**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Vanzacaftor–tezacaftor–deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over [ID6372]

## Response to stakeholder organisation comments on the draft remit and draft scope

**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.

### Comment 1: the draft remit and proposed process

| Section | Stakeholder | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | Vertex (company) | [redacted] a cost-comparison analysis vs elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor (ELX/TEZ/IVA) is appropriate for this topic.<br><br>A cost-comparison approach is appropriate for the following reasons:<br>• The comparator, ELX/TEZ/IVA, is NICE approved following the publication of TA988 earlier this year (1).<br>• Direct evidence from head-to-head clinical trials supports non-inferiority of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) to ELX/TEZ/IVA in terms of improvements in lung function and superiority in terms of restoration of CFTR function (2).<br>• As the efficacy outcomes for VNZ/TEZ/D-IVA are likely to provide similar or greater overall health benefits to patients than ELX/TEZ/IVA, a cost-comparison analysis is appropriate to determine whether VNZ/TEZ/D- | Thank you for your comment. A cost-comparison approach has been chosen to evaluate vanzacaftor–tezacaftor–deutivacaftor. |

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| | | IVA is likely to result in similar or reduced overall costs to the NHS, relative to ELX/TEZ/IVA.<br><br>As ELX/TEZ/IVA currently makes up [redacted]% of total CFTR modulator use in England (3), Vertex considers it to be the only relevant comparator (as discussed further in Comment 2 – Comparators).<br><br>[redacted] there is the opportunity to build on the successful MTA for the existing CF medicines and support a rapid streamlined assessment for the next generation CF therapy. This would support NICE's aim to deliver timely guidance to new medicines which stand to improve the lives of patients living with rare and severe diseases. | |
| | ACPCF | It is felt that a cost comparison evaluation is an appropriate process | Thank you for your comment. A cost-comparison approach has been chosen to evaluate vanzacaftor–tezacaftor–deutivacaftor. |
| | British Thoracic Society | A cost comparison evaluation seems an appropriate process head to head clinical trials comparing vanza/TEZ/D-IVA to ETI show non inferiority | Thank you for your comment. A cost-comparison approach has been chosen to evaluate vanzacaftor–tezacaftor–deutivacaftor. |

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| | Cystic Fibrosis Nursing Association | As the recent review Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis (2024) NICE technology appraisal guidance 988 covered the appraisal of these drugs in great length, a cost comparison method would be appropriate.<br>This method will not only address the effective comparison, it will reduce the emotional burden that our people with CF and their families faced during the above review. It is also more efficient use of NICE appraisal teams time and reduces stakeholders workload. | Thank you for your comment. A cost-comparison approach has been chosen to evaluate if vanzacaftor–tezacaftor–deutivacaftor is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology guidance for the same indication. |
| | Cystic fibrosis pharmacist group | We feel that the cost comparison evaluation process current being considered could be an appropriate method for this evaluation as the effects are similar to Kaftrio as the new technology showed non-inferiority in trials from a ppFEV1 perspective and slight improvement in sweat chloride reduction | |
| | Cystic Fibrosis Trust | Cystic Fibrosis Trust support all efforts to ensure that new treatments that could improve the health and long-term outcomes of people with cystic fibrosis are evaluated swiftly, and we welcome the opportunity to comment on the draft scope for the appraisal of vanzacaftor–tezacaftor–deutivacaftor.<br><br>Cystic Fibrosis Trust believes it is appropriate to use a cost-comparison approach as the recent appraisal TA988 recommended the CFTR modulators Orkambi, Symkevi and Kaftrio for use on the NHS. We encourage NICE to carefully consider the wealth of evidence submitted by the Trust and other stakeholders throughout the appraisal process on the impact of cystic fibrosis and the huge benefits transformative treatments can have. | |
| | Genetic Alliance UK | Genetic Alliance UK welcomes the opportunity to comment on the draft scope for the appraisal of vanzacaftor–tezacaftor–deutivacaftor. Genetic Alliance UK had a meeting with the Cystic Fibrosis Trust to discuss this consultation and understands that a cost-comparison approach is appropriate following the | |

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| | | recent appraisal recommending the CFTR modulators Orkambi, Symkevi and Kaftrio for use on the NHS (TA988). | |
| | Neonatal and Paediatric Pharmacy Group (NPPG) RIG | Appropriate | |
| | NHS England Specialised Commissioning | NHS England considered that this is an appropriate topic to evaluate, and that the evaluation route is appropriate | |
| Wording | Vertex (company) | Vertex considers the wording of the remit to be appropriate.<br>In the event that there may be patients with rare non-F508del mutations who are deemed eligible for treatment with VNZ/TEZ/D-IVA, it has been agreed with NHS England that these will be covered by a commissioning policy, as is the case for ELX/TEZ/IVA. | Thank you for your comment. No action required. |
| | ACPCF | Yes | Thank you for your comment. No action required. |
| | British Thoracic Society | A cost comparison evaluation seems an appropriate process. There may be patients with non-F508del mutations who may be eligible for this therapy (just as there are for ETI therapy currently) | Thank you for your comment. A cost-comparison approach has been chosen to evaluate vanzacaftor–tezacaftor–deutivacaftor. |

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| | Cystic Fibrosis Nursing Association | Wording is appropriate | Thank you for your comment. No action required. |
| | Cystic Fibrosis Trust | Cystic Fibrosis Trust believes this section to be accurate. | Thank you for your comment. No action required. |
| | Genetic Alliance UK | Genetic Alliance UK understands this section to be accurate. | Thank you for your comment. No action required. |
| | NHS England Specialised Commissioning | Yes | Thank you for your comment. No action required. |
| Timing Issues | Vertex (company) | VNZ/TEZ/D-IVA is a next-generation CFTR modulator that builds on the success of ELX/TEZ/IVA in the treatment of CF, and provides another treatment option that:<br>• Has the potential to further improve CF manifestations and reduce disease burden by further restoring CFTR function towards normal<br>• Provides a simpler once-daily treatment regimen that reduces the overall treatment burden<br>• Can be used in people for whom the current CFTR modulators are unsuitable<br>Therefore, it is important that VNZ/TEZ/D-IVA should be prioritized for evaluation to ensure access as close to marketing authorisation as possible | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |

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| | ACPCF | Urgent review would be welcomed given this treatment may offer improved outcomes and reduced costs | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |
| | British Thoracic Society | This treatment may offer improved outcomes and reduced costs, so an urgent review would be welcomed. Particularly potentially improved gains in sweat chloride drops (significance not fully understood) and once daily dosing with potential improvements in adherence. Might also be tolerated by patients who have been unable to tolerate ETI and some people with CF might not have had huge response to ETI. In vitro data suggests the new combination may be more effective. Could replace mutation with variant to reflect current standards in genomic medicine | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |
| | Cystic Fibrosis Nursing Association | As Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis (2024) NICE technology appraisal guidance 988 demonstrated these medicines are life changing for people with CF. As VNZ/TEZ/D-IVA is effective in a wider patient group for those who do not currently receive any genetic modifiers the sooner they can have access to the medications, the higher the potential to reduce disease progression and improve their outcome. These will also reduce treatment burden for those already established on modifiers. Therefore we would urge a timely review. | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |

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| | Cystic Fibrosis Trust | People with cystic fibrosis experienced and long, and at times challenging appraisal process for TA988, and we welcome a timely assessment process for vanzacaftor–tezacaftor–deutivacaftor. Additionally, there are people with cystic fibrosis who may be eligible for existing CFTR modulators, who are unable to benefit as they cannot tolerate them. For this group, vanzacaftor–tezacaftor–deutivacaftor could be transformational. | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |
| | Genetic Alliance UK | Based on discussions with the Cystic Fibrosis Trust, Genetic Alliance UK understands that people living with cystic fibrosis experienced a long, and at times challenging, appraisal process for TA988, and therefore welcomes a timely assessment process for vanzacaftor–tezacaftor–deutivacaftor.<br>Additionally, as there is a group of people with cystic fibrosis eligible for existing CFTR modulators that have until now been unable to benefit from these therapeutic options due to the inability to tolerate them, vanzacaftor–tezacaftor–deutivacaftor could be transformational. This highlights the importance of having multiple treatment options available to allow people to choose the best treatment option for them, and that this ultimately improves patient outcomes. Therefore, to ensure continuity and equity of access to treatment options for the condition, it is important to progress with the appraisal without delay. | Thank you for your comment. The appraisal will follow cost-comparison timelines, which are typically faster than single technology appraisal timelines. No action required |
| | NHS England Specialised Commissioning | It is important to carry out this evaluation. | Thank you for your comment. |

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| Additional comments on the draft remit | Cystic fibrosis pharmacist group | We believe vanzacaftor-tezacaftor-deutivacaftor should be prescribed in secondary care with routine follow-up in secondary care, in keeping with the current prescribing model for CFTR modulators. | Thank you for your comment. NICE does not influence the prescribing location but the committee will take it into consideration during the appraisal. No action required. |

**Comment 2: the draft scope**

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| Background information | Vertex (company) | Vertex considers that the following information on current treatment landscape and remaining unmet needs should be included in the background for completeness:<br><br>Since ELX/TEZ/IVA became available in the UK in 2020, it has been widely used and has become the standard of care for eligible patients with at least one *F508del* mutation. As stated in TA988, clinical trial and real-world evidence shows that ELX/TEZ/IVA improves lung function and prevents its decline, improves growth and weight gain, and reduces the number of lung infections more than the previous standard treatment (1). It has also been shown to improve survival. According to the UKCF registry 2022 annual data report, the 5-year predicted median survival increased from 50.6 in 2016-2020 to 56.1 in 2018-2022 (4). Age-specific simulation modelling accepted by NICE in the MTA has demonstrated near-normal life expectancy of 82.5 years in patients treated with ELX/TEZ/IVA if treatment is initiated under the age of 18 years (5). Despite their transformative effects, ELX/TEZ/IVA and other | Thank you for your comment. The scope is intended to be a broad overview of the topic. No action required. |

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| | | existing CFTR modulators only partially restore CFTR function, with persistence of residual inflammation and infection, as well as other CF manifestations, providing a rationale for development of more efficacious CFTR modulator treatments. | |
| | British Thoracic Society | Satisfactory | Thank you for your comment. No action required. |
| | Cystic Fibrosis Nursing Association | This provides a good basis, however it does not fully capture the treatment burden associated with CF (which was demonstrated in the previous appraisal). As VNZ/TEZ/D-IVA would reduce this it is an important consideration.<br>Further reference to the usage of generic modifiers in current care and the impact they have had already might be beneficial. | Thank you for your comment. The scope is intended to be a broad overview of the topic. No action required. |
| | Cystic Fibrosis Trust | The background section is accurate and broadly mirrors the scope of TA988[1] although we advise NICE that the background information should include further information on the different types of treatments people with cystic fibrosis require. Treatments can be broadly classified as: nutritional repletion (for example, pancreatic enzymes and nutritional supplements); relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators); treatment of acute infections; suppression of chronic infection; suppression of inflammation (for example, steroids, high dose ibuprofen) and organ transplantation, including lung, liver or pancreas. | Thank you for your comment. The scope is intended to be a broad overview of the topic. No action required. |

[1] https://www.nice.org.uk/guidance/TA988

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| | Genetic Alliance UK | Genetic Alliance UK understands this section to be accurate. | Thank you for your comment. No action required. |
| | NHS England Specialised Commissioning | The information is accurate and complete. | Thank you for your comment. No action required. |
| Population | Vertex (company) | Vertex considers the population to be defined appropriately. | Thank you for your comment. No action required. |
| | ACPCF | Yes | Thank you for your comment. No action required. |
| | British Thoracic Society | Seems appropriate | Thank you for your comment. No action required. |
| | Cystic Fibrosis Nursing Association | Appropriate definition of population | Thank you for your comment. No action required. |
| | Cystic fibrosis pharmacist group | Used in people with no F508del variant in RIDGELINE trial and the FDA application is for those with at least 1 F508del variant or another responsive mutation in the cystic fibrosis transmembrane conductance regulator gene responsive to the vanza triple. Therefore, no F508del variant needed for potential use in USA depending on outcome of the application. | Thank you for your comment. NICE can only appraise a treatment within its UK marketing authorisation. No action required. |

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| | Cystic Fibrosis Trust | As vanzacaftor–tezacaftor–deutivacaftor does not currently have a marketing authorisation, it is possible the licensed population could be broader than the draft scope identifies. If so, we urge NICE and NHS England to ensure that the appropriate access arrangements are made in a timely, parallel manner to ensure there is no access delay for these populations. | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | Genetic Alliance UK | Genetic Alliance UK understands that in light of concerns around access to vanzacaftor–tezacaftor–deutivacaftor, the licensed population could be broader than the draft scope identifies. If so, Genetic Alliance UK aligns with the Cystic Fibrosis Trust's stance on this in urging NICE and NHS England to ensure that the appropriate access arrangements are made in a timely, parallel manner to ensure there is no access delay for these populations. | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | Neonatal and Paediatric Pharmacy Group (NPPG) RIG | Could this be opened up to those currently ineligible for modulators? | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | NHS England Specialised Commissioning | Yes | Thank you for your comment. No action required. |
| Subgroups | Vertex (company) | Given that the cost-comparison process is appropriate for VNZ/TEZ/D-IVA, Vertex considers there to be no subgroups of interest. | Thank you for your comment. No action required. |

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| | Cystic Fibrosis Nursing Association | No subgroups for consideration | Thank you for your comment. No action required. |
| | Cystic fibrosis pharmacist group | Similar to above we have noted there is a difference between the proposed subgroups and the FDA application for this new technology. The FDA application is for people with CF 6 years and older who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator gene responsive to the vanza triple.<br>Therefore, it could be used in people with no F508del variant which is in keeping with the RIDGELINE trial eligibility criteria. | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | NHS England Specialised Commissioning | We do not believe so. | Thank you for your comment. No action required. |
| Comparators | Vertex (company) | The NICE Methods Guide states that the chosen comparator must be established in practice and have substantial use in the NHS in England for the same indication. In the population of interest, ELX/TEZ/IVA is therefore the only relevant comparator:<br>• The European Cystic Fibrosis Society recommends that all people with CF aged 6 years or older with at least one *F508del* mutation should initially be prescribed ELX/TEZ/IVA.<br>• ELX/TEZ/IVA currently represents [redacted]% of CFTR modulator use in England, making it by far the most commonly used CFTR modulator (3).<br>• Clinical experts consulted by Vertex have confirmed that ELX/TEZ/IVA is the most appropriate comparator in the population of interest. | Thank you for your comment. The scope is intended to be broadly inclusive of all potential comparators. However the comparator list has been simplified. |

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| | | The CFTR modulators ELX/TEZ/IVA, TEZ/IVA and LUM/IVA are positioned alongside each other in the treatment pathway and the choice of modulator depends on the patients' age and genotype. In the population of interest, VNZ/TEZ/D-IVA is positioned as an alternative option to ELX/TEZ/IVA.<br><br>VNZ/TEZ/D-IVA and ELX/TEZ/IVA work in the same way. They are both triple combination therapies comprising two correctors (vanzacaftor/elexacaftor and tezacaftor) and one potentiator (deutivacaftor or ivacaftor). Correctors increase the amount of CFTR at the cell surface and potentiators increase the channel open probability of the CFTR protein to improve the flow of salt and water across the cell membrane.<br><br>Both VNZ/TEZ/D-IVA and ELX/TEZ/IVA are oral treatments. VNZ/TEZ/D-IVA is taken once-daily, requiring only one fat-containing meal per day, and offers a more convenient option than ELX/TEZ/IVA, which has a twice-daily dosing regimen (morning dose with ELX/TEZ/IVA and evening dose with IVA, both requiring a fat-containing meal). Both are prescribed in secondary care and have the same routine follow-up and monitoring (also in secondary care).<br><br>The other comparators listed in the draft scope do not meet the criteria set out in the NICE Methods Guide, as they are not widely used in the population of interest, and are therefore not relevant to this appraisal. | |
| | ACPCF | To clean up the inhaled treatments listed feel relevant to change wording to:<br>1. Inhaled antibiotics<br>2. Inhaled mucolytics including Mannitol dry powder for inhalation, Hypertonic saline and dornase alfa | Thank you for your comment. The comparator list has been simplified and the 'inhaled mucolytic' bullet point in the comparators section has been changed to |

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| | | | "inhaled mucolytics including mannitol dry powder for inhalation, hypertonic saline and dornase alfa" with the duplicate bullets deleted. |
| | British Thoracic Society | To clean up the inhaled treatments listed:<br>1. Inhaled antibiotics<br>2. Inhaled mucolytics including Mannitol dry powder for inhalation, HTS and dornase alfa<br>Extra-pulmonary manifestations are a significant aspect of cystic fibrosis (CF) management, and would be useful to consider how vanzacaftor–tezacaftor–deutivacaftor compares with existing therapies in addressing these complications (CFLD, CFRD, Bone and sinus disease etc | Thank you for your comment. The comparator list has been simplified and the 'inhaled mucolytic' bullet point in the comparators section has been changed to "inhaled mucolytics including mannitol dry powder for inhalation, hypertonic saline and dornase alfa" with the duplicate bullets deleted. |
| | Cystic Fibrosis Nursing Association | Yes, however it should be noted that VNZ/TEZ/D-IVA and ELX/TEZ/IVA are TRIPLE therapy genetic modifiers, whereas<br>TEZ/IVA and LUM/IVA are not. | Thank you for your comment. No action required. |

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| | Cystic Fibrosis Trust | The standard treatments used for cystic fibrosis are the CFTR modulator therapies (Orkambi, Symkevi and Kaftrio) alongside the treatments listed as part of established clinical management. There are some people with cystic fibrosis who cannot benefit from CFTR modulators, due to tolerability or genetic eligibility, and some of these may be eligible for vanzacaftor–tezacaftor–deutivacaftor. | Thank you for your comment. No action required. |
| | Neonatal and Paediatric Pharmacy Group (NPPG) RIG | If the license is going to include non DF508 variants which will open up this combination to people currently ineligible for modulators then the scope needs to include this (and relevant comparators) | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | NHS England Specialised Commissioning | ELX/TEZ/IVA should be the main comparator although there are only small numbers of patients on IVA alone or TEZ/IVA) | Thank you for your comment. No action required. |
| Outcomes | Vertex (company) | Vertex proposes the following outcome measures, where head-to-head or comparative evidence exists, to support the cost-comparison approach for VNZ/TEZ/D-IVA vs ELX/TEZ/IVA:<br>• change in percentage predicted forced expiratory volume in 1 second ($ppFEV_1$)<br>• sweat chloride<br>• pulmonary exacerbation requiring IV antibiotic therapy and/or hospitalization<br>• health-related quality of life<br>• respiratory symptoms<br>• lung clearance index 2.5 | Thank you for your comment. ‘pancreatic function’ and ‘inflammation’ have been added to the outcomes |

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| | | • body mass index<br>• height<br>• weight<br>• pancreatic secretion<br>• inflammatory markers<br>• adverse effects of treatment | |
| | ACPCF | Yes | Thank you for your comment. No action required. |
| | British Thoracic Society | Potential additional gains—such as education, carer demands reduced<br>Potentially longer term outcomes regarding disease progression<br>Consider including : Regular monitoring of liver enzymes (ALT, AST) and bilirubin levels to detect early signs of liver damage or potential improvements in liver health.<br><br>The scope mentions health-related quality of life but would be helpful to explicitly state that validated CF-specific patient-reported outcome measures (PROMs) such as the Cystic Fibrosis Questionnaire-Revised (CFQ-R) will be used.<br><br>Consider , clearly defining pulmonary exacerbations (e.g., including criteria such as worsening symptoms, need for antibiotics, or hospitalization) will help standardize this outcome. | Thank you for your comment. 'liver function' has been added to the outcomes. NICE does not specify any particular scales or instruments in the scope. |

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| | Cystic Fibrosis Nursing Association | As per feedback from stakeholders in the pervious appraisal, importance should be placed on QoL.<br>Faecal elastase | Thank you for your comment. 'pancreatic function' has been added to the outcomes. |
| | Cystic Fibrosis Trust | As Cystic Fibrosis Trust consistently demonstrated in our submissions for TA988, there are a wealth of substantial health-related benefits which may be unlikely to be included in the QALY calculations. These include increased health stability, more energy and the potential for a reduction in the high treatment burden caused by CF. We are also aware of the significant benefits to transformative medicines seen outside of health-related benefits, such as increased opportunities for education and employment. | Thank you for your comment. The committee will consider any benefits that are unlikely to be captured during the cost-comparison process. |
| | Genetic Alliance UK | Genetic Alliance UK notes that there are a significant number of potential health-related outcomes that are unlikely to be included in the QALY calculations. For example, following discussions with The Cystic Fibrosis Trust, Genetic Alliance UK understands that health stability is considered a valuable indicator of quality of life by the patient community, although this is often absent from more commonly used QoL instruments like the EQ5RD.<br><br>Outcomes such as a reduction in the burden of treatment and having more energy can be transformative to the experience of people living with the condition, e.g. a reduced frequency of the need to receive IV antibiotics that may require a hospital visit and therefore time away from work or education; assessing whether individuals are able to reduce the number of medicines they take as part of their daily routine; the number of affected women who are able to have a baby as a result of receiving treatment. Additionally, improvements in these outcomes can present benefits to the wider family, not just affected individuals, e.g. parents of affected children may have to give up work to be able to care for their child and take them to various appointments. | Thank you for your comment. The committee will consider any benefits that are unlikely to be captured during the cost-comparison process. |

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| | | For these reasons, consideration of measures that extend beyond the short-term, more clinical outcome measures in these appraisals can help serve as potential indicators of the 'true impact' such therapies could have on the patient community**.** | |
| | NHS England Specialised Commissioning | The outcome measures to be considered include:<br>• mortality<br>• ~~change in the percentage of~~ predicted forced expiratory volume<br>• *percentage of predicted* forced vital capacity<br>• lung function, including transplantation – *does not make sense, should be lung transplantation only*<br>• body mass index<br>• respiratory symptoms – *presume using CFQR? But if so, not all centres routinely measure this but data will be available from the clinical trials*<br>• pulmonary exacerbations, including frequency and severity of acute infections<br>• sweat chloride - *not all centres routinely measure this*<br>• lung clearance index 2.5 – *most centres do not routinely measure this, those that do are more likely to be paediatric but will it be licensed for age 12yrs onwards phase 3 clinical trials or will the safety study in 6-11yr old also allow licensing at the same time? not a great outcome measure as not all centres routinely measure this but data will be available from the clinical trials*<br>• pulmonary bacterial colonisation<br>•need for hospitalisation ~~and other treatments including antibiotics~~<br>• adverse effects of treatment – *how will this be captured?* | Thank you for your comment. The outcomes have been updated as suggested. |

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| | | • health-related quality of life*. - not all centres routinely measure this but data will be available from the clinical trials* | |
| Equality | Vertex (company) | Given that the cost-comparison process is appropriate for VNZ/TEZ/D-IVA, Vertex does not anticipate that the draft remit/scope would raise any equality issues.<br><br>In the event that there may be patients with rare non-F508del mutations who are deemed eligible for treatment with VNZ/TEZ/D-IVA, it has been agreed with NHS England that these will be covered by a commissioning policy, as is the case for ELX/TEZ/IVA, in order to ensure broad and equitable access. | Thank you for your comment. No action required. |
| | ACPCF | This consultation states this treatment will be considered for people with CF with at least one DF508 mutation. UK access to Kaftrio is currently broader with emerging evidence of its effect in some other genetic mutations. Reassurance that access to this technology will be equally expanded would be welcome<br><br>Consideration of the 10% ineligible:<br><br>Approximately 10% of people with CF are ineligible for 'technologies'. Since the interim access to Kaftrio we have seen a significant gap in health and health care demand between people who are and who are not eligible. Those without access continue to experience a deterioration in their health annually and rates of lung transplant referral and death remain ISQ. Patients from black, Asian and minority ethnic backgrounds are significantly less likely to be eligible for Kaftrio based on the current prescribing policy in the UK. The CF community need to urgently address the unmet need for effective targeted therapies for patients without F508del 1. 1. 1. Who are the 10%? - Non | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |

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| | | eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies - ScienceDirect | |
| | British Thoracic Society | This consultation states this treatment will be considered for people with CF with at least one DF508 mutation. UK access to Kaftrio is currently broader with evidence of its effect in some other genetic mutations. Reassurance that access to this technology will be equally expanded would be welcome<br><br>**The 10% ineligible**<br>Approximately ~10% of people with CF are ineligible for 'technologies'. Since the interim access to Kaftrio we have seen a significant gap in health and health care demand between people who are and who are not eligible. Those without access continue to experience a deterioration in their health annually and rates of lung transplant referral and death remain ISQ.<br><br>Patients from black, Asian and minority ethnic backgrounds are significantly less likely to be eligible for Kaftrio based on the current prescribing policy in the UK. The CF community need to urgently address the unmet need for effective targeted therapies for patients without F508del 1.<br>1. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies - ScienceDirect | Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation. No action required. |
| | Cystic Fibrosis Nursing Association | No perceived problems with equality & opportunity. | Thank you for your comment. No action required. |
| | Cystic Fibrosis Trust | Black, Asian and minority ethnic people with cystic fibrosis are less likely to be eligible for current CFTR modulators as they are more likely to have rare mutations . | Thank you for your comment. The committee will consider whether its |

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| | | | recommendations could have a different impact on people protected by the equality legislation than on the wider population. The issue has been added to the equalities impact assessment (EIA). |
| | NHS England Specialised Commissioning | None Identified | Thank you for your comment. No action required. |
| Other considerations | British Thoracic Society | There will be additional health care costs initially in instituting this therapy for patients switching from ETI to Vanz/tez/ D-IVA. Initially would need to be set up on home care and initial prescriptions issued and presumably Liver function tests at baseline and at shorter intervals than ETI currently—may need to be factored into costs or clinical teams have additional support during transition | Thank you for your comment. Liver function has been added to the outcomes. |
| | Cystic Fibrosis Nursing Association | Learning from the previous appraisal I would urge the NICE team to consider carefully the timing, and wording of announcements if made publicly. Where possible, prior warning to health professionals/The CF Trust would be appreciated, as this places us in a position to prepare so we can best support those with CF and their families. | Thank you for your comment. NICE will release updates as appropriate though the appraisal process. |
| | NHS England Specialised Commissioning | Impact on mental health as issues have been reported with elexacaftor, ivacaftor, tezacaftor (Kaftrio). | Thank you for your comment. The committee will also consider any benefits |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | | that are unlikely to be captured during the cost-comparison process. |
| Questions for consultation | Vertex (company) | **Would vanzacaftor–tezacaftor–deutivacaftor be a candidate for managed access?**<br>VNZ/TEZ/D-IVA is not anticipated to be a candidate for managed access. Pivotal trials show that VNZ/TEZ/D-IVA is non-inferior to ELX/TEZ/IVA in lung function improvement, yet superior in CFTR function improvement as measured by sweat chloride (2). Similar or numerically better results were also demonstrated for other efficacy outcomes and the safety profile of VNZ/TEZ/D-IVA was similar to ELX/TEZ/IVA (2).<br>ELX/TEZ/IVA was subject to extensive data collection via the NICE and NHS England agreed interim access agreement. The UK RWE data on ELX/TEZ/IVA from this agreement was presented to, and accepted by, NICE as part of TA988, and as such VNZ/TEZ/D-IVA is suitable for routine commissioning.<br>**Do you consider that the use of vanzacaftor–tezacaftor–deutivacaftor can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>Vertex proposes that the cost-comparison route is appropriate for VNZ/TEZ/D-IVA, therefore QALYs would not be captured in the modelling.<br>**Please provide comments on the appropriateness of appraising this topic through the cost-comparison process** | Thank you for your comment. A cost-comparison approach has been chosen to evaluate vanzacaftor–tezacaftor–deutivacaftor. |

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| | | As described in our comments above, Vertex considers the cost-comparison route to be the most appropriate for VNZ/TEZ/D-IVA based on:<br>• Similarities in clinical effectiveness and safety profile (as shown in head-to-head trials (2)) and resource use to the relevant comparator, ELX/TEZ/IVA<br>• Its proposed position in the treatment pathway as an alternative to ELX/TEZ/IVA in the population of interest<br>• The likelihood that the efficacy outcomes for VNZ/TEZ/D-IVA will provide similar or greater overall health benefits to patients than ELX/TEZ/IVA<br>• Ability for this proportionate approach to deliver more streamlined and rapid access to important new clinical options, such as VNZ/TEZ/D-IVA | |
| | British Thoracic Society | It should be prescribed in secondary care, particularly in specialist cystic fibrosis centers, given the complexity of the treatment and its potential adverse effects. Routine follow-up should occur in secondary care.<br>Yes, managed access might be appropriate given that it is a novel therapy with limited long-term data. A managed access agreement would allow for ongoing data collection on safety and effectiveness while making the drug available to patients who could benefit immediately.<br>Yes, potential benefits such as a reduction in the frequency of hospital admissions, better quality of life due to fewer pulmonary exacerbations, and improved lung function may not be fully captured in QALY metrics. Additionally, the treatment may reduce the long-term need for lung transplantation, which is a significant outcome not easily reflected in cost-utility analyses. | Thank you for your comment. The committee will consider any benefits that are unlikely to be captured during the cost-comparison process. |

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| | | The committee would need data from multiple sources and categories to properly account for the potential benefits of **vanzacaftor–tezacaftor–deutivacaftor** in treating cystic fibrosis.<br>1. Phase 3 data<br>2. Saftey outcomes<br>3. Data on subpopulation<br>4. Real word data: registry data/ Post-marketing surveillance<br>5. PRO /HRQoL data<br>6. Cost per QALY<br><br>Patient /caregiver feedback | |
| | Cystic Fibrosis Nursing Association | Where do you consider vanzacaftor–tezacaftor–deutivacaftor will fit into the existing care pathway for cystic fibrosis?<br><br>Please select from the following, will vanzacaftor–tezacaftor–deutivacaftor be:<br><br>C. Prescribed in secondary care with routine follow-up in secondary care<br><br>Would vanzacaftor–tezacaftor–deutivacaftor be a candidate for managed access?<br><br>Managed access not applicable, should be available to all who qualify<br><br>Do you consider that the use of vanzacaftor–tezacaftor–deutivacaftor can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?<br><br>Limitations of the QALY were highlighted in the previous appraisal (Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis (2024) NICE technology appraisal guidance 988). | Thank you for your comment. The committee will consider any benefits that are unlikely to be captured during the cost-comparison process. |

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| Additional comments on the draft scope | Cystic Fibrosis Trust | Cystic Fibrosis Trust encourages NICE to commit to regular and transparent communications to the cystic fibrosis community as this appraisal proceeds. | Thank you for your comment. NICE will release updates as appropriate though the appraisal process. |
| | NHS England Specialised Commissioning | We expect that the intervention would be prescribed, and patients followed up within the existing Cystic Fibrosis centres within England. | Thank you for your comment. No action required. |

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

British Dietetic Association CF Dietitians group