated with CFTR modulator therapies or other therapy that can tackle the root cause of this life-threatening condition. This technology could reduce that to around 10% as well as improving the lives of 40% of those currently treated. The real possibility of this technology saving and improving lives should place this appraisal to the highest level of urgency. Every day of delay means irreversible damage to patients health and life expectancy. |
| | UK Cystic Fibrosis Pharmacists Group | Significant pressure from the CF community. Also, current inequity due to availability of oral disease modifiers for some, but not all people with CF. This technology has the potential to address a significant amount of that inequity. |
| | UK Clinical Pharmacy | Very urgent – this is the fourth and final CFTR modulator in the Vertex catalogue. Triple therapy is currently available in England via a compassionate use programme, currently using |

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| | Assocation (UKCPA) Respiratory Group | trial (non-commercial) stock and some hospitals cannot agree with the Vertex contract leading to some very sick CF patients not having any form of CFTR modulator therapy which could potentially be life changing. |
| | UK Cystic Fibrosis Medical Association | Urgent.<br>This treatment is highly effective and offers a step change in care over and above existing CFTR modulator therapy. A significant number of patients currently have no access to modulator therapy and this treatment will address this. |
| | Vertex | Given the potential positive impact of this technology for patients with CF, it is appropriate that this topic is referred for consideration by NICE in line with regulatory timelines. CF is a life-limiting condition, with median life expectancy of 32 years for UK patients.1 Therefore, there is a need for expanded and improved treatment options in this area. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] |
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| Background information | Association of Chartered Physiotherapists in Cystic Fibrosis | Whilst the background outlines the current management of the person with CF, it does not consider the impact of the modulator drugs that are now available and the positive effects they and this proposed therapy have had on the lives of people with CF. |
| | British Thoracic Society | The background does not adequately cover the context of this new modulator. It does not explain which patients ( CF patients homozygous for DF508) benefit from Symkevi and Orkambi - compared with triple modulator ( CF patient with only 1 copy of DF508) this information is important context when discussing this new triple therapy |

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| | | Triple therapy will be able to treat (almost) all DF508/ other mutations including DF508/DF508 and replace Symvevi and Orkambi as treatments. |
| | Cochrane | Information is accurate and complete. |
| | Cystic Fibrosis Trust | Please update the wording of the final paragraph to make clear the indications for ivacaftor, ivacaftor-lumacaftor, and ivacaftor-tezacaftor and that there are a group of patients not eligible for any existing treatments. |
| | CF Voices | In the last paragraph, add approximate number and percentage of eligible patients in England that may access treatment with ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor. |
| | UK Cystic Fibrosis Pharmacists Group | We don't believe that the statement "Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease" is now true due to the availability and clinical use of Ivacaftor, Lumacaftor/Ivacaftor and Tezacaftor/ivacaftor in the UK. The statement reads as though the access to disease modifiers is completely new, whereas Ivacaftor has been in use for a number of years, and people with CF have achieved access to Lumacaftor/Ivacaftor and Tezacaftor/Ivacaftor through access schemes. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | The statement in paragraph 3 'Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease.' Is now no longer the case with the availability of the 3 CFTR modulators via the NHS for certain genotypes. |
| | UK Cystic Fibrosis Medical Association | It would be helpful to detail the indications for existing CFTR modulators: Ivacaftor, ivacaftor-lumacaftor, and ivacaftor-tezacaftor and to make it clear that there are a significant number of patients who do not have access to any existing CFTR modulator treatments currently. |

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| | Vertex | The background information states that current treatments for CF manage the symptoms rather than the cause of the disease. This is not completely accurate, prior to the advent of CFTR modulators, treatments for cystic fibrosis were aimed at manging symptoms and complications rather than the underlying cause of disease. In recent years ivacaftor has been standard of care for patients aged six years and above who have at least one copy of a licensed gating mutation since the publication of the commissioning policy in 2013.2 Since then, this has also been expanded to patients with R117H mutations and patients aged six months and above with at least one copy of a licensed gating mutation, and the vast majority of eligible patients are treated with ivacaftor.<br><br>This established practice is reflected in clinical guidelines such as the European Cystic Fibrosis Society's best practice guidelines, which state that ivacaftor should be considered as part of the standard of care in patients with gating mutations.3<br><br>Equally, CFTR modulators tezacaftor/ivacaftor and lumacaftor/ivacaftor are both available for patients under the terms of the commissioning policy effective in November 2019.4 Since this agreement, approximately [redacted] of eligible patients aged 12 and above have received a prescription and based on the rate of adoption of these therapies in other jurisdictions, it is expected that the vast majority will be on treatment by the time VX-445 (elexacaftor), tezacaftor and ivacaftor receives marketing authorisation.<br><br>Therefore, we anticipate that most patients with CF in England if eligible based on their genotype will be prescribed a CFTR modulator, in accordance with the relevant commissioning policy. |

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| The technology/ intervention | Association of Chartered Physiotherapists in Cystic Fibrosis | Yes |
| | British Thoracic Society | Yes |
| | Cochrane | Description is accurate. |
| | CF Voices | yes |
| | UK Cystic Fibrosis Pharmacists Group | The wording of the intervention is a little confusing: “Elexacaftor, tezacaftor and ivacaftor combination therapy, followed by ivacaftor monotherapy” suggests that people treated would receive the combination treatment for a fixed period followed by Ivacaftor single agent treatment which is not the case. We believe the intention is to describe treatment with the triple combined tablet in the morning and the single agent ivacaftor in the evening on an ongoing basis. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | Yes |
| | UK Cystic Fibrosis Medical Association | Yes |
| | Vertex | VX-445 (elexacaftor), tezacaftor and ivacaftor should be referred to as a CFTR protein modulator throughout, rather than a systemic protein modulator. |
| Population | Association of Chartered | This is an appropriate population. |

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| | Physiotherapists in Cystic Fibrosis | |
| | British Thoracic Society | The population is defined appropriately as CF patient with at least one DF508 mutation. Perhaps it should be made clearer that “at least one DF508 mutation” also includes DF508/DF508 – therefore covers the group already treated with Symkevi and Orkambi |
| | Cochrane | The population is appropriate. |
| | Cystic Fibrosis Trust | Please update the wording of the final paragraph to make clear the indications for ivacaftor, ivacaftor-lumacaftor, and ivacaftor-tezacaftor and that there are a group of patients not covered by any existing treatments |
| | CF Voices | Yes |
| | UK Cystic Fibrosis Pharmacists Group | Agree |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | Yes, the population is listed appropriately |

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| | UK Cystic Fibrosis Medical Association | The population is defined appropriately and would include patients who have two copies of the DF508 mutation. It may be helpful to make this clearer. |
| | Vertex | It is appropriate that the patient population under consideration is people aged 12 years and above with CF with at least one F508del mutation. |
| Comparators | Association of Chartered Physiotherapists in Cystic Fibrosis | Established clinical management treatments for cystic fibrosis address the symptoms and complications rather than the cause of the disease.<br>However, these are still considered best alternative care for the population carrying at least 1 copy of the F508del mutation. |
| | British Thoracic Society | The standard treatment should be described as “usual treatment” or “standard treatment” and not “best supportive care”<br><br>However the technology should be compared with Symkevi and Orkambi and not be compared with usual treatment. |
| | Cochrane | The current established clinical management of people with CF treats the symptoms and complications rather than addressing the underlying cause of the disease.<br>However, these treatment regimens are still considered the best alternative care for patients with CF and at least 1 copy of the F508del mutation. |
| | Cystic Fibrosis Trust | Ivacaftor, lumacaftor-ivacaftor, and tezacaftor-ivacaftor are important comparator therapies for this technology that, alongside supportive care, represent the best standard of care for eligible individuals. |
| | CF Voices | Comparators should be sub grouped by those;<br>- not treated with CFTR modulators, best supportive care. |

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| | | - treated with Ivacaftor monotherapy (Kalydeco)<br>- treated with Lumacaftor/Ivacaftor (Orkambi)<br>- treated with Tezacaftor/Ivacaftor (Symkevi)<br>as Kalydeco, Orkambi & Symkevi are now routinely commissioned and are considered part of the best standard of care. Elexacaftor/tezacaftor/ivacaftor will replace the use of Orkambi and Symkevi, therefore offsetting the current cost of these treatments. |
| | Neonatal and Paediatric Pharmacists Group | Triple therapy should be compared against tezacaftor/ivacaftor for >12yr as it is the current gold standard, as opposed to placebo as comparing to placebo would inflate its benefits much more. |
| | UK Cystic Fibrosis Pharmacists Group | Needs to expressly include treatment with tezacaftor/ivacaftor as current standard of care for people homozygous for F508. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | The standard treatments now include the three CFTR modulators – Kalydeco, Orkambi and Symkevi & Kalydeco for CF patients with the correct genotypes for each treatment.<br>Of these treatments, the Symkevi & Kalydeco should be included as a comparator for F508del homozygotes and other applicable genotypes as this is 'best alternate care' treatment for patients who fall into the correct CFTR genotypes for treatment, and Kalydeco monotherapy should be included as standard care for appropriate genotypes such as G551d and R117H.<br>Orkambi should not be included as a comparator.<br>The list of key treatments currently mentioned is not exhaustive and does not include airway clearance, NIV, oxygen therapy and insulin for CFRD at present. |
| | UK Cystic Fibrosis Medical Association | Ivacaftor, ivacaftor-lumacaftor, and tezacaftor-lumacaftor are important comparator therapies for sub-populations of this technology which have now become standard care for these groups and should be included as comparator therapies in this appraisal. |

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| | Vertex | The appropriate comparators for this assessment are the following, and depend on the genotypes:<br>• **tezacaftor/ivacaftor** – licenced for the following mutations: homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.[5]<br>• **ivacaftor** – licenced for the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R, P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G, or 3849+10kbC→T.[6]<br>• **Best Supportive Care**<br><br>There are several reasons why BSC alone should not be considered as the only relevant comparator for all patients.<br><br>• NICE methods clearly state that the comparator should be established clinical practice in the NHS in England.[7] Within 2 months of the commissioning policy for lumacaftor/ivacaftor and tezacaftor/ivacaftor [redacted] of eligible patients 12 years and above have received prescriptions. Of those patients, [redacted] have been prescribed tezacaftor/ivacaftor. Based on the rate of adoption of these therapies in other jurisdictions, it is anticipated that most eligible patients will be on tezacaftor/ivacaftor by the time VX-445 (elexacaftor), tezacaftor and ivacaftor receives marketing authorisation. Therefore, tezacaftor/ivacaftor should be considered a relevant comparator.<br><br>• Ivacaftor has been established practice for the treatment of CF patients with gating mutations since 2013, as stated in the NHS England commissioning policy.[2] Currently, the vast majority of eligible patients for ivacaftor are being treated with this CFTR modulator. |

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| | | • The importance of the consideration of established practice in identification of relevant comparator(s) was demonstrated in the assessment of treatments for Wet Age related Macular Degeneration (TA294) where NICE stated that it was appropriate to consider the unlicensed bevacizumab (Avastin) as the comparator.[8] This decision was made on the basis that bevacizumab was clearly established clinical practice in England, despite the fact a NICE TA had not taken place for bevacizumab in that indication.<br><br>• Also, a successful appeal against the result of TA459 for the treatment of Dupuytren's Contracture, was partly based on the fact that the comparator chosen by NICE was not considered established practice.[9]<br><br>In conclusion, based on current clinical practice and depending on genotypes the appropriate comparators for this assessment are:<br>• tezacaftor/ivacaftor<br>• ivacaftor<br>• Best Supportive Care |
| Outcomes | Association of Chartered Physiotherapists in Cystic Fibrosis | This outcome list is fairly comprehensive; however we think it should also consider exercise tolerance/capacity. |
| | British Thoracic Society | Exercise tolerance / capacity should be considered as an additional outcome measure.<br><br>Triple therapy is likely to reduce the number of exacerbations in the short term (and therefore length of hospital stay) and requirement for lung transplantation longer term for our patients (freeing up organs for a very long waiting list). |

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| | Cochrane | There is a comprehensive list of outcome measures planned, but exercise, physical activity capacity and exercise tolerance should also be considered. |
| | Cystic Fibrosis Trust | The limited timeframe of the trial and the relatively small trial populations may increase uncertainty in modelling clinical- and cost- effectiveness.<br><br>The Cystic Fibrosis Trust believes that the UK CF Registry is a valuable tool for real-world outcomes observation that can support Health Technology Appraisal bodies to address areas of uncertainty over longer-term or wider impacts of a technology in routine practice. |
| | CF Voices | Also include:<br>- need for lung transplantation<br>- mental health-related quality of life for patient<br>- mental health-related quality of life for patient carers<br>- physical health-related quality of life for patient carers<br>socio-economic effects of treatment, patient's and carer's ability to remain in employment, days in school, level of education obtained, life earnings, financial independence etc. |
| | UK Cystic Fibrosis Pharmacists Group | We would propose adding in two additional outcomes:<br>- Pulmonary bacterial (or microbial) colonisation pre- and post-treatment<br>- Ability to deprescribe current standard treatments (and hence save costs and possibly improve QoL) |
| | UK Clinical Pharmacy Assocation (UKCPA) | Yes |

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| | Respiratory Group | |
| | UK Cystic Fibrosis Medical Association | Yes |
| | Vertex | In addition to those outcomes listed in the draft scope, it is important that NICE considers the following:<br>• Overall survival – the relationship between risk factors and mortality in CF is well established and given the impact of VX-445 (elexacaftor), tezacaftor and ivacaftor in clinical studies it is reasonable to expect survival gains with VX-445 (elexacaftor), tezacaftor and ivacaftor.[10]<br>• Weight gain - Weight and lung function are linked, and better nutrition is associated with living a longer and healthier life. CF patients struggle to achieve healthy weight levels therefore the importance of this outcome within the scope of this appraisal.[11]<br>• Care-giver quality of life (QoL) to reflect the significant burden the disease has on carers<br>• Extra-pulmonary manifestations of CF |
| Economic analysis | Association of Chartered Physiotherapists in Cystic Fibrosis | Selection of the most appropriate time horizon is challenging as we cannot predict how these medications will affect respiratory function in all patients with differing degrees of respiratory compromise.<br>Longitudinal changes rather than acute changes in ppFEV1 are more clinically relevant for assessing long-term outcomes of cystic fibrosis, and an increase in ppFEV1 would be associated with a lower risk of exacerbation thus requiring fewer medical interventions. Therefore, from a health economics perspective, a person benefiting from this life-altering medication will rely less on inpatient hospitalisation, the need for intravenous medications and the need for inhaled |

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| | | therapies. This will subsequently ease the current pressures on the capacity of the specialist CF centres.<br><br>With the implementation of this new therapy there is a potential for reduction in costs both as a consequence of delayed pulmonary deterioration (i.e. inhaled antibiotics and mucoactive drugs) and those relating to the development of significant co-morbidities associated with CF.<br><br>The availability of this medication will have a positive impact on quality of life and the effective contribution to the economy when the young person can then seek employment, gain employment, and to stay in employment as a result of expected improved health status. |
| | British Thoracic Society | Difficult to identify an appropriate time horizon. Response to therapy may vary between patients with mild – severe lung disease. Improvement in FEV1 and reduction in pulmonary exacerbations will have an impact on long term cost of supportive treatments required.<br><br>These improvements in combination with improved quality of life are likely to increase opportunity for people with CF to have improved engagement in education and fulfil meaningful employment thereby having a positive contribution to the wider economy. |
| | Cochrane | It is a challenge to select the most appropriate time horizon.<br><br>Significant economic benefits are unlikely to be seen in the short term and any economic effect will be limited. However, on consideration of the health economics, it would be expected that a patient benefiting from this life-changing treatment will likely need fewer periods of inpatient hospitalisation and the reduced need for both intravenous medications and inhaled therapies. In turn, this will ease the current pressures on the capacity of the specialist CF centres.<br><br>This treatment will also positively impact on a patient's quality of life and enable a young patient to effectively contribute to the economy as they will be in a position to seek employment. |
| | Cystic Fibrosis Trust | The limited timeframe of the trial and the relatively small trial populations may increase uncertainty in modelling clinical- and cost- effectiveness. |

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| | | The Cystic Fibrosis Trust believes that the UK CF Registry is a valuable tool for real-world outcomes observation that can support Health Technology Appraisal bodies to address areas of uncertainty over longer-term or wider impacts of a technology in routine practice. |
| | CF Voices | This is a life-long treatment for a life-long condition and economic analysis needs to reflect the life-changing potential of this technology, particularly when administered at an early age. Cystic fibrosis can become a manageable outpatient condition with early intervention and the true value of this cannot possibly be gleaned from short term clinical trial data. In many respects this is a preventive technology, not an intervention technology, so a high proportion of the effects are seen in the mid-long term future rather than immediately or over the short term. For this reason a managed access scheme was devised for Orkambi/Symkevi/Kalydeco which can inform the appraisal of this technology, but data will not be available for nearly 2 years. Patients cannot be allowed to wait that long, so a managed access mechanism to allow urgent availability of Trikafta as soon as possible after licensing must be worked out, particularly for those patients currently untreated. We urge the company to submit such a proposal and NICE and NHSE to begin constructive talks to negotiate an agreement as soon as possible. Results could then be seen over the next few years and a price relative to the performance of the technology in the real world can be reimbursed.<br><br>Given that generic forms of Ivacaftor and Lumacaftor are commercially available elsewhere in the world, it is reasonable to assume availability of a generic version of Elexacaftor and tezacaftor after a period of time. |
| | UK Cystic Fibrosis Pharmacists Group | Agree |
| | Vertex | A lifetime horizon |

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| Equality and Diversity | Association of Chartered Physiotherapists in Cystic Fibrosis | In October 2019, NHS England announced they and Vertex concluded an access agreement to enable eligible patients in England access to treatment with ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor via the NHS. This was in line with the devolved nations.<br><br>However, these recently approved modulator therapies are not effective in 90% of the CF population carrying only 1 copy of the F508del mutation.<br><br>If this medication cannot be prescribed for this population beyond those who warrant it on compassionate access – there may be serious implications for the physical and mental health and well-being of the young person with CF. Long periods of hospitalisation will impact on their ability to appropriately socialise with their peers, thus impacting on personal growth and development. Additionally, periods of hospitalisation impact on schooling and educational opportunities.<br><br>Registry data from the UK CF Trust can outline how many adolescents and young adults (who are likely to benefit from this medication) progress into higher or further education. This in turn has an impact on the Health and Social wellbeing of the current CF population.<br><br>Due to the unpredictable nature of the condition, it can be difficult to make plans for the future and this has a substantial impact on psychological wellbeing (for example, causing symptoms of stress, anxiety and depression) in all individuals with CF. |
| | British Thoracic Society | Modulator therapies currently available are not effective in a large proportion of patients who carry only one copy of F508 del mutation.<br><br>This triple therapy treatment will widen access to those patients with only one copy of DF508. |

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| | Cochrane | Some modulator therapies (ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor) have recently been approved for eligible patients in England to access via the NHS. This brings England into line with Scotland and Wales. However, these therapies are not effective in 90% of people with CF who only have 1 copy of the F508del mutation.<br><br>If triple therapy can not be prescribed for these CF patients except for those given it on compassionate grounds, there may be serious implications for the physical and mental health and well-being of young CF patients.<br><br>Long periods of hospitalisation will affect their ability to socialise with their peers appropriately, and so affect their personal growth and development. Such periods of hospitalisation also affect schooling and other educational opportunities. |
| | CF Voices | Consideration must be made to the moral case of genetic discrimination, should the technology receive a negative recommendation. This would lead to a situation where approx. 50% of the patient population would be able to access a life extending treatment under the existing commissioning of Kalydeco, Orkambi & Symkevi, yet 40% of people with the same condition will not be able to access a marketed treatment with superior clinical effectiveness. Given that the consequence of not receiving treatment is life threatening this situation would cause immeasurable harm to those patients and must act as an incentive for all sides to use the managed entry mechanisms available to prevent such an outcome. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | Regarding the question in the questions for consultation in appendix B:<br><br>'Do you consider elexacaftor in combination with tezacaftor and ivacaftor to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?'<br><br>I consider the answer to be yes – the phase 3 data are a huge step change in my opinion. |

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| | Vertex | The current wording of the remit appropriately covers the expected patient population, as all patients with at least one F508del mutation would be considered. |
| Other considerations | Association of Chartered Physiotherapists in Cystic Fibrosis | In clinical trials of the triple combination therapy, people with two copies of the F508del mutation had a 10% increase in lung function compared to treatment with Tezacaftor/Ivacaftor (Symkevi), and people with a single copy of F508del had more than a 14% increase in lung function compared to treatment with the placebo. The impact of this improvement in respiratory function should not be understated.<br>A diagnosis of CF significantly impacts on the lives of families and carers of an affected individual. This can also impact on the financial and health economics of the nation. |
| | British Thoracic Society | The population is defined appropriately as CF patient with at least one DF508 mutation. Perhaps it should be made clearer that “at least one DF508 mutation” also includes DF508/DF508 – therefore covers the group already treated with Symkevi and Orkambi |
| | Cochrane | Recently published studies, showed that compared to a placebo, elexacaftor/ tezacaftor/ivacaftor led to:<br>- better lung function as measured by forced expiratory volume in 1 second (FEV1) % predicted – at four weeks this was 13.8 points higher and at 24 weeks it was 14.3 points higher;<br>- a lower pulmonary exacerbation rate (63% lower);<br>- higher scores in the quality of life (QoL) respiratory domain from the CF questionnaire (20.2 points higher) indicating patients judged they had a better quality of life in terms of respiratory symptoms; and<br>- lower sweat chloride concentration was (41.8 mmol/L lower, $P < 0.001$) for all comparisons.<br>The further implications of these results will definitely impact positively on the ongoing morbidity and health-related QoL of patients with CF. |

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| | CF Voices | This technology is in a class of drugs currently being provided by NHSE through a managed access scheme. The third of these drugs; Symkevi is provided ahead of NICE appraisal on the basis of its similarity to Orkambi and Kalydeco. It is appropriate and necessary that the same approach is taken towards this technology, which is shown to be far superior in clinical trials and meets the unmet need of 3,300 patients.<br>We urge NICE and NHSE to work with the company on a similar scheme to begin swiftly after EMA approval. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | It would be helpful to address whether triple therapy is more effective than ivacaftor monotherapy in F508del/G551D patients – I do not think this was included the Middleton NEJM paper/ |
| Innovation | Association of Chartered Physiotherapists in Cystic Fibrosis | Yes - this is indeed a significant and effective step change in the management of the condition. |
| | British Thoracic Society | YES – highly innovative. This is a 'step change' in the management of CF disease for eligible patients |
| | Cochrane | This treatment will significantly and substantially affect and change the management of people with CF. |
| | Cystic Fibrosis Trust | This is a step change therapy across all populations above comparator combination treatments (ivacaftor-lumacaftor, ivacaftor-tezacaftor), while showing comparable levels of efficacy to |

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| | | ivacaftor monotherapy for a much larger eligible population. The availability of rapidly impactful, highly effective modulator therapy is a step-change moment in the treatment of cystic fibrosis.<br><br>The effect of modulator therapies on cystic fibrosis co-morbidities including sinus issues, cystic fibrosis related diabetes, digestive issues, arthritis, and pain is not well represented in evidence and only just starting to be understood.<br><br>The limited timeframe of the trial and the relatively small trial populations may increase uncertainty in modelling clinical- and cost- effectiveness.<br><br>The Cystic Fibrosis Trust believes that the UK CF Registry is a valuable tool for real-world outcomes observation that can support Health Technology Appraisal bodies to address areas of uncertainty over longer-term or wider impacts of a technology in routine practice. https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry |
| | CF Voices | Yes, it is innovative.<br>The QALY calculation needs to include the significant benefits to the mental-health of the patient and the many impacts on carer quality of life. CF Voices has been formed to provide insights and inform data collection to assist the current managed access scheme to enable this benefit to be taken into account. Impact on carer health-related quality of life was listed as a key area of uncertainty by NICE. |
| | UK Cystic Fibrosis Pharmacists Group | Yes. People with CF have derived significant tangible benefit from the introduction of disease-modifying agents (particularly ivacaftor and tezacaftor/ivacaftor) but by their nature these exclude a significant number of people with CF from treatment (as they are not effective in people with all genotypes). |

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| | | This technology will provide treatment for a large number of those people currently without a treatment option.<br><br>It may be very difficult to capture, but we see the effect on this exclusion from treatment on the wellbeing of people with CF who don't have access. Particularly on their mental health and emotional wellbeing. |
| | UK Clinical Pharmacy Assocation (UKCPA) Respiratory Group | Yes |
| | UK Cystic Fibrosis Medical Association | YES<br>This treatment is a 'major step change in the management of Cystic Fibrosis for eligible patients (around 90% of the CF population) |
| | Vertex | Results of the clinical trial program of VX-445 (elexacaftor), tezacaftor and ivacaftor combination therapy demonstrated unprecedented improvements in lung function relative to placebo and clinically meaningful and significantly greater improvement in lung function compared to other CFTRm.12 In addition, substantial improvements in health-related quality of life as measured by the CFQ-R were also reported across multiple aspects of QoL, and importantly substantial and significant reductions in pulmonary exacerbations, which are debilitating events in the lives of CF patients, were significantly reduced vs. placebo. |

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| | | By expanding highly effective disease modifying treatment to a substantial population of patients without a current CFTR modulator treatment, and by providing robust additional benefit to patients currently eligible for CFTR modulators, VX-445 (elexacaftor), tezacaftor and ivacaftor combination therapy represents a step-change innovation in the treatment for CF patients with at least one F508del allele.<br><br>CF is a multisystemic disease that impacts multiple organ systems and aspects of quality of life. The QALY calculation for prior CF products has only considered the pulmonary impacts of CF.13 VX-445 (elexacaftor), tezacaftor and ivacaftor has demonstrated substantial improvements across multiple aspects of quality of life. Moreover, CF places a considerable burden upon carers, with great impact on their quality of life. This may manifest in days taken off work due to the need to care for a patient, frequent and unplanned hospitalisation, a lack of productivity and poor mental health. The impact to caregivers should be reflected in the QALY calculation.<br><br>Available Data<br><br>• VX16-445-001 (Study 001) evaluated the efficacy and safety of VX-445 (elexacaftor) in combination with tezacaftor and ivacaftor in patients ≥18 years of age with an F/MF or F/F genotype.14<br><br>• Study 102, compared the efficacy and safety of VX-445 (elexacaftor) in combination with tezacaftor and ivacaftor and placebo treatment in patients ≥12 years of age with an F/MF genotype.12<br><br>• Study 103, compared VX-445 (elexacaftor) in combination with tezacaftor and ivacaftor and tezacaftor and ivacaftor in F/F patients.15 |

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| | | • VX17-445-105 (Study 105), a combined 96-week open label extension (OLE) safety study.16 |
| Questions for consultation | British Thoracic Society | Do you consider that there will be any barriers to adoption of this technology into practice?<br>No – there infrastructure for modulator drugs is already set up (as clinics have recently rolled out Symveki and Orkambi to patients in their clinics0. |
| | Cystic Fibrosis Trust | Which treatments are considered to be established clinical practice in the NHS for cystic fibrosis with a F508del mutation?<br><br>Ivacaftor, ivacaftor-lumacaftor, and tezacaftor- ivacaftor are the most important comparator therapies for this technology.<br><br>How should best supportive care be defined?<br><br>Best supportive care should include the treatments ivacaftor, ivacaftor-lumacaftor, and tezacaftor- ivacaftor alongside symptomatic management. The European Cystic Fibrosis Society's best practice guidelines for the management of CF 2018 (https://www.cysticfibrosisjournal.com/article/S1569-1993(18)30029-8/fulltext) include ivacaftor monotherapy, and lumacaftor-ivacaftor therapy as treatment options that should be available to eligible individuals.<br><br>**Do you agree that this appraisal should focus on elexacaftor in combination with tezacaftor and ivacaftor compared with best supportive care? And therefore not on the comparison with tezacaftor/ivacaftor or lumacaftor/ivacaftor, because these combinations have either not been appraised or recommended by NICE for routine use in the NHS in England?**<br><br>No. Ivacaftor, lumacaftor-ivacaftor, and tezacaftor-ivacaftor are important comparator therapies for this technology. |

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| | | If not<br>• Should tezacaftor/ivacaftor be included as a comparator?<br>Yes<br>• Should lumacaftor/ivacaftor be included as a comparator?<br>Yes<br><br>Are the outcomes listed appropriate?<br><br>Yes.<br><br>**Do you consider elexacaftor in combination with tezacaftor and ivacaftor to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br><br>Yes, the results for elexacaftor in combination with tezacaftor and ivacaftor from the two pivotal phase III studies of the combination regimen show improvements of an unprecedented magnitude in the target population. Ivacaftor monotherapy has been considered the benchmark for a highly effective modulator therapy, while evidence from the triple therapy combination clinical trials show comparable levels of improvement for a much greater eligible population. The significance of this is the vast majority of the CF community are now eligible for a life-changing, highly effective modulator therapy and is a step-change moment in the treatment of cystic fibrosis.<br><br>**Do you consider that the use of elexacaftor in combination with tezacaftor and ivacaftor can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** |

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| | | Yes, the effect of modulator therapies on debilitating cystic fibrosis co-morbidities such as sinus issues, cystic fibrosis related diabetes, digestive issues, nausea, arthritis, and pain is not well represented in evidence and only just starting to be understood.<br><br>**Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**<br><br>The Cystic Fibrosis Trust believes that the UK CF Registry is a valuable tool for real-world outcomes observation that can support Health Technology Appraisal bodies to address areas of uncertainty over longer-term or wider impacts of a technology in routine practice.<br><br>The limited timeframe of the trial and the relatively small trial populations may increase uncertainty in modelling clinical- and cost- effectiveness.<br><br>The Cystic Fibrosis Trust believes that the UK CF Registry is a valuable tool for real-world outcomes observation that can support Health Technology Appraisal bodies to address areas of uncertainty over longer-term or wider impacts of a technology in routine practice. |
| | CF Voices | The appraisal should consider ivacaftor, tezacaftor/ivacaftor and lumacaftor/ivacaftor as comparators, and the patient population should be sub-grouped by these treatment options.<br><br>We strongly encourage that this appraisal is carried out in parallel to the EMA marketing authorisation process. The timeline could be brought forward if the two appraisals are conducted in parallel. |
| | UK Clinical Pharmacy Assocation (UKCPA) | The phase three study: Middleton PG, Mall MA et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med 2019; 381:1809-1819. should be reviewed and referenced This was published in November 2019 and the data needs to be considered for this NICE appraisal. |

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| | Respiratory Group | |
| | UK Cystic Fibrosis Medical Association | Questions for consultation have been covered in the above domains except:<br><br>Do you consider that there will be any barriers to adoption of this technology into practice? Response: No – CF clinics have already rolled out licenced CFTR modulators for currently eligible patients and the infrastructure is therefore in place for triple therapy |
| | Vertex | Barriers to access<br>We do not consider it likely that there will be any barriers to adoption of this technology once a commissioning policy is in place.<br><br>All other questions have been addressed in the above sections. |
| Additional comments on the draft scope | British Thoracic Society | It should be emphasised that this HTA assessment is for patients>12 years. Those CF patients with one copy of DF508, <12 years need to have their own HTA which currently will only be for Orkambi (Lumacaftor/Ivacaftor).<br><br>CF modulators are expensive drugs prescribed by genotype, not clinical severity. For instance DF508/DF508 functionally limited ion a transplant list, will be treated as well as DF508/DF508 running marathons with normal lung function at the same age. If there is any consideration of restricting drugs on cost, then you would need to consider stratifying according to baseline health.<br><br>There are also ongoing clinical trials using Trikafta in the U.K, so it is likely that more information on its efficacy could be available in due course. |

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| | CF Voices | We reiterate the essential nature of innovative thinking in this situation to prevent loss of life and health. The example of the managed access scheme for the currently funded modulators from Vertex must be emulated and urgency must be applied by all parties. |
| | UK Cystic Fibrosis Medical Association | Further evidence is likely to be available to this appraisal as there are ongoing clinical trials of elexacaftor-tezacaftor-ivacaftor in the U.K |
| | Vertex | The Clinical Commissioning Urgent Policy Statement for Cystic Fibrosis Modulator Therapies has been omitted from the list of relevant national policy documents and should be included.<br><br>https://www.england.nhs.uk/wp-content/uploads/2019/11/Cystic-Fibrosis-Modulator-Therapies.pdf |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

None

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