NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Vertex:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Cystic Fibrosis Trust
   b. Association of Chartered Physiotherapists in Cystic Fibrosis
   c. British Dietetic Association Cystic Fibrosis Specialist Group
   d. British Thoracic Society
   e. Cystic Fibrosis Nursing Association
   f. Neonatal and Paediatric Pharmacists Group (NPPG)
   g. UK Cystic Fibrosis Medical Association – endorsed by the British Paediatric Respiratory Society
   h. UK Cystic Fibrosis Pharmacy Group
   i. UK Psychosocial Professionals in Cystic Fibrosis Group

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more *F508del* mutation in the *CFTR* gene in people aged 6 years and over

[ID6372]

Document B

Company evidence submission

January 2025

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate transferase
BMI	Body mass index
CC	Complication and comorbidity
CCA	Cost-comparison analysis
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CFQ-R 8D	Cystic Fibrosis Questionnaire – Revised 8 dimensions
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator gene
CFTR	Cystic fibrosis transmembrane conductance regulator protein
CFTRm	Cystic fibrosis transmembrane conductance regulator modulator
CI	Confidence interval
DIOS	Distal intestinal obstruction syndrome
ELX/TEZ/IVA	Elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor
F/F	Homozygous for the *F508del*-CFTR mutation
F/G	Heterozygous for the *F508del* mutation and a gating mutation
F/MF	Heterozygous for the *F508del*-CFTR mutation and another mutation that produces no CFTR protein or is unresponsive to CFTR modulators ('minimal function')
F/RF	Heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full analysis set
FDA	Food and Drug Administration
FE-1	Faecal elastase-1
FEV_1	Forced expiratory volume in 1 second
GEE	Generalised estimating equations
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HCRU	Healthcare resource use
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICD-10	International classification of diseases, tenth revision
ICER	Incremental cost-effectiveness ratio

IRT	Immunoreactive trypsinogen
ITT	Intention to treat
IVA	Ivacaftor
LCI	Lung clearance index
LFT	Liver function test
LS	Least squares
LUM/IVA	Lumacaftor/ivacaftor
MBW	Multiple breath washout
MF	Minimal function
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed effects model for repeated measures
MTA	Multiple technology appraisal
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OWSA	One-way sensitivity analysis
PEx	Pulmonary exacerbation
PFAS	Pooled full analysis set
P-gp	P-glycoprotein
$ppFEV_1$	Percentage of predicted FEV_1
PT	Preferred term
QoL	Quality of life
RCT	Randomized clinical trial
RD	Respiratory domain
RF	Residual function
RTI	Respiratory tract infection
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SwCl	Sweat chloride
TCR	Triple combination responsive
TRSAE	Treatment related serious adverse event
TEZ/IVA	Tezacaftor/ivacaftor in combination with ivacaftor
UKCFR	UK Cystic Fibrosis Registry
VAT	Value added tax
VNZ/TEZ/D-IVA	Vanzacaftor/tezacaftor/deutivacaftor
WFAZ	Weight-for-age z score

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The decision problem population for this appraisal is people with CF aged 6 years and older with at least one *F508del* mutation (hereafter referred to as the F-any population). This submission is for a cost-comparison appraisal with elexacaftor/tezacaftor/ivacaftor in combination with IVA (ELX/TEZ/IVA) as the comparator.

ELX/TEZ/IVA was recommended by NICE in July 2024 as part of the multiple technology appraisal (MTA) TA988, for treating CF in people aged 2 years and over who have at least one *F508del* mutation in the CFTR gene.(1)

In TA988, the introduction of the CFTR modulators (CFTRms) was regarded by patient and clinical experts as a transformative step in the treatment pathway for patients with CF. During the appraisal, the committee concluded that both the clinical trial evidence, and extensive real-world data, shows that ELX/TEZ/IVA improves lung function, growth and weight gain and reduces the number of lung infections more than standard treatment. It was considered likely that these benefits last while people are having treatment.

When considering the condition's severity, and its effect on quality and length of life, the committee concluded that cost-effectiveness estimates for ELX/TEZ/IVA were within what NICE considers an acceptable use of NHS resources. Therefore, it was recommended within its marketing authorisation.

In the event that the MHRA label for VNZ/TEZ/D-IVA includes patients with non-F triple combination responsive mutations, these will be commissioned via an NHS England commissioning policy, as currently agreed for ELX/TEZ/IVA for people with non-*F508del* responsive mutations that are approved by the FDA in the US (2).

The decision problem addressed in the submission is shown in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 6 years and over with CF with at least 1 *F508del* mutation	People aged 6 years and over with CF with at least 1 *F508del* mutation	N/A
Intervention	VNZ/TEZ/D-IVA	VNZ/TEZ/D-IVA	N/A
Comparator(s)	• ELX/TEZ/IVA • Established clinical management including but not limited to: antibiotics, inhaled mucolytics (including mannitol dry powder for inhalation, hypertonic saline and dornase alfa), anti-inflammatory agents, bronchodilators For people with specific mutations, treatment may include: • TEZ/IVA • LUM/IVA • IVA monotherapy	ELX/TEZ/IVA	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: • 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. • ELX/TEZ/IVA currently represents [redacted]% of CFTR modulator use in England, making it by far the most commonly used CFTR modulator (3). • Clinical experts consulted by Vertex have confirmed that ELX/TEZ/IVA is the most appropriate comparator in the population of interest. 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. 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. 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). The other comparators listed in the 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.
Outcomes	The outcome measures to be considered include: • Mortality	• Change in percentage predicted forced expiratory volume in 1 second ($ppFEV_1$) • SwCl	Vertex considers these to be the appropriate outcomes to support the cost-comparison approach for VNZ/TEZ/D-IVA

	• Predicted forced expiratory volume (ppFEV) • Percentage of predicted forced vital capacity • Lung function • Lung transplantation • Body mass index • Respiratory symptoms • Pulmonary exacerbations (PEx), including frequency and severity of acute infections • Sweat chloride (SwCl) • Lung clearance • Pulmonary bacterial colonisation • Need for hospitalisation • Pancreatic function • Inflammation • Liver function • Adverse effects of treatment • Health-related quality of life	• PEx requiring IV antibiotic therapy and/or hospitalization • Health-related quality of life • Respiratory symptoms • Lung clearance index 2.5 • Body mass index • Height • Weight • Pancreatic secretion • Inflammatory markers • Adverse effects of treatment	vs ELX/TEZ/IVA, as head-to-head or comparative evidence exists
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the	A cost-comparison analysis with a 5-year time horizon is considered appropriate for this appraisal.	VNZ/TEZ/D-IVA has demonstrated positive results in its efficacy outcomes (non-inferiority in the primary endpoint in SKYLINE 102 and SKYLINE 103 [$ppFEV_1$], and superiority in its secondary endpoints [SwCl]; Section B.3.6.1) and a similar safety profile to ELX/TEZ/IVA in the treatment of CF (Section B.3.10.1). As the efficacy outcomes for VNZ/TEZ/D-IVA are likely to provide similar or greater overall health benefits to patients than the comparator, a CCA is appropriate to

	same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account		determine whether VNZ/TEZ/D-IVA is likely to result in similar or reduced overall costs to the NHS, relative to ELX/TEZ/IVA. A five-year time horizon is expected to demonstrate sufficient differences in the costs associated with VNZ/TEZ/D-IVA and ELX/TEZ/IVA given that key aspects of resource use are either time-invariant (e.g., adverse event treatment requirements) or are likely to be the same across treatments (e.g., administration costs).
Subgroups to be considered	People who have • 2 copies of the CFTR gene with *F508del* mutations • 1 copy of the CFTR gene with a *F508del* mutation and 1 copy with another mutation	None	Given that the cost-comparison process is appropriate for VNZ/TEZ/D-IVA, Vertex considers there to be no subgroups of interest.
Special considerations including issues related to equity or equality	Not specified	Vertex does not anticipate that the draft remit/scope would raise any equality issues. 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	

B.1.2 Description of the technology being evaluated

Table 2 provides an overview of VNZ/TEZ/D-IVA. The draft Summary of Product Characteristics (SmPC) is included in Appendix C1.1. At the time of submission, there was no UK public assessment report available.

Table 2 Technology being evaluated

UK approved name and brand name	Approved name: Vanzacaftor/tezacaftor/deutivacaftor Brand name: ALYFTREK™
Mechanism of action	In people with CF, mutations in the *CFTR* gene lead to decreased quantity and/or function of the CFTR protein channel at the cell surface. This causes disease in epithelia-lined organs throughout the body. Vanzacaftor and tezacaftor are correctors designed to increase the amount of CFTR protein at the cell surface by facilitating the processing and trafficking of the CFTR protein. Deutivacaftor is a potentiator designed to increase the channel open probability of the CFTR protein delivered to the cell surface to improve the flow of salt and water across the membrane. Deutivacaftor is a deuterated isotopologue of ivacaftor with an increased half-life that allows once daily dosing. The triple combination of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) therefore increases both the quantity and function of CFTR at the cell surface, resulting in increased chloride ion transport.
Marketing authorisation/CE mark status	VNZ/TEZ/D-IVA does not yet have a marketing authorisation in the UK. A marketing authorisation application was submitted to the MHRA in May 2024, with approval expected in March 2025.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication for VNZ/TEZ/D-IVA is the treatment of CF in people aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis conductance regulator (*CFTR*) gene. Note that the decision problem for this cost-comparison appraisal is people aged 6 years and over with CF with at least one *F508del* mutation (i.e. the F-any population) in line with the licensed indication for the comparator, ELX/TEZ/IVA. In the event that the MHRA label for VNZ/TEZ/D-IVA includes patients with non-F triple combination responsive mutations, these will be commissioned via NHS England commissioning policy, as currently agreed for ELX/TEZ/IVA for people with non-*F508del* responsive mutations that are approved by the FDA in the US (3).

<table>
<tr><td>Method of administration and dosage</td><td>VNZ/TEZ/D-IVA is available as an oral tablet that is administered once-daily with fat-containing food. It can be taken at any time of the day, but should be taken at approximately the same time each day.
The recommended doses are shown below:
<table><tr><th>Age</th><th>Weight</th><th>Daily dose (once-daily)</th></tr><tr><td rowspan="2">≥6 years</td><td><40 kg</td><td>3 tablets of VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg</td></tr><tr><td>≥40 kg</td><td>2 tablets of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg</td></tr></table></td></tr>
<tr><td>Additional tests or investigations</td><td>For existing CF patients, additional genotype testing is not needed, as their genotype will already be known.
For newly-diagnosed patients, genotype testing will be the same as for other CFTRms.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td><u>Proposed list price (to be approved by the Department of Health and Social Care following MHRA marketing authorisation):</u>
VNZ 4 mg/TEZ 20mg/D-IVA 50 mg: £16,110.00 (price per 84 tablet pack for 28-day supply)
VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg: £16,110.00 (price per 56 tablet pack for 28-day supply)

<u>Average cost of course of treatment (acquisition costs only)</u>
£210,149.20 annually</td></tr>
<tr><td>Patient access scheme/commercial arrangement (if applicable)</td><td>A complex portfolio arrangement is in place with NHS England for the currently licensed CFTRms. [redacted]</td></tr>
</table>

Key: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm; CFTR modulator; D-IVA, deutivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of CF

CF is a rare autosomal recessive disease caused by mutations in the *CFTR* gene on chromosome 7 which encodes the CFTR protein, an ion channel responsible for the transport of chloride and bicarbonate across cell membranes (4, 5). In people with CF, mutations in both copies of the *CFTR* gene (one gene from each parent) lead to disordered expression and/or function of CFTR protein, resulting in impaired salt and fluid transport across the surface of the epithelia lining multiple organs. The disrupted ion concentration gradient causes thick mucus to accumulate within the lungs and other organs (6, 7). Mucus obstruction in the airways creates conditions for a chronic inflammatory response triggered and/or exacerbated by infection, leading to gradual airway damage. Abnormal mucus clearance and subsequent mucus stasis predispose the damaged airway to further infection, perpetuating the cycle. Damage to the airways causes a decline in lung function over time, with respiratory failure being the primary cause of death among people with CF (8). For people with CF born in the five years before the introduction of CFTRms in the UK in 2013, median predicted survival was just 45 years (9).

Dysfunctional CFTR protein also leads to progressive damage of other organs, including the pancreas, intestinal tract and liver. Patients therefore experience severe symptom burden associated not only with lung damage, but also malabsorption, constipation, CF-related diabetes (CFRD) and CF-related liver disease (10). Other complications of CF include infertility and reduced bone mineral density. In the severest cases, symptom burden starts at birth (11, 12). Further details on the clinical burden of CF are given in Section B.1.3.4.1.

B.1.3.2 CFTR function and the role of sweat chloride

As described above, the multi-organ clinical manifestations of CF are caused by CFTR protein dysfunction. In the sweat gland, CFTR dysfunction results in elevated levels of chloride in the sweat that can be detected by the sweat chloride (SwCl) test (13-15). The SwCl test is a clinically validated, quantitative direct measure of CFTR protein function and a key diagnostic measure of CF (16):

- SwCl levels of ≥60 mmol/L are consistent with a diagnosis of CF (although other conditions can cause elevated SwCl) (17)
- SwCl <30 mmol/L is considered normal and indicates that CF is unlikely (17). It is also the level seen in CF carriers (those who carry 1 copy of a *CFTR* mutation), who have a normal lifespan and no CF disease
- SwCl between 30 and 59 mmol/L indicates that CF is possible and additional testing is needed

As a direct measure of CFTR function, SwCl concentration is a predictor of severity and disease course in CF. Natural history data show that higher SwCl concentrations (indicative of lower CFTR function) are associated with more severe disease and decreased survival (18-20). There is also an association between a reduction in SwCl levels (indicative of restored CFTR function) following CFTRm treatment initiation and improved lung function and other outcomes, including respiratory symptoms, nutritional endpoints and pulmonary exacerbations (PEx) in people with CF (Figure 1) (21).

Figure 1 Correlation of SwCl levels with clinical outcomes in CF

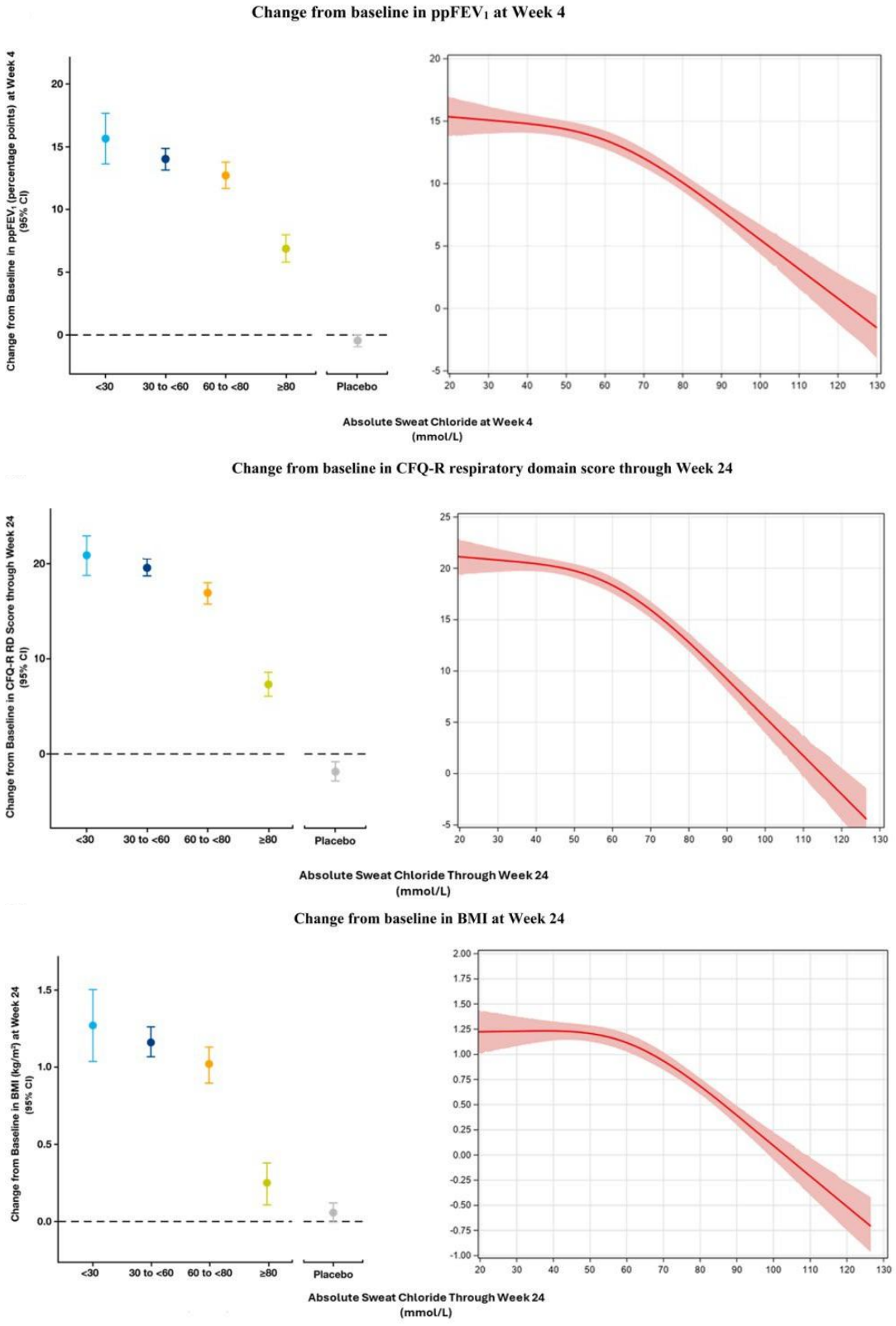
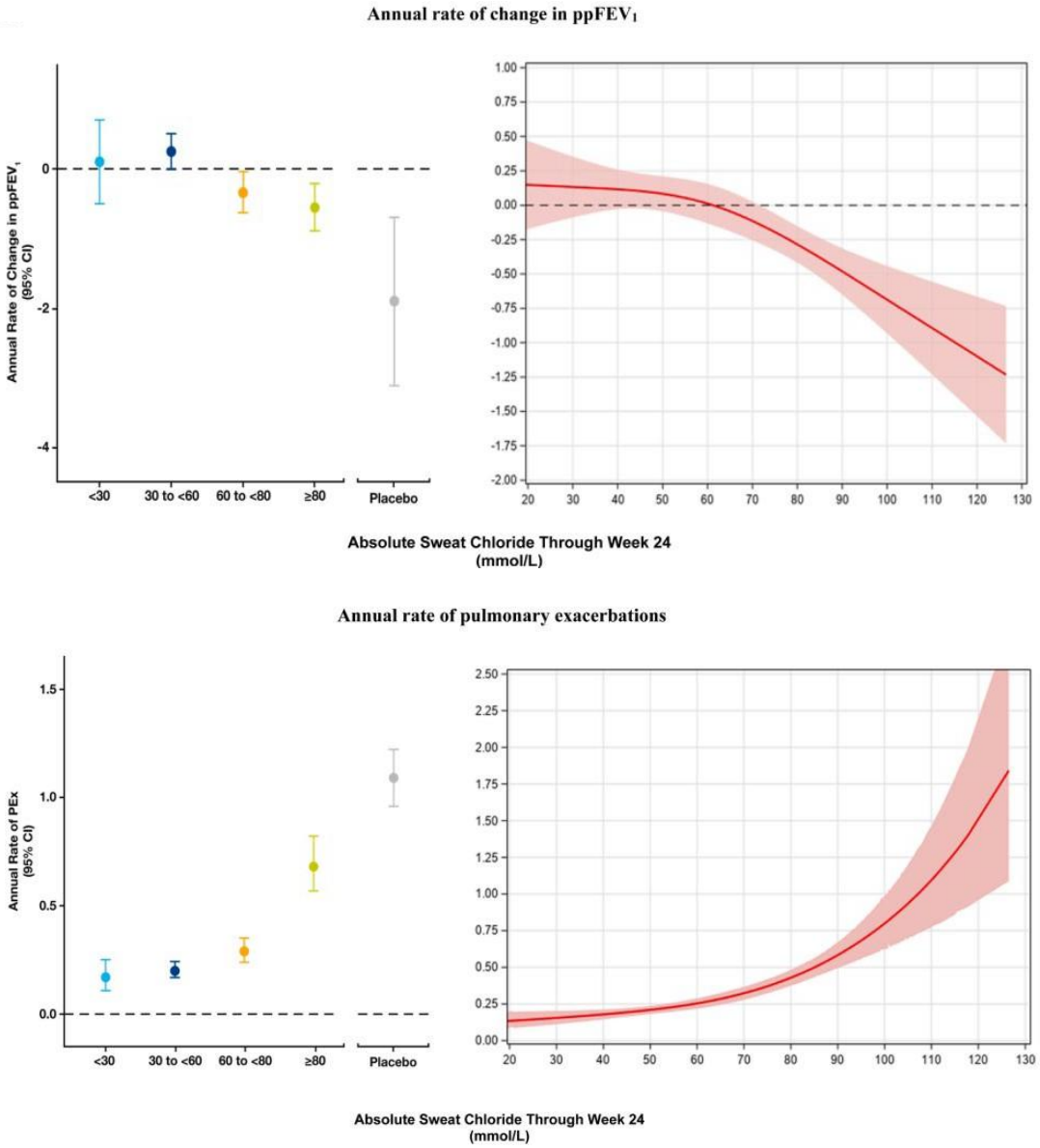


Figure 1 Correlation of SwCl levels with clinical outcomes in CF (cont.)



Pooled data from Phase 3 trials and open-label extension studies of TEZ/IVA, ELX/TEZ/IVA and VX-659/TEZ/IVA in people with CF aged ≥12 years. Categorical data are shown on the left; continuous data are shown on the right. For the continuous analyses, the red line represents the predicted mean value and the shaded red area represents the 95% CI
Key: BMI, body mass index; CI, confidence interval; CFQ-R RD, Cystic Fibrosis Questionnaire – Revised Respiratory Domain; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride
Source: Zemanick et al, 2025 (21)

The therapeutic goal of highly effective CFTRms, such as ELX/TEZ/IVA and VNZ/TEZ/D-IVA, is to restore CFTR function to normal levels, allowing people with CF to live without the manifestations of the disease. The mechanism of action for CFTRms is to improve CFTR function by increasing the amount of CFTR protein at the cell surface and increasing its channel open probability to improve the flow of chloride and water across the cell membrane (thereby reducing SwCl levels). CFTRms therefore target the underlying cause of CF and have the potential to prevent organ damage and reverse disease progression, particularly if initiated early.

B.1.3.3 Epidemiology

In 2023, there were 11,318 people with CF in the UK (9). Of these, 9,364 live in England and 473 live in Wales (9). Approximately 90% of people with CF in the UK have an F-any genotype (89.3% in England and 89.6% in Wales) (9).

The UK has the second highest incidence of CF in Europe at 1:2800, second only to Ireland (22) and similar to that seen in the US (23).

UK registry data reveals that in December 2023, 8,212 people with CF in the UK were receiving CFTRms (9). Market share data show that ELX/TEZ/IVA is the most commonly used CFTRm in England: [redacted]% of people receiving CFTRms are taking ELX/TEZ/IVA (3). Before the introduction of CFTRms in 2013, the median age at death for people in the UK with CF was 26 years and median predicted survival (for those born between 2009 and 2013) was 45 years. However, there has been a significant improvement since CFTRms became available, with the median age at death in 2023 being 46 years and the median predicted survival age increasing to 50.6 years (95% CI: 48.2, 53.1) in people with CF born between 2016 and 2020 and to 64.1 years (95% CI: 58.9, 67.0) in those born between 2019 and 2023 (9). If treatment with ELX/TEZ/IVA starts under the age of 18 years, the predicted median life expectancy is at least 82.5 years, which is equivalent to that of the UK general population (24).

B.1.3.4 Burden of CF

B.1.3.4.1 Clinical burden

The clinical presentation of CF varies considerably; however the most common manifestations include structural lung damage, lung infection and inflammation,

pancreatic insufficiency, gastrointestinal (GI) symptoms and liver complications that worsen over a person's lifetime (25, 26). Key drivers of both morbidity and mortality in people with CF include a decline in lung function, number of PEx and poor nutritional status (27, 28).

Pulmonary CF manifestations

Structural lung damage associated with CF often occurs at a very early age, with many infants presenting with structural abnormalities at diagnosis (11, 29). Structural lung damage worsens with age (30-32) and as the disease progresses, irreversible changes develop, such as bronchiectasis, a condition in which airways become permanently damaged and widened due to persistent infection (33). The extent and presence of structural lung abnormalities in early childhood can predict subsequent lung function; severe abnormalities are associated with significantly worse lung function in later life (34).

PEx are characterized by periodic worsening of respiratory health, including an acute increase in the signs and symptoms of lung infection, coupled with worsening lung function (35). People with CF who experience PEx have a faster rate of lung function decline, at more than twice the rate in people without PEx (27), and often need to be treated in hospital for these event. Additionally, PEx are associated with an increased risk of lung transplant or death (36).

Extra-pulmonary CF manifestations

Extra-pulmonary manifestations of CF include pancreatic dysfunction, CFRD, gastrointestinal disease, nutrient deficiencies and poor growth, liver disease, and reduced fertility.

Most people with CF are born with exocrine pancreatic insufficiency, which is characterized by the deficient production of digestive enzymes, leading to inadequate digestion of food. As a result, many individuals require life-long pancreatic replacement therapy to improve nutrient absorption; in the UK, 80% of people with CF were recorded as using pancreatic enzyme supplements in 2023 (37).

As people with CF get older they can also develop endocrine pancreatic dysfunction which can lead to CFRD. CFRD is common, occurring in approximately 2% of

children, 19% of adolescents, and 40% to 50% of adults with CF (38, 39). CFRD is a predictor of decreased survival (27, 28).

The absence of functional CFTR also affects other organs of the digestive system, such as the small intestine, liver, and biliary tract. Around 40% of people with CF have liver abnormalities, which can lead to health problems such as gallstones, fibrosis and cirrhosis in 5% to 10% of the CF population (40).

People with CF struggle to obtain normal nutritional status prior to CFTRm treatment, which leads to a low body mass index (BMI) and failure to thrive (i.e. insufficient weight gain and growth). This in turn increases susceptibility to lung infections (41, 42). BMI has been shown to correlate with FEV_1 in both children and adults with CF (43, 44).

CF can also have an impact on an individual's ability to conceive and reproduce. In men with CF, glandular tissue in the vas deferens is dysfunctional, resulting in obstruction and infertility. Reduced fertility has also been reported in women with CF; dysfunctional CFTR is hypothesized to cause alterations of the cervical mucus viscosity and pH, leading to impaired sperm penetration (45).

B.1.3.4.2 Patient/caregiver burden

The clinical manifestations of CF have an impact on the mental and physical health-related quality of life (HRQoL) for both people with CF and their families/caregivers (46-49). Disease-related factors associated with reduced HRQoL among adults and children with CF include reduced lung function, pulmonary infections, PEx, poor nutrition and low BMI (50-52).

26% of adolescents and 28% of adults with CF have experienced anxiety; the corresponding figures for depression are 19% and 27%, respectively (53). Parents of children with CF are two to three times more likely to experience anxiety and depression than the general population (54).

Day to day symptom-based care (in addition to CFTRms) imposes a substantial burden as the intensive regimen of nebulised and inhaled therapies and airway clearance techniques can take approximately 2 to 3 hours each day (55, 56). Adolescents with CF report that poor health and time-consuming treatments restrict their freedom (57).

Life-long nutritional support is required to achieve and maintain normal growth, development and nutritional status. This includes a high-calorie diet and fat-soluble vitamin supplements. People who struggle to gain enough weight or for whom dietary supplements are not sufficient may need enteral nutrition via a nasogastric or gastronomy tube (58).

Day-to-day care of people with CF imposes a considerable burden, with caregivers of children with CF providing, on average, nearly 75 hours of informal care per week (46). Several studies have shown that caregiving for people with CF has a substantial impact on caregiver quality of life (QoL), particularly for caregivers of children and during PEx (55, 59, 60). CFTRms have been shown to provide broad societal and humanistic benefits by reducing the life-limiting impact of CF on patients as well as improving caregiver quality of life. Recent studies using both qualitative and quantitative methods [redacted] The importance of caregiver burden was further highlighted during the recent appraisal of CFTRms (TA988), with several consultation respondents including it in their responses (63).

B.1.3.4.3 Economic burden

People with CF incur substantial direct medical costs, including the costs of medications and frequent hospitalizations, particularly in advanced disease stages as lung function declines (48, 64).

The number of PEx a person experiences per year and the severity of lung function impairment have been identified as strong predictors of economic burden in the UK (65). The average annual healthcare cost for a person with severe lung function impairment could be as much as seven times higher than for a person with mild disease (66). Low BMI (P=0.001), low baseline ppFEV$_1$ (P<0.001), female gender

and the presence of *Pseudomonas aeruginosa* infection (P=0.02) are also significant predictors of increased total annual costs (65).

Hospitalization costs represent a large component of total direct medical costs in CF (67). Treatment of PEx often requires hospitalization (68, 69). People who experience a greater number of PEx have a higher number of subsequent hospitalizations with longer length of stay, which contributes to higher overall healthcare costs (70).

People with CF who require lung transplant incur significant costs, including the initial transplant cost, followed by the annual cost associated with post-transplantation care. Lung transplants are substantial cost-drivers of total CF-related management costs; in the UK, the cost for a lung transplant and a decade of subsequent care is approximately £140,000) (71, 72). Suitable lungs for transplant are a limited resource; in 2023, of the 21 people with CF accepted onto the transplant list, fewer than five received one (9).

Indirect costs are also an important contributor to the economic burden of CF. In a study of 254 CF patients in the UK, 40% reported that they had resigned from a job due to CF (73). Chevreul et al (2016) found that the mean annual labour productivity loss was £10,186 per patient per year in the UK (74, 75). Families of CF patients also incur indirect medical costs as a result of caregiving responsibilities that lead to lower availability to work, productivity loss, greater absenteeism and obstacles to career progression (74, 76).

B.1.3.5 Clinical care pathway and positioning of VNZ/TEZ/D-IVA

There is currently no cure for CF, but sustained early intervention is critical to improving long-term outcomes (77). Existing treatment consists of long-term, uninterrupted use of CFTRms (which target the underlying cause of the disease) plus best supportive care to treat the symptoms (i.e. mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, anti-inflammatory agents and physiotherapy) (78, 79).

Several CFTRms (ELX/TEZ/IVA, TEZ/IVA and lumacaftor/ivacaftor [LUM/IVA]) have recently been approved by NICE for treatment of CF, following a number of years of

interim access and local data collection (1). IVA is also available through baseline commissioning (2). These treatments are positioned alongside each other and the choice of modulator depends on the patient's age and genotype. The majority of eligible patients are prescribed/switched to ELX/TEZ/IVA as it provides further benefits to mono- or dual therapy, unless a good reason exists not to. The European Cystic Fibrosis Society recommends that all people with CF aged 6 years and older with at least one *F508del* mutation should have access to ELX/TEZ/IVA (79). In line with this guidance, ELX/TEZ/IVA is the most commonly used CFTRm in England and Wales (used in [redacted] % of patients receiving CFTRms (3)) and is therefore the appropriate comparator to VNZ/TEZ/D-IVA.

Table 3 shows which CFTRms are suitable for people with common CF genotypes. In the population of interest (F-any), VNZ/TEZ/D-IVA is positioned as an alternative option to ELX/TEZ/IVA.

Table 3 CFTR modulators in common CF genotypes

Genotype	Genotype prevalence[a] (80)	Treatments	Guidance
Homozygous for the *F508del*-CFTR mutation (F/F)	[redacted] %	TEZ/IVA	TA988
		LUM/IVA	TA988
		ELX/TEZ/IVA	TA988
		VNZ/TEZ/D-IVA	-
		Best supportive care	NG78
Heterozygous for the *F508del*-CFTR mutation and another 'minimal function' mutation with no/minimal CFTR protein activity (F/MF)	[redacted] %	**ELX/TEZ/IVA**	TA988
		VNZ/TEZ/D-IVA	-
		Best supportive care	NG78
Heterozygous for the *F508del*-CFTR mutation and a 'residual function' mutation associated with residual CFTR protein activity (F/RF)	[redacted] %	TEZ/IVA	TA988
		ELX/TEZ/IVA	TA988
		VNZ/TEZ/D-IVA	-
		Best supportive care	NG78

Genotype	Genotype prevalence[a] (80)	Treatments	Guidance
Heterozygous for the *F508del*-CFTR mutation and a gating mutation (F/Gating)	[redacted]%	IVA	Baseline commissioning
		ELX/TEZ/IVA	TA988
		VNZ/TEZ/D-IVA	-
		Best supportive care	NG78
Heterozygous for the *F508del* CFTR mutation with other or unknown mutation (F/Other)	NR	**ELX/TEZ/IVA**	TA988
		VNZ/TEZ/D-IVA	-
		Best supportive care	NG78

Notes: IVA available for patients aged ≥1 month; LUM/IVA available for patients aged ≥6 years; TEZ/IVA available for patients aged ≥6 years; ELX/TEZ/IVA available for patients aged ≥2 years. [a]Denominator is number of patients aged 6 years or older in the UK with at least one *F508del* mutation: n = 8307 (2021 registry data)
Key: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELX, elexacaftor; IVA, ivacaftor; IVA/TEZ/ELX, elexacaftor-tezacaftor-ivacaftor in combination with ivacaftor; LUM/IVA, lumacaftor-ivacaftor; NR, not reported; TEZ/IVA, tezacaftor-ivacaftor in combination with ivacaftor.

B.1.3.6 Unmet need

There is a need for alternative CFTRm therapies that:

- have the potential to further reduce CF manifestations and disease burden by further restoring CFTR function towards normal levels in more people, at as early an age as possible, enabling them to live a near-normal life;
- provide a simpler treatment regimen and reduce the overall treatment burden;
- provide an option for people who have discontinued current CFTRms

B.1.3.6.1 Most people treated with ELX/TEZ/IVA do not achieve restoration of CFTR function to normal levels

Despite the transformative benefits that current CFTRms have brought, most people, even on ELX/TEZ/IVA treatment, do not achieve normal levels of CFTR function (i.e. SwCl levels <30 mmol/L) (81-84). Improvement of CFTR function (as indicated by lower levels of SwCl) is associated with improved outcomes such as better and more

stable lung function, fewer PEx, and better quality of life (21). Restoring CFTR function to normal levels (i.e. SwCl levels <30 mmol/L) has the potential to bring the best clinical outcomes for people with CF, particularly if treatment is initiated early in life before significant organ damage has occurred (21).

B.1.3.6.2 People treated with ELX/TEZ/IVA continue to experience clinical manifestations and hospitalizations

Despite improvements in lung function, most people treated with ELX/TEZ/IVA continue to experience certain clinical manifestations of the disease, such as persistent residual inflammation and airway infection, PEx, GI symptoms, CFRD and exocrine pancreatic insufficiency, as well as CF-related hospitalizations (85-91). Affected individuals have expressed a preference for treatments that can bring further improvements in clinical symptoms (92).

B.1.3.6.3 People with CF continue to face a high treatment burden and could benefit from simpler dosing regimens

Currently available CFTRms require twice-daily dosing with fat-containing meals, which can be inconvenient for both patients and caregivers. Research has shown that people with CF often prioritise treatments that fit better into their daily routine (93). In addition, people with CF rely on best supportive care regimens alongside CFTRms, which are associated with a high treatment burden. Both patients and carers consistently highlight the need for simplifying the best supportive care treatment burden (94).

People with CF and their caregivers would therefore benefit from a new treatment with a simplified dosing schedule that is more manageable and convenient to daily life, with the potential to reduce the need for best supportive care therapies when initiated early in life.

B.1.3.6.4 Some people with CF have discontinued current CFTRms and require another highly effective treatment option

Some people with CF have discontinued CFTRm treatment because of tolerability issues and/or lack of perceived clinical benefit (95). There is therefore a need for an alternative highly effective treatment option in this patient group.

B.1.4 Equality considerations

We do not anticipate that this appraisal raises any equality issues according to the current scope, although subgrouping the F-any population under review according to CFTR genotype or baseline lung function would raise equality concerns.

NHS England has agreed to make treatment available to people with non-F VNZ/TEZ/D-IVA responsive mutations via a commissioning statement, similar to current arrangements for ELX/TEZ/IVA (2), so those people with rarer mutations will not be disadvantaged by the scope of this appraisal.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

ELX/TEZ/IVA, the comparator in the company evidence submission, was recommended by NICE in July 2024 as part of the multiple technology appraisal (MTA) TA988, for treating CF in people two years and over who have at least one *F508del* mutation in the CFTR gene (1).

In TA988, the introduction of the modulators was regarded by patient experts as a transformative step in the treatment pathway for patients with CF. During the appraisal, the committee concluded that the clinical trial evidence shows that ELX/TEZ/IVA improves lung function, growth and weight gain and reduces the number of lung infections more than standard treatment. It was considered likely that these benefits last while people are having treatment.

When considering the condition's severity, and its effect on quality and length of life, the committee concluded that cost-effectiveness estimates for ELX/TEZ/IVA were within what NICE considers an acceptable use of NHS resources. So, it was recommended within its marketing authorisation.

The following sections outline the key topics that were discussed in detail as part of the submission for ELX/TEZ/IVA. However, given the comparability in the health benefits between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, these key topics are not expected to form an integral part of the economic evaluation for VNZ/TEZ/D-IVA in this submission.

B.2.1.1 Treatment effectiveness

In the economic model, CFTRms were assumed to have a treatment effect on a patient's lung function, measured via ppFEV$_1$, number of PEx, and weight-for-age z score. These effects were considered to be conservative assumptions as evidence has shown that CFTRms can also reduce the number of respiratory infections and development of CFRD and/or reverse pancreatic insufficiency, especially if initiated

at an early age (96, 97). However, these potential benefits were not explicitly captured within the cost-effectiveness analysis.

The committee concluded that there is a large and robust evidence base for the acute benefits of CFTRms. It noted that comparisons with standard of care alone show substantial effectiveness for ELX/TEZ/IVA.

The four key influential clinical outcomes from the cost-effectiveness analysis included:

1. $ppFEV_1$
    i. $ppFEV_1$ was used in the economic analysis to better predict survival, based on the Cox proportional hazards model from Liou et al., as well as to determine lung transplantation requirements (27).
    ii. The committee concluded that the long-term relative reduction in $ppFEV_1$ decline with ELX/TEZ/IVA was likely to be greater than the estimate using UK Cystic Fibrosis Registry (UKCFR) data, due to people taking these readings at home, but less than the 100% predicted from clinical trials, because this implied that progression of CF would stop in all patients having treatment (1). Due to this, the committee ultimately agreed on a relative reduction in $ppFEV_1$ decline of [redacted]
2. PEx
    i. The committee concluded that CFTRms have a substantial impact on reducing PEx, leading to reductions in hospitalizations and intravenous (IV) antibiotics – and their associated costs.
3. Change in weight-for-age z scores
    i. Used to help predict survival, based on the Cox proportional hazards model from Liou et al., a treatment effect on a patient's weight-for-age z score was applied during the acute period (27). Within this period, patients on CFTRms experienced an increase in the weight-for-age z score from baseline, thereby reducing their risk of mortality.

4. Lung transplantations
    i. Patients were eligible for lung transplant in the model once their ppFEV$_1$ fell below 30%. As this was anticipated to take longer for patients receiving ELX/TEZ/IVA, the model estimated a reduced requirement for lung transplants in those patients receiving ELX/TEZ/IVA.

The key areas of clinical focus from TA988 are less relevant for this submission as they are assumed to be equivalent across both VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatments hence not included in the cost-comparison analysis (CCA). This is considered a conservative approach because direct evidence from SKYLINE 102 and SKYLINE 103 show that VNZ/TEZ/D-IVA was non-inferior to ELX/TEZ/IVA in improving ppFEV$_1$, yet superior to ELX/TEZ/IVA in improving CFTR function towards normal (i.e. lowering levels of SwCl; Section B.3.6.1) which may lead to better disease trajectories in the long-term.

Table 4 provides a summary of the key clinical outcomes and measures appraised during MTA TA988 and their impact on the cost-effectiveness analysis.

Table 4 Clinical outcomes and measures appraised in published NICE guidance for the comparator(s)

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
NICE TA988	Lung function	Rate of change in $ppFEV_1$	Yes	A smaller relative reduction in $ppFEV_1$ decline for ELX/TEZ/IVA results in a higher ICER due to the relative worsening of predicted survival, and increased risk of requiring a lung transplant. This parameter was amongst the most influential parameters in the model (as reported in the company and EAG OWSA analysis)	Long-term relative reduction in $ppFEV_1$ decline was likely to be greater than the estimate from UKCFR data (confidential), but less than 100% as the committee found it implausible to assume a relative reduction of 100%. Due to this, the committee ultimately agreed on a relative reduction in $ppFEV_1$ decline of [redacted] Rate of $ppFEV_1$ decline was assumed to slow over time and was concluded to be represented by a non-linear decline in $ppFEV_1$	Long-term relative reduction in $ppFEV_1$ Rate of $ppFEV_1$ decline over time
	Pulmonary exacerbations (PEx)	Rate of PEx (formula based on age and $ppFEV_1$)	Yes	Reduced rate of PEx for ELX/TEZ/IVA results in a lower ICER. This parameter was amongst the most influential parameters in the model, although substantially less influential than the other key drivers (e.g. lung function)	The committee concluded that CFTRms have a substantial impact on reducing PEx. In addition to the rate of PEx, CFTRms lead to reductions in hospitalizations and intravenous antibiotics when treating PEx.	The duration of the impact of CFTR on rate of PEx was uncertain. The committee concluded that it was reasonable to assume that the effect would be sustained while people remained on treatment.
	Weight-for-age z score (WFAZ)	A child's body weight for their age and sex	Yes	A reduction in the WFAZ for ELX/TEZ/IVA results in an increased ICER due to the	A treatment effect on a patient's WFAZ (mean increase) is applied during	None identified

		relative to the reference population		relative worsening of predicted survival. Acute changes in WFAZ score for CFTRm treatments for age subgroups was amongst the most influential parameters in the model, although substantially less influential than the other key drivers.	the acute period in which patients on CFTRms experience an increase in the WFAZ from baseline. Following the period of acute change, all patients' WFAZ is assumed to be constant for the remainder of the model simulation.	
	Lung transplantations	Receive or do not receive a lung transplant	Yes	Reducing the $ppFEV_1$ limit required for a patient to be eligible for lung transplant has a limited impact on the ICER. The fewer transplants required for patients receiving ELX/TEZ/IVA, the lower the ICER.	Patients with a $ppFEV_1$ below 30% may receive a lung transplant.	$ppFEV_1$ limit required for a patient to be eligible for lung transplant. The committee acknowledged that the decision to have a transplant is complex and does not depend on a $ppFEV_1$ cut-off alone.

Key: CF, cystic fibrosis; CFRD; cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm; CFTR modulator; EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; ELX/TEZ/IVA, ivacaftor–tezacaftor–elexacaftor; NICE, National Institute for Health and Care Excellence; OWSA, one-way sensitivity analysis; PEx; pulmonary exacerbations; $ppFEV_1$, percent predicted Forced Expiratory Volume in 1 second; UKCFR, UK cystic fibrosis registry; WFAZ, weight-for-age z score

B.2.2 Resource use assumptions

The cost-effectiveness analysis from TA988 highlighted the impact ELX/TEZ/IVA has on several key cost categories, including:

1. Disease management costs
    i. The introduction of ELX/TEZ/IVA was expected to reduce the need for, and associated costs of, established clinical medicines (e.g. inhaled antibiotics, dornase alfa, hypertonic saline solution, azithromycin) as these treatments tended to be used more frequently in more severe CF patients.
    ii. The committee concluded that the EAG's scenario, assuming a 40% reduction in established clinical management medication costs for people on CFTRms, was most appropriate and best aligned with the available evidence, in addition to clinical and patient expert testimony.
    iii. The committee ultimately agreed that there were likely to be reductions in prescribed medicines and healthcare resource use for people on CFTRms. Therefore, these costs were deemed important factors to consider in the cost-effectiveness analysis.
2. PEx
    i. CF patients and clinical experts agreed that since starting ELX/TEZ/IVA PEx are easier to treat with oral antibiotics and are now resolved more quickly.
    ii. The committee concluded it was appropriate to assume a 50% reduction in PEx episode costs for people on CFTRms compared with standard care.
3. Monitoring costs
    i. Monitoring costs for liver function tests (bilirubin, aspartate transaminase [AST] and alanine transaminase [ALT]) and ophthalmologist visits are applied to all patients on CFTRm treatments, in line with guidance in the Summary of Product Characteristics (SmPC).

4. Lung transplantation
    i. Patients with low levels of $ppFEV_1$ would be at risk of undergoing a lung transplantation. Therefore, the long-term relative reduction in $ppFEV_1$ decline with ELX/TEZ/IVA is expected to reduce costs associated with lung transplants.
5. Adverse events
    i. The model considered a reduction in AEs (excluding PEx) for patients receiving ELX/TEZ/IVA based on data from the 445-102 study that recorded AEs occurring in at least 5% of patients treated with CFTRm and had at least 1%-point difference between patients treated with a CFTRm and placebo.

In terms of relevance to the decision problem for VNZ/TEZ/D-IVA, direct evidence from SKYLINE 102 and SKYLINE 103 showed that VNZ/TEZ/D-IVA provides similar or greater clinical benefits than ELX/TEZ/IVA, as reflected by similar improvement in $ppFEV_1$ and better restoration of CFTR function (as indicated by lowering SwCl levels). These findings suggest that healthcare resource use (HCRU) required to manage disease symptoms is likely to also be similar between the two treatments. Consequently, based on expected cost similarities tied to disease progression and SmPC guidance, the current economic analysis uses a cost-comparison model. Therefore, health state-specific HCRU estimates and associated costs from the ELX/TEZ/IVA submission (TA988) are not deemed relevant for this submission.

The only HCRU differences expected between VNZ/TEZ/D-IVA and ELX/TEZ/IVA are from their marginal differences in number of AEs, which are accounted for in the CCA in this submission (Section B.4). For this reason, lung transplantation, PEx, miscellaneous, and end-of-life costs were not included in the base case CCA for VNZ/TEZ/D-IVA.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was carried out to identify relevant clinical evidence. Full details of the SLR are given in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

Two phase 3 randomized clinical trials (RCTs) and one single-arm trial provide relevant clinical effectiveness evidence for this submission:

- The SKYLINE 102 and SKYLINE 103 RCTs provide head-to-head evidence for the efficacy and safety of VNZ/TEZ/D-IVA vs ELX/TEZ/IVA in people with CF aged ≥12 years
- The single arm RIDGELINE 105 trial provides evidence for the efficacy and safety of VNZ/TEZ/D-IVA in children with CF aged 6 to 11 years

Details of these trials are given in Table 5.

Table 5 Clinical effectiveness evidence

Study	**SKYLINE 102 (VX20-121-102) (98, 99)** (NCT05033080)	**SKYLINE 103 (VX20-121-103) (99, 100)** (NCT05076149)	**RIDGELINE 105 (VX21-121-105) (101, 102)** (NCT05422222)
Study design	Phase 3, randomized, double-blind, parallel group, 52-week study	Phase 3, randomized, double-blind, parallel group 52-week study	Phase 3, single-arm, 24-week study
Population	People aged ≥12 years of age with CF who are heterozygous for *F508del* and a minimal function mutation (F/MF)	People aged ≥12 years with CF who are homozygous for *F508del* (F/F), heterozygous for *F508del* and a gating (F/G) or a residual function (F/RF) mutation, or have at least one other triple combination-responsive (TCR) *CFTR* mutation and no *F508del* mutation	People aged 6 to 11 years of age (inclusive) with CF who have at least one triple combination-responsive (TCR) mutation[a]
Intervention(s)	VNZ/TEZ/D-IVA	VNZ/TEZ/D-IVA	VNZ/TEZ/D-IVA
Comparator(s)	ELX/TEZ/IVA	ELX/TEZ/IVA	N/A
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes	Yes
Reported outcomes specified in the decision problem	• Change in $ppFEV_1$ • Sweat chloride • PEx requiring IV antibiotic therapy and/or hospitalization • Health-related quality of life • Respiratory symptoms • Body mass index • Weight • Adverse effects of treatment	• Change in $ppFEV_1$ • Sweat chloride • PEx requiring IV antibiotic therapy and/or hospitalization • Health-related quality of life • Respiratory symptoms • Body mass index • Weight • Adverse effects of treatment	• Change in $ppFEV_1$ • Sweat chloride • PEx requiring IV antibiotic therapy and/or hospitalization • Health-related quality of life • Respiratory symptoms • $LCI_{2.5}$ • Body mass index • Height • Weight • Pancreatic secretion

Study	SKYLINE 102 (VX20-121-102) (98, 99) (NCT05033080)	SKYLINE 103 (VX20-121-103) (99, 100) (NCT05076149)	RIDGELINE 105 (VX21-121-105) (101, 102) (NCT05422222)
			• Inflammatory markers • Adverse effects of treatment
All other reported outcomes	N/A	N/A	N/A

[a]Represents Cohort B1 from the study, which is the focus of this submission; the full study population included participants aged 1 to 11 years (inclusive)

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Trial design and methodology

B.3.3.1.1 SKYLINE 102 & SKYLINE 103

SKYLINE 102 and SKYLINE 103 were phase 3, randomized, double-blind, parallel-group studies to compare the efficacy and safety of VNZ/TEZ/D-IVA with ELX/TEZ/IVA in people aged ≥12 years with cystic fibrosis who are:

- heterozygous for *F508del* and a minimal function (MF) mutation (F/MF) (SKYLINE 102)
- homozygous for *F508del* (F/F), heterozygous for *F508del* and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive (TCR, defined as responsive to ELX/TEZ/IVA) *CFTR* mutation and no *F508del* mutation (TCR/non-F) (SKYLINE 103)

Both studies consisted of a 28-day run-in period, a 52-week treatment period and a 28-day safety follow-up (Figure 2). All participants who entered the run-in period received ELX 200 mg once-daily/TEZ 100 mg once-daily and IVA 150 mg q12h (in line with MHRA licenced dosing). Those who completed the run-in period were randomized 1:1 to VNZ/TEZ/D-IVA or ELX/TEZ/IVA (see Table 6 for dosing information). Randomization was stratified by age at the screening visit (<18 versus ≥18 years of age), percent predicted forced expiratory volume in 1 second ($ppFEV_1$) determined during the run-in period (Day -14 clinic assessment; <70 versus ≥70), SwCl determined during the run-in period (Day -14 assessment; <30 versus ≥30 mmol/L), prior CFTRm use (yes versus no), and genotype group (F/F, F/G, F/RF, and TCR/non-F; SKYLINE 103 only).

Figure 2 Study design: SKYLINE 102 & SKYLINE 103

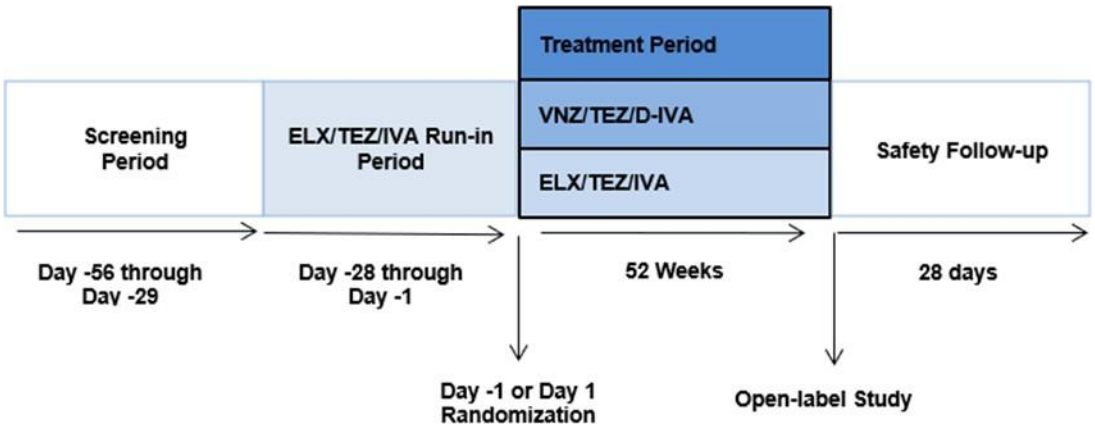


Figure is not drawn to scale
Key: D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100)

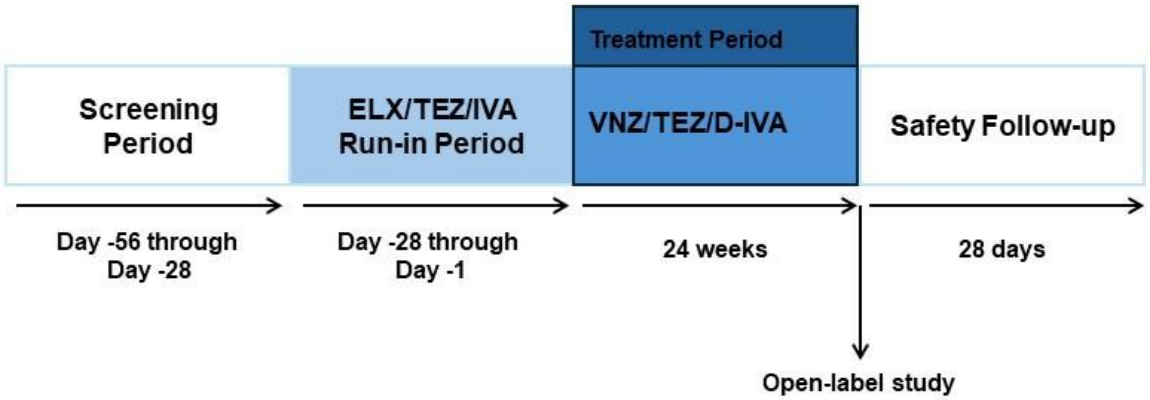
B.3.3.1.2 RIDGELINE 105

RIDGELINE 105 was a phase 3, single arm study to assess the efficacy and safety of VNZ/TEZ/D-IVA in children aged 1 to 11 years with CF who had at least one triple-combination-responsive (TCR) mutation (defined as responsive to ELX/TEZ/IVA).

This submission describes results from children aged 6 to 11 years (Cohort B1 in the study).

RIDGELINE 105 was a 2-part study. Part A was used to determine doses and weight cut-offs for Part B and is not described further. Part B consisted of a 4-week run-in period, a 24-week treatment period and a 4-week safety follow-up (Figure 3). Eligible patients who were already receiving stable ELX/TEZ/IVA had the run-in period waived and entered the treatment period within 28 days of the screening visit. Those not already receiving stable ELX/TEZ/IVA entered the run-in, during which they received ELX/TEX/IVA. Participants who completed the run-in period entered the treatment period, during which they received open-label VNZ/TEZ/D-IVA. Doses and weight cut-offs for the run-in and treatment periods are shown in Table 6. Participants who completed the treatment period were given the option to enter an open label extension study evaluating the long-term safety of VNZ/TEZ/D-IVA.

Figure 3 Study design: RIDGELINE 105



Notes: Figure is not drawn to scale. [a]Participants who were receiving stable ELX/TEZ/IVA treatment had the run-in period waived and entered the treatment period within 28 days following the screening visit. [b]Participants who were not on stable ELX/TEZ/IVA treatment entered the 4-week run-in period and received ELX/TEZ/IVA. [c]Participants who were eligible were offered the opportunity to enroll in an optional open-label extension safety study evaluating VNZ/TEZ/D-IVA. [d]The safety follow-up visit was scheduled to occur 4 weeks (±7 days) after the last dose of study drug. This visit was not required for participants who enrolled in an optional open-label extension safety study within 28 days of the last dose.
Key: D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor
Source: RIDGEWAY 105 interim clinical study report (101); Hoppe et al, 2025 (102)

The methodology for all three studies is summarised in Table 6.

Table 6 Comparative summary of trial methodology

Trial	SKYLINE 102 (NCT05033080)	SKYLINE 103 (NCT05076149)	RIDGELINE 105 (NCT05422222)
Location	International: North America, Europe (including UK), Israel, Australia, New Zealand		International: North America, Europe (including UK), Australia
Trial design	Randomized, double-blind, active-controlled, parallel group study to evaluate VNZ/TEZ/D-IVA in people aged ≥12 years with CF who have the F/MF genotype 4-week run-in period; 52-week treatment period	Randomized, double-blind, active-controlled, parallel group study to evaluate VNZ/TEZ/D-IVA in people aged ≥12 years with CF who have the following genotypes: F/F, F/G, F/RF or TCR/non-F 4-week run-in period; 52-week treatment period	Two-part, single-arm study to evaluate VNZ/TEZ/D-IVA in people aged 1 to 11 years[a] with CF with at least one TCR mutation in the *CFTR* gene Part A determined doses and weight cut-offs for Part B and is not described further Part B: 4-week run-in period (for eligible patients[b]); 24-week treatment period
Eligibility criteria for participants	Key inclusion criteria: • Heterozygous for *F508del* and a minimal function mutation (F/MF genotype) • FEV_1 value ≥40% and ≤90% of predicted mean for age, sex and height for participants currently receiving ELX/TEZ/IVA or ≥40% and ≤80% for those not currently receiving ELX/TEZ/IVA Key exclusion criteria: • Lung infection with organisms associated with a more rapid decline in pulmonary status • History of solid organ or haematological transplantation	Key inclusion criteria: • One of the following genotypes: ○ Homozygous for *F508del* (F/F) ○ Heterozygous for *F508del* and a gating mutation (F/G) ○ Heterozygous for *F508del* and a residual function mutation (F/RF) ○ At least one other TCR *CFTR* gene mutation identified as responsive to ELX/TEZ/IVA and no *F508del* mutation (TCR/non-F) • FEV_1 value ≥40% and ≤90% of predicted mean for age, sex and height for participants currently receiving CFTRm therapy or ≥40% and ≤80% for those not currently receiving CFTRm therapy	Key inclusion criteria: • Stable CF and at least one TCR mutation (including *F508del*) in the *CFTR* gene Key exclusion criteria: • Lung infection with organisms associated with a more rapid decline in pulmonary status • History of solid organ or haematological transplantation • Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9) or severe hepatic impairment (Child Pugh Score 10 to 15) • History of intolerance to the study drug that would pose an additional

Trial	SKYLINE 102 (NCT05033080)	SKYLINE 103 (NCT05076149)	RIDGELINE 105 (NCT05422222)
	• Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9) or severe hepatic impairment (Child Pugh Score 10 to 15) • Acute upper or lower respiratory tract infection, PEx, or changes in medication for sinopulmonary disease in the 28 days before the run-in period • An acute illness not related to CF in the 14 days before the run-in period • History of intolerance to the study drug that would pose an additional risk to the participant in the opinion of the investigator (e.g. participants with a history of liver function test elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to the study drug)	<u>Key exclusion criteria:</u> • Lung infection with organisms associated with a more rapid decline in pulmonary status • History of solid organ or haematological transplantation • Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9) or severe hepatic impairment (Child Pugh Score 10 to 15) • Acute upper or lower respiratory tract infection, PEx, or changes in medication for sinopulmonary disease in the 28 days before the run-in period • An acute illness not related to CF in the 14 days before the run-in period • History of intolerance to the study drug that would pose an additional risk to the participant in the opinion of the investigator (e.g. participants with a history of liver function test elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to the study drug)	risk to the participant in the opinion of the investigator (e.g. participants with a history of liver function test elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to the study drug)

Trial	SKYLINE 102 (NCT05033080)	SKYLINE 103 (NCT05076149)	RIDGELINE 105 (NCT05422222)
Trial drugs	Run-in: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h Treatment period: VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h All study drugs were administered orally with a fat-containing meal or snack. To maintain the blind, patients also received matching placebos and took the same number of tablets each day.		Run-in: • <30 kg at Day -28: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h • ≥30 kg at Day -28: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h Treatment period: • <40 kg at Day 1: VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 75 mg qd • ≥40 kg at Day 1: VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd All study drugs were administered orally with a fat-containing meal or snack.
Number of participants	VNZ/TEZ/D-IVA (n = 200) ELX/TEZ/IVA (n = 205)	VNZ/TEZ/D-IVA (n = 285) ELX/TEZ/IVA (n = 289)	VNZ/TEZ/D-IVA (n = 78)
Permitted and disallowed concomitant medication	Permitted: • Medications taken as part of a stable CF treatment regimen • Prednisone/prednisolone up to 10 mg/day chronically. Prednisone/prednisolone >60 mg qd for longer than 5 days was not allowed • The following medications could be used with caution: o Substrates of OATP1B1/1B3 (e.g. statins, glyburide, nateglinide, repaglinide) o Substrates of P-gp (e.g. digoxin, cyclosporine, everolimus, sirolimus, tacrolimus) o Substrates of CYP2C9 (e.g. warfarin, glimeprimide, glipizide) Disallowed: • Moderate and strong CYP3A inducers/inhibitors (except ciprofloxacin) • Non-sponsor CFTR modulators (investigational or approved) Sponsor CFTR modulators (investigational or approved), except for study drugs		

Trial	SKYLINE 102 (NCT05033080)	SKYLINE 103 (NCT05076149)	RIDGELINE 105 (NCT05422222)
Primary outcomes (including scoring methods and timings of assessments)	• Absolute change from baseline in ppFEV$_1$ through Week 24		• Safety and tolerability through Week 24
Pre-planned subgroups	• Age at screening (<18, ≥18 years) • ppFEV$_1$ at baseline (<70; ≥70 percentage points) • SwCl at baseline (<30, ≥30 mmol/L) • Sex (male, female) • Geographic region (North America, Rest of World)		None

Notes: [a]This submission describes results from participants aged 6 to 11 years old (Cohort B1 in the study). [b]Participants who were receiving stable ELX/TEZ/IVA treatment had the run-in period waived and entered the treatment period within 28 days following the screening visit; participants who were not on stable ELX/TEZ/IVA treatment entered the 4-week run-in period and received ELX/TEZ/IVA

Key: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, CFTR modulator; ELX/TEZ/IVA, elaxacaftor/tezacaftor/ivacaftor; FEV$_1$, forced expiratory volume in 1 second; F/F, homozygous for F508del; F/G, heterozygous for F508del and a gating mutation; F/MF, heterozygous for F508del and a minimal function mutation; F/RF, heterozygous for F508del and a residual function mutation; PEx, pulmonary exacerbation; P-gp, P-glycoprotein; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TCR, triple combination responsive; TCR/non-F, at least one TCR CFTR gene mutation identified as responsive to ELX/TEZ/IVA and no F508del mutation; VNZ/TEZ/D-IVA, vanzacaftor/tezacaftor/deutivacaftor

Source: SKYLINE 102 clinical study report (98); SKYLINE 102 protocol (103); SKYLINE 102 statistical analysis plan (104); SKYLINE 103 clinical study report (100); SKYLINE 103 protocol (105); SKYLINE 103 statistical analysis plan (106); Keating et al, 2025 (99); RIDGEWAY 105 interim clinical study report (101); RIDGELINE 105 protocol (107); Hoppe et al, 2025 (102)

B.3.3.2 Baseline characteristics

Table 7 shows the patient demographics and baseline characteristics in the SKYLINE 102 and SKYLINE 103 studies.

In both studies, demographics and baseline characteristics were generally similar between treatment groups. Most participants were white. The mean (SD) age of participants at Day 1 was 30.8 (11.0) years in SKYLINE 102 and 33.7 (12.5) years in SKYLINE 103. Fifty-nine percent of participants in SKYLINE 102 and 51% in SKYLINE 103 were male. The mean (SD) ppFEV$_1$ at baseline was 67.1 (15.0) percentage points in SKYLINE 102 and 66.8 (14.7) percentage points in SKYLINE 103. Most participants (86.7% in SKYLINE 102 and 67.9% in SKYLINE 103) had received ELX/TEZ/IVA as prior medication.

In SKYLINE 102, all participants had the F/MF genotype. In SKYLINE 103, 531 participants (92.7%) had at least one *F508del* mutation.

Table 7 Baseline demographics and characteristics: SKYLINE 102 and SKYLINE 103 (FAS)

	SKYLINE 102			SKYLINE 103		
	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	Total N = 398	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284	Total N = 573
Sex, n (%)						
Male	119 (58.9)	116 (59.2)	235 (59.0)	144 (49.8)	149 (52.5)	293 (51.1)
Female	83 (41.1)	80 (40.8)	163 (41.0)	145 (50.2)	135 (47.5)	280 (48.9)
Age at Day 1 (years)						
n	202	196	398	289	284	573
Mean (SD)	30.9 (11.4)	30.8 (10.5)	30.8 (11.0)	34.0 (12.4)	33.3 (12.6)	33.7 (12.5)
Median (range)	31.3 12.2, 71.6	30.3 12.4, 61.7	31.0 12.2, 71.6	33.8 (12.7, 63.4)	32.6 (12.2, 71.2)	33.1 (12.2, 71.2)
Race, n (%)						
White	197 (97.5)	191 (97.4)	388 (97.5)	262 (90.7)	270 (95.1)	532 (92.8)
Black or African American	1 (0.5)	4 (2.0)	5 (1.3)	0	0	0
Asian	0	1 (0.5)	1 (0.3)	1 (0.3)	1 (0.4)	2 (0.3)
Southeast Asian	0	0	0	0	1 (0.4)	1 (0.2)
Other Asian	0	1 (0.5)	1 (0.3)	1 (0.3)	0	1 (0.2)
American Indian or Alaska Native	0	0	0	1 (0.3)	0	1 (0.2)
Other	1 (0.5)	0	1 (0.3)	1 (0.3)	1 (0.4)	2 (0.3)
Not collected per local regulations	0	0	0	23 (8.0)	10 (3.5)	33 (5.8)
More than 1 race	3 (1.5)	0	3 (0.8)	1 (0.3)	2 (0.7)	3 (0.5)
Ethnicity, n (%)						
Hispanic or Latino	11 (5.4)	13 (6.6)	24 (6.0)	5 (1.7)	4 (1.4)	9 (1.6)
Not Hispanic or Latino	190 (94.1)	183 (93.4)	373 (93.7)	261 (90.3)	265 (93.3)	526 (91.8)
Not collected per local regulations	1 (0.5)	0	1 (0.3)	23 (8.0)	15 (5.3)	38 (6.6)
Weight (kg)						
n	202	195	397	289	280	569
Mean (SD)	64.54 (13.75)	65.08 (13.32)	64.81 (13.52)	65.05 (13.35)	66.58 (13.98)	65.80 (13.67)
Median (range)	63.00	63.00	63.00	63.00	65.00	64.00
Min, max	33.00, 116.57	33.00, 130.18	33.00, 130.18	32.00, 106.00	34.00, 122.47	32.00, 122.47
Height (cm)						
n	201	196	397	289	283	572
Mean (SD)	166.9 (9.5)	168.8 (9.5)	167.8 (9.5)	167.8 (10.1)	168.7 (9.4)	168.3 (9.8)
Median	167.0	169.0	168.0	167.0	169.0	168.0
Min, max	137.2, 192.0	147.0, 195.0	137.2, 195.0	140.0, 200.0	139.7, 191.0	139.7, 200.0
BMI (kg/m^2)						
n	202	195	397	289	280	569
Mean (SD)	23.03 (3.85)	22.71 (3.40)	22.87 (3.63)	22.92 (3.27)	23.27 (4.02)	23.09 (3.66)
Median	22.40	22.31	22.34	22.83	22.48	22.66
Min, max	15.81, 44.72	14.28, 35.31	14.28, 44.72	15.43, 35.42	15.56, 44.98	15.43, 44.98

	SKYLINE 102			SKYLINE 103		
	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	Total N = 398	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284	Total N = 573
BMI z-score (participants ≤20 years old at baseline)						
n	40	32	72	42	53	95
Mean (SD)	-0.14 (0.88)	-0.36 (1.09)	-0.24 (0.97)	-0.30 (0.98)	-0.17 (0.95)	-0.23 (0.96)
Median	-0.29	-0.31	-0.29	-0.26	-0.13	-0.17
Min, max	-2.06, 1.98	-4.15, 1.92	-4.15, 1.98	-3.07, 1.21	-2.62, 2.12	-3.07, 2.12
Prior CFTRm use, n (%)						
Yes	177 (87.6)	170 (86.7)	347 (87.2)	250 (86.5)	241 (84.9)	491 (85.7)
IVA	0	1 (0.5)	1 (0.3)	5 (1.7)	11 (3.9)	16 (2.8)
LUM/IVA	0	0	0	17 (5.9)	19 (6.7)	36 (6.3)
TEZ/IVA	0	1 (0.5)	1 (0.3)	24 (8.3)	26 (9.2)	50 (8.7)
ELX/TEZ/IVA	177 (87.6)	168 (85.7)	345 (86.7)	204 (70.6)	185 (65.1)	389 (67.9)
No	25 (12.4)	26 (13.3)	51 (12.8)	39 (13.5)	43 (15.1)	82 (14.3)
Genotype group, n (%)						
F/MF	202 (100)	196 (100)	398 (100)	N/A	N/A	N/A
F/F	N/A	N/A	N/A	224 (77.5)	222 (78.2)	446 (77.8)
F/G	N/A	N/A	N/A	20 (6.9)	19 (6.7)	39 (6.8)
F/RF	N/A	N/A	N/A	23 (8.0)	23 (8.1)	46 (8.0)
TCR/non-F	N/A	N/A	N/A	22 (7.6)	20 (7.0)	42 (7.3)
$ppFEV_1$ at baseline (percentage points)						
n	201	193	394	286	279	565
Mean (SD)	67.2 (14.6)	67.0 (15.3)	67.1 (15.0)	66.4 (14.9)	67.2 (14.6)	66.8 (14.7)
Median	68.1	67.7	68.0	66.9	66.9	66.9
Min, max	31.0, 100.1	28.0, 108.6	28.0, 108.6	36.4, 104.6	38.3, 112.5	36.4, 112.5
$ppFEV_1$ category at baseline, n (%)						
<40 percentage points	3 (1.5)	6 (3.1)	9 (2.3)	7 (2.4)	5 (1.8)	12 (2.1)
≥40 to <70 percentage points	111 (55.0)	95 (48.5)	206 (51.8)	160 (55.4)	149 (52.5)	309 (53.9)
≥70 to ≤90 percentage points	79 (39.1)	85 (43.4)	164 (41.2)	107 (37.0)	112 (39.4)	219 (38.2)
>90 percentage points	8 (4.0)	7 (3.6)	15 (3.8)	12 (4.2)	13 (4.6)	25 (4.4)
Missing	1 (0.5)	3 (1.5)	4 (1.0)	3 (1.0)	5 (1.8)	8 (1.4)
SwCl at baseline (mmol/L)						
n	201	194	395	282	282	564
Mean (SD)	54.3 (18.2)	53.6 (17.0)	53.9 (17.6)	42.1 (17.9)	43.4 (18.5)	42.8 (18.2)
Median	54.3	52.0	53.8	41.6	43.0	42.4
Min, max	10.0, 113.5	20.5, 106.8	10.0, 113.5	10.0, 109.3	10.0, 113.3	10.0, 113.3
SwCl category at baseline, n (%)						
<30 mmol/L	19 (9.4)	17 (8.7)	36 (9.0)	80 (27.7)	72 (25.4)	152 (26.5)

	SKYLINE 102			SKYLINE 103		
	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	Total N = 398	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284	Total N = 573
≥30 to <60 mmol/L	105 (52.0)	114 (58.2)	219 (55.0)	154 (53.3)	158 (55.6)	312 (54.5)
≥60 mmol/L	77 (38.1)	63 (32.1)	140 (35.2)	48 (16.6)	52 (18.3)	100 (17.5)
Missing	1 (0.5)	2 (1.0)	3 (0.8)	7 (2.4)	2 (0.7)	9 (1.6)
CFQ-R RD score at baseline						
n	197	192	389	282	280	562
Mean (SD)	82.9 (15.7)	85.8 (14.7)	84.4 (15.3)	85.6 (13.2)	85.7 (13.2)	85.7 (13.2)
Median	83.3	88.9	88.9	88.9	88.9	88.9
Min, max	22.2, 100.0	27.8, 100.0	22.2, 100.0	27.8, 100.0	33.3, 100.0	27.8, 100.0
Negative	90 (44.6)	83 (42.3)	173 (43.5)	136 (47.1)	128 (45.1)	264 (46.1)

Notes: Except for SwCl, baseline was defined as the pre-dose Day 1 value. If the pre-dose Day 1 value was missing, the most recent pre-dose, non-missing value on or after the Day -14 visit, including unscheduled visits, was used as baseline. For SwCl, baseline was defined as the average of the 2 most recent pre-dose, non-missing values on or after the Day -14 visit, including unscheduled visits. If only 1 non-missing value was available during this interval, the available value was considered as baseline. For subjects with age at informed consent >21 years, height at screening was used as baseline. Prior CFTR modulator use included the most recent CFTR modulator prior to informed consent for each subject.

[a]If the Day -14 value was not valid or was not available, the most recent available clinic-assessed value was used.

[b]Included medications administered during the 56 days prior to the first dose of treatment in the Treatment Period excluding the ones that started in the Run-in Period

Key: BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire – Revised; CFTRm, CFTR modulator; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; F/F, homozygous for *F508del*; F/G, heterozygous for *F508del* and a gating mutation; F/MF, heterozygous for *F508del* and a minimal function mutation; F/RF, heterozygous for *F508del* and a residual function mutation; IVA, ivacaftor; LUM, lumacaftor; max, maximum value; min, minimum value; n, size of subsample; N, total sample size; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; RD, respiratory domain; SD, standard deviation; SwCl, sweat chloride; TCR/non-F, heterozygous for a triple combination responsive mutation and no *F508del* mutation; TEZ, tezacaftor; VNZ, vanzacaftor

Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (102)

Table 8 shows the baseline demographics and patient characteristics in RIDGELINE 105. Most participants were white. More than half the participants (56.4%) were male and the mean (SD) age at Day 1 was 9.1 (1.7) years. The mean (SD) ppFEV$_1$ was 99.7 (15.1) percentage points and mean SwCl was 40.4 (20.9) mmol/L. Seventy-two participants (92.3%) had at least one *F508del* mutation. Most participants (62 [79.5%]) had received ELX/TEZ/IVA as prior medication.

Table 8 Baseline demographics and characteristics: RIDGELINE 105 (FAS)

	VNZ/TEZ/D-IVA N = 78
Sex, n (%)	
Male	44 (56.4)
Female	34 (43.6)
Age at Day 1 (years)	
n	78
Mean (SD)	9.1 (1.7)
Median	9.3
Min, max	6.2, 12.0
Race, n (%)	
White	71 (91.0)
Black or African American	1 (1.3)
Not collected per local regulations	5 (6.4)
More than 1 race	1 (1.3)
Ethnicity, n (%)	
Hispanic or Latino	9 (11.5)
Not Hispanic or Latino	62 (79.5)
Not collected per local regulations	7 (9.0)
***CFTR* genotype group, n (%)**	
F/F	37 (47.4)
F/MF	24 (30.8)
F/G	3 (3.8)
F/RF	1 (1.3)
F/other[a]	2 (2.6)
TCR/any	11 (14.1)
TCR/F	5 (6.4)
TCR/non-F	6 (7.7)
Weight (kg)	
n	78
Mean (SD)	30.21 (7.48)
Median	28.90
Min, max	19.30, 54.00
Weight z-score	
n	78
Mean (SD)	0.00 (0.89)
Median	0.04
Min, max	-1.89, 1.59
Weight category, n (%)	
<40 kg	70 (89.7)
≥40 kg	8 (10.3)
Height (cm)	
n	78
Mean (SD)	133.0 (10.5)

	VNZ/TEZ/D-IVA N = 78
Median	133.1
Min, max	111.5, 153.7
Height z-score	
n	78
Mean (SD)	-0.03 (0.94)
Median	-0.05
Min, max	-2.18, 2.06
BMI (kg/m^2)	
n	78
Mean (SD)	16.83 (2.13)
Median	16.33
Min, max	13.40, 23.43
BMI z-score	
n	78
Mean (SD)	0.07 (0.87)
Median	0.08
Min, max	-1.75, 1.84
ppFEV$_1$ (%)	
n	77
Mean (SD)	99.7 (15.1)
Median	100.5
Min, max	29.3, 146.0
ppFEV$_1$ category, n (%)	
<40 percentage points	1 (1.3)
≥40 to <70 percentage points	1 (1.3)
≥70 to ≤90 percentage points	15 (19.2)
>90 percentage points	60 (76.9)
Missing	1 (1.3)
SwCl (mmol/L)	
n	77
Mean (SD)	40.4 (20.9)
Median	39.0
Min, max	11.5, 109.5
SwCl category, n (%)	
<30 mmol/L	30 (38.5)
≥30 to <60 mmol/L	35 (44.9)
≥60 mmol/L	12 (15.4)
Missing	1 (1.3)
CFQ-R RD score (child version)	
n	75
Mean (SD)	84.8 (16.1)
Median	91.7
Min, max	16.7, 100.0
Prior CFTRm use, n (%)	
Yes	66 (84.6)
IVA	2 (2.6)
LUM/IVA	2 (2.6)
ELX/TEZ/IVA	62 (79.5)
No	12 (15.4)

Notes: For reporting purposes, North America included subjects from the United States, and Rest of the World included subjects from Europe and Australia. For efficacy endpoints (e.g., ppFEV$_1$, SwCl, CFQ-R, nutritional parameters), baseline was defined as the predose Day 1 value. For subjects who were on stable ELX/TEZ/IVA, if the predose Day 1 value was missing, the most recent available predose value, including the screening assessment, was used as baseline.
[a]F/Other: a genotype in which the other non-F mutation does not fit into one of the other specified categories (i.e., G, RF, MF, TCR). [b]Included medications administered during the 28 days before the first dose of study drug in the Treatment Period. For

ELX/TEZ/IVA-naïve subjects, this included medications administered during the 56 days before the first dose of study drug in the Treatment Period excluding the medications that were started in the Run-in Period.
Key: BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, CFTR modulator; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a gating mutation; F/MF: heterozygous for *F508del* and a minimal function mutation; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; LUM, lumacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR: triple combination responsive; TEZ: tezacaftor; VNZ: vanzacaftor
Source: RIDGELINE 105 clinical study report (101); Hoppe et al, 2024 (109); Hoppe et al, 2025 (102)

B.3.4 Critical appraisal of the relevant clinical effectiveness evidence

B.3.4.1 SKYLINE 102 and SKYLINE 103

Table 9 includes a summary of the quality assessment for the SKYLINE 102 and 103 RCTs. The full assessment is included in Appendix D.

Table 9 Quality assessment of SKYLINE 102 and SKYLINE 103 (summary)

Trial number (acronym)	SKYLINE 102	SKYLINE 103
Was randomization carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

B.3.4.2 RIDGELINE 105

Table 10 includes a summary of the quality assessment for the single-arm RIDGELINE 105 study. The full assessment is included in Appendix D.

Table 10 Quality assessment of RIDGELINE 105 (summary)

Trial number (acronym)	RIDGELINE 105
Is the hypothesis/aim/objective of the study clearly described?	Yes
Are the main outcomes clearly described?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes
Are the interventions of interest clearly described?	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A
Are the main findings of the study clearly described?	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes
Have the characteristics of patients lost to follow-up been described?	No
Have actual probability values (i.e. 0.035 rather than <0.05) been reported for the main outcomes except where the probability value is less than 0.001?	N/A
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes
If any of the results of the study were based on “data dredging”, was this made clear?	N/A
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?	N/A
Were the statistical tests used to assess the main outcomes appropriate?	N/A
Was compliance with the intervention/s reliable?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N/A
Were losses of patients to follow-up taken into account?	Unable to determine
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N/A

Adapted from Downs & Black 1998 (110); excludes items only applicable to randomized studies

B.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.5.1 Statistical methods

SKYLINE 102 and 103 were non-inferiority trials, with a null hypothesis that the mean absolute change in $ppFEV_1$ through Week 24 for VNZ/TEZ/D-IVA was inferior by >3 percentage points compared to ELX/TEZ/IVA. The selected non-inferiority margin of -3.0 percentage points is consistent with a statistical approach using the Rothmann method, which recommends that the non-inferiority margin should preserve at least 50% of the treatment effect of the active control (ELX/TEZ/IVA) compared to placebo, where the treatment effect is estimated by the lower bound of the 95% CI (111, 112). In the overall population eligible for these studies, the lower bound of the 95% CI of the treatment effect for ELX/TEZ/IVA is approximately 12 percentage points for $ppFEV_1$. The non-inferiority margin is also consistent with clinical precedence from studies evaluating symptomatic CF treatments (113, 114).

The statistical methods used in each study are summarised in Table 11.

Table 11 Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SKYLINE 102 **SKYLINE 103**	Primary null hypothesis: the mean absolute change from baseline in $ppFEV_1$ through Week 24 for VNZ/TEZ/D-IVA was inferior by >3 percentage points compared to ELX/TEZ/IVA	MMRM Absolute change from baseline through Week 24 in • $ppFEV_1$ • SwCl • CFQ-R RD Absolute change from baseline through Week 52 in • $ppFEV_1$ • SwCl • CFQ-R RD • BMI • Weight GEE model with logit link function and unstructured working correlation matrix • % of patients with SwCl <60 mmol/L through Week 24 • % of patients with SwCl <30 mmol/L through Week 24 • % of patients with SwCl <60 mmol/L through Week 52 • % of patients with SwCl <30 mmol/L through Week 52	Absolute change from baseline in $ppFEV_1$ through Week 24 (primary endpoint) Assuming a within-group SD of 8 and a 10% drop-out rate at Week 24, and a treatment difference of 0 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, the following sample sizes provided more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample *t*-test at a significance level of 0.025: • SKYLINE 102: 200 per treatment group • SKYLINE 103: 275 per treatment group Absolute change from baseline in SwCl through Week 24 (key secondary endpoint) Assuming a within-group SD of 14 mmol/L and a 10% dropout rate at Week 24, the following sample sizes provided more than 90% power to detect a difference between the treatment groups of -5 mmol/L for the absolute change from baseline in SwCl through Week 24, based on a 2-sided, 2-sample *t*-test at a significance level of 0.05:	Primary analysis Missing data were assumed to be missing at random (MAR) SwCl measurements The SwCl value at a given visit was calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point was missing, the other was used as the mean. A volume ≥15 µL is required for an accurate determination of SwCl. Any results reported as having volume <15 µL were considered missing, Any values >160 mmol/L were considered missing. Any value reported as <10 mmol/L were imputed as 10 mmol/L

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Hierarchical testing Hierarchical testing was used to control the overall type I error at an alpha of 0.05. This meant that the key secondary endpoints were formally tested only if the primary analysis of absolute change from baseline in $ppFEV_1$ at Week 24 was statistically significant (i.e. the null hypothesis was rejected)	• SKYLINE 102: 200 per treatment group • SKYLINE 103: 275 per treatment group Patients from SKYLINE 102 and 103 were pooled in order to have sufficient power for analysis of the proportion of subjects with SwCl <60 or <30 mmol/L through Week 24.	

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
RIDGELINE 105	There was no hypothesis testing in this study	MMRM: Absolute change from baseline through/at Week 24 in • SwCl • $ppFEV_1$ • CFQ-R RD • BMI and BMI-for-age z-score • Weight and weight-for-age z-score • Height and height-for-age z-score Descriptive statistics: • Drug acceptability assessment • PEx and CF-related hospitalizations through Week 24 • % of patients with SwCl <60 mmol/L or <30 mmol/L through Week 24 • Absolute change in FE-1, IRT, faecal calprotectin; $LCI_{2.5}$ through/at Week 24	There was no formal power calculation for Part B (cohort B1). Approx. 65 patients were planned for enrolment to meet the primary safety objective. With approx. 55 patients expected to complete Part B (in cohort B1), the study had a 94% chance of observing an AE in at least 1 patient if the true incidence rate was 5% and a >99% chance of observing an AE in at least 1 patient if the true incidence rate was 10%.	For MMRM analyses, missing data were assumed to be missing at random. SwCl measurements: The SwCl value at a given visit was calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point was missing, the other was used as the mean. A volume ≥15 µL was required for an accurate determination of SwCl. Any results reported as having volume <15 µL were considered missing, Any values >160 mmol/L were considered missing. Any value reported as <10 mmol/L was imputed as 10 mmol/L. LCI measurements: The LCI assessments were derived from N2-multiple-breath washout (MBW) testing. Each MBW was performed in multiple replicates for each visit, and the final LCI value was calculated from the technically acceptable washout replicates as graded and determined by a central reader. When there was only one acceptable replicate at the visit, LCI was not calculated. The assessment for that subject at

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				the corresponding visit was missing.

Key: BMI, body mass index; CF, cystic fibrosis; CFQ-R RD, Cystic Fibrosis Questionnaire – Revised Respiratory Domain; FE-1, fecal elastase-1; GEE, generalised estimating equation; IRT, immunoreactive trypsinogen; LCI, lung clearance index; $LCI_{2.5}$, number of lung turnovers required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value; MMRM, mixed model for repeated measures; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation; SwCl, sweat chloride
Source: SKYLINE 102 clinical study report (98); SKYLINE 102 statistical analysis plan (104); SKYLINE 103 clinical study report (100); SKYLINE 103 statistical analysis plan (106); RIDGELINE 105 interim clinical study report (101); RIDGELINE 105 statistical analysis plan (115)

B.3.5.2 Populations analysed

In all three trials, efficacy analyses were carried out on the full analysis set (FAS), i.e. all participants who carried the intended CFTR allele mutation(s) and received at least one dose of study drug during the treatment period. In SKYLINE 102 and 103, pooled analyses of selected endpoints (proportion of participants with SwCl <60 mmol/L and <30 mmol/L) were carried out on the pooled full analysis set (PFAS), i.e. all randomized participants from both SKYLINE 102 and 103 who carried the intended CFTR mutation(s) and received at least one dose of study drug during the treatment period. Safety analyses were conducted on the safety set, i.e. all participants who received at least one dose of study medication during the run-in (safety set for the run-in period) or treatment period (safety set for the treatment period).

B.3.5.3 Participant flow

In SKYLINE 102, 398 participants were randomized to treatment and received at least one dose of study drug: 202 in the ELX/TEZ/IVA group and 196 in the VNZ/TEZ/D-IVA group (99). Sixteen participants (7.9%) in the ELX/TEZ/IVA group and 15 (7.7%) in the VNZ/TEZ/D-IVA group discontinued the study. The most common reasons for discontinuation were AE (10 patients in the ELX/TEZ/IVA group and 4 in the VNZ/TEZ/D-IVA group) and refused dosing (two patients in the ELX/TEZ/IVA group and five in the VNZ/TEZ/D-IVA group).

In SKYLINE 103, 573 participants were randomized to treatment and received at least one dose of study medication: 289 in the ELX/TEZ/IVA group and 284 in the VNZ/TEZ/D-IVA group (99). Sixteen participants (5.5%) in the ELX/TEZ/IVA group and 25 (8.8%) in the VNZ/TEZ/D-IVA group discontinued the study. The most common reasons for discontinuation were AE (nine participants in the ELX/TEZ/IVA group and 14 in the VNZ/TEZ/D-IVA group) and pregnancy (three participants in the ELX/TEZ/IVA group and four in the VNZ/TEZ/D-IVA group).

CONSORT diagrams showing participant flow (including reasons for discontinuation) through SKYLINE 102 and 103 are provided in Appendix D.

In RIDGELINE 105, 78 patients were enrolled (102). One participant discontinued treatment owing to AEs.

B.3.6 Clinical effectiveness results of the relevant studies

The efficacy results from SKYLINE 102 and 103 support a cost-comparison analysis

- In both SKYLINE 102 and SKYLINE 103, the primary endpoint of absolute change from baseline in ppFEV$_1$ through Week 24 was met and showed that treatment with VNZ/TEZ/D-IVA was non-inferior to treatment with ELX/TEZ/IVA (see Section B.3.6.1.1)
- Head-to head against ELX/TEZ/IVA, on the first key secondary endpoint, VNZ/TEZ/D-IVA was superior in reducing SwCl levels through Week 24 (see Section B.3.6.1.2)
- In the second and third key secondary endpoints, VNZ/TEZ/D-IVA also achieved superiority in the proportion of patients with SwCl below 60 mmol/L (the diagnostic threshold for CF) and below 30 mmol/L (normal levels of CFTR function) (see Section B.3.6.1.2)
- Results from other secondary endpoints (e.g. PEx, nutritional parameters, CFQ-R RD scores) were similar between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups (see Sections B.3.6.1.3 to B.3.6.1.6)
- Results at 52 weeks were consistent with results at 24 weeks

As the secondary objective, the RIDGELINE 105 study demonstrated the efficacy of VNZ/TEZ/D-IVA in children with CF aged 6 to 11 years

- VNZ/TEZ/D-IVA resulted in reductions in SwCl with a mean absolute change through Week 24 of -8.6 mmol/L compared to ELX/TEZ/IVA baseline of 40.4 mmol/L (see Section B.3.6.2.1)

- 95% of children achieved SwCl levels below 60 mmol/L and 53% treated with VNZ/TEZ/D-IVA achieved normal levels of CFTR function with SwCl levels below 30 mmol/L (see Section B.3.6.2.1)
- Treatment with VNZ/TEZ/D-IVA resulted in similar values in $ppFEV_1$ compared to ELX/TEZ/IVA baseline of 99.7%

B.3.6.1 Efficacy vs ELX/TEZ/IVA (patients aged ≥12 years)

Note: The efficacy results from SKYLINE 102 and 103 are based on change from baseline ELX/TEZ/IVA treatment, i.e. following the 4 weeks of ELX/TEZ/IVA treatment in the run-in period.

The primary endpoint of SKYLINE 102 and 103 was non-inferiority of VNZ/TEZ/D-IVA vs ELX/TEZ/IVA in improving lung function, as measured by $ppFEV_1$. The key secondary endpoints aimed to detect difference in CFTR function improvement (as measured by SwCl) between VNZ/TEZ/D-IVA vs ELX/TEZ/IVA.

Historically, clinical trials in CF focus primarily on $ppFEV_1$ improvement given its clinical value and that it is a regulatory enabling primary endpoint. However, for the majority of people with CF, further improvements in $ppFEV_1$ beyond that provided by highly effective CFTRms (e.g. ELX/TEZ/IVA) may not be possible in clinical trials due to irreversible lung damage or relatively preserved lung function (82, 83).

Further, FEV_1 may not be sensitive enough for detecting mild or moderate lung damage in children with CF (116, 117). In a study that compared different tools for evaluating respiratory system dysfunction in children with CF, spirometry-based classifications of normal lung function ($ppFEV_1$ ≥90) and mild lung disease ($ppFEV_1$ 70–89) failed to detect lung impairment in children with CF (117). As such, with a continued roll-out of newborn screening programs and early treatment initiation, $ppFEV_1$ can no longer be considered a sensitive enough measure to detect early lung function impairment in children with CF.

These are some of the factors that led to the decision to perform a non-inferiority analysis for $ppFEV_1$ and include key secondary endpoints focusing on CFTR function improvement (as measured by SwCl).

B.3.6.1.1 $ppFEV_1$

In both studies, the primary endpoint of absolute change in $ppFEV_1$ from baseline through Week 24 was met and showed VNZ/TEZ/D-IVA to be non-inferior to ELX/TEZ/IVA (i.e. the lower bound of the 95% CI for the treatment difference was greater than the pre-specified non-inferiority margin of -3.0 percentage points) (Table 12).

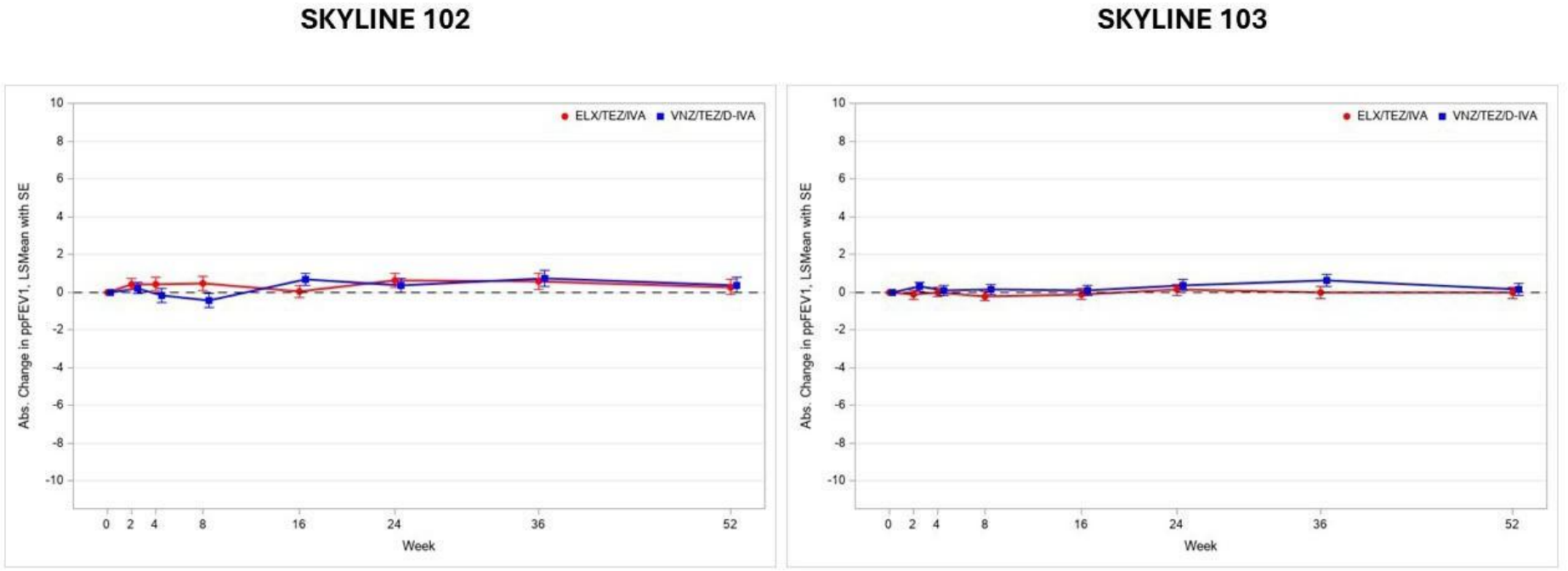
Table 12 Absolute change from baseline in $ppFEV_1$ (percentage points) through Week 24 (SKYLINE studies; MMRM analysis; FAS)

	SKYLINE 102		SKYLINE 103	
	E X/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284
Baseline				
n	201	193	286	279
Mean (SD)	67.2 (14.6)	67.0 (15.3)	66.4 (14.9)	67.2 (14.6)
Absolute change through Week 24				
n	193	187	276	268
LS mean (SE)	0.3 (0.3)	0.5 (0.3)	0.0 (0.2)	0.2 (0.3)
95% CI of LS mean	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference, 95% CI	--	**0.2 (-0.7, 1.1)**	--	**0.2 (-0.5, 0.9)**
1-sided P value for non-inferiority	--	<0.0001	--	<0.0001

Key: D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (99)

The $ppFEV_1$ results through Week 52 were consistent with values through Week 24 (Figure 4); the LS mean treatment difference in the absolute change from baseline was 0.1 percentage points (95% CI: -0.8, 1.0) in SKYLINE 102 and 0.3 percentage points (95% CI: -0.4, 1.0) in SKYLINE 103 (99).

Figure 4 Absolute change from baseline in ppFEV$_1$ (percentage points) through Week 52 (SKYLINE studies; MMRM; FAS)



Key: D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Keating et al, 2024 (108); Keating et al, 2025 (99)

B.3.6.1.2 SwCl

In both studies, for the first key secondary endpoint of absolute change from baseline in SwCl through Week 24, there was a statistically significant improvement in CFTR function (as assessed by a reduction in SwCl) after treatment with VNZ/TEZ/D-IVA compared with ELX/TEZ/IVA (Table 13).

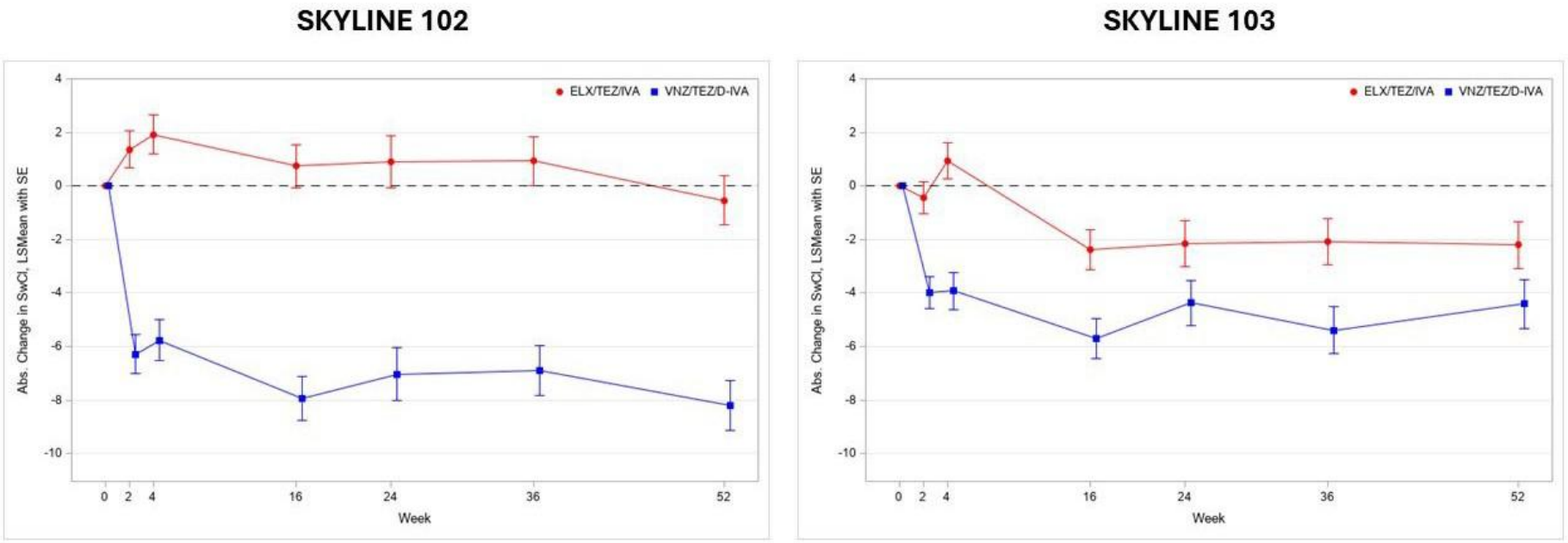
Table 13 Absolute change from baseline in SwCl (mmol/L) through Week 24 (SKYLINE studies; MMRM analysis; FAS)

	SKYLINE 102		SKYLINE 103	
	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284
Baseline				
n	201	194	282	282
Mean (SD)	54.3 (18.2)	53.6 (17.0)	42.1 (17.9)	43.4 (18.5)
Absolute change through Week 24				
n	194	185	276	270
LS mean (SE)	0.9 (0.8)	-7.5 (0.8)	-2.3 (0.7)	-5.1 (0.7)
95% CI of LS mean	(-0.6, 2.3)	(-9.0, -6.0)	-3.6, -0.9	-6.4, -3.7
LS mean difference (95% CI)	--	**-8.4 (-10.5, -6.3)**	--	**-2.8 (-4.7, -0.9)**
P value	--	<0.0001	--	0.0034

Key: D-IVA, deutivacaftor; ELX: elexacaftor; FAS: full analysis set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (99)

The SwCl results through Week 52 were consistent with values through Week 24 (Figure 5); the LS mean treatment difference in the absolute change from baseline was -8.0 mmol/l (95% CI: -9.9, -6.1) in SKYLINE 102 and -2.8 mmol/l (95% CI: -4.6, -1.0) in SKYLINE 103 (99).

Figure 5 Absolute change from baseline in SwCl (mmol/l) through Week 52 (SKYLINE studies; MMRM; FAS)



Key: D-IVA: deutivacaftor; ELX: elexacaftor; FAS: full analysis Sset; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Keating et al, 2024 (108); Keating et al, 2025 (99)

For the second and third key secondary endpoints, evaluation of the pooled data from SKYLINE 102 and 103 showed that 86% and 31% of participants who received VNZ/TEZ/D-IVA achieved SwCl <60 mmol/L (diagnostic threshold for CF) and <30 mmol/L (normal levels of CFTR function), respectively, compared with 77% and 23% in the ELX/TEZ/IVA group. Overall, participants who received VNZ/TEZ/D-IVA had statistically significant greater likelihood of achieving SwCl <60 mmol/L and <30 mmol/L than those who received ELX/TEZ/IVA (Table 14).

Table 14 Proportion of patients with SwCl <60 mmol/L and <30 mmol/L through Week 24 (SKYLINE studies; GEE analysis; pooled FAS)

	SKYLINE 102 and 103 pooled data			
	Number (%) of response			
	ELX/TEZ/IVA N = 491 (n/N1[a] [%])	VNZ/TEZ/D-IVA N = 480 (n/N1[a] [%])	Estimated OR (95% CI)	P value
SwCl <60 mmol/L				
Baseline	358/483 (74)	361/476 (76)		
Average through Week 24	367/479 (77)	399/465 (86)	**2.21 (1.55, 3.15)**	<0.0001
SwCl <30 mmol/L				
Baseline	99/483 (21)	89/476 (19)		
Average through Week 24	108/479 (23)	142/465 (31)	**2.87 (2.00, 4.12)**	<0.0001

Key: D-IVA: deutivacaftor; ELX: elexacaftor; GEE: generalized estimating equations; IVA: ivacaftor; N: total sample size; PFAS: Pooled Full Analysis Set; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Keating et al, 2025 (99)

B.3.6.1.3 PEx

In both studies, treatment with VNZ/TEZ/D-IVA resulted in similar rates of PEx through Week 52 compared to ELX/TEZ/IVA (Table 15).

Table 15 Summary of PEx during the PEx analysis period (SKYLINE studies; FAS)

	SKYLINE 102		SKYLINE 103	
	EI X TEZ/IVA N = 202	**VNZ/TEZ/D-IVA N = 196**	**ELX/TEZ/IVA N = 289**	**VNZ/TEZ/D-IVA N = 284**
PEx through Week 52				
Number of participants with events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of events	90	67	79	86
Event rate per year	0.42	0.32	0.26	0.29
Rate difference versus ELX/TEZ/IVA (95% CI)	--	**-0.10 (-0.24, 0.04)**	--	**0.03 (-0.07, 0.13)**
PEx requiring hospitalization				
Number of participants with events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]	[redacted]
Observed event rate per year	[redacted]	[redacted]	[redacted]	[redacted]
PEx requiring IV antibiotic therapy				
Number of participants with events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]	[redacted]
Observed event rate per year	[redacted]	[redacted]	[redacted]	[redacted]
PEx requiring hospitalization or IV antibiotic therapy				
Number of participants with events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]	[redacted]
Observed event rate per year	[redacted]	[redacted]	[redacted]	[redacted]

Notes: PEx were defined as any new or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms. Total number of days = sum of the individual duration (actual number of days) of the PEx analysis period across all subjects. Total number of years = total number of days / 336; for analysis purposes, 1 year is defined as 48 weeks or 336 days.
Key: D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IV: intravenous; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (99)

B.3.6.1.4 CFQ-R RD

In both studies, treatment with VNZ/TEZ/D-IVA resulted in a similar absolute change from baseline in CFQ-R RD score through Week 24 compared to ELX/TEZ/IVA (Table 16).

Table 16 Absolute change from baseline in CFQ-R RD score through Week 24 (SKYLINE studies; MMRM analysis; FAS)

	SKYLINE 102		SKYLINE 103	
	E X/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	ELX/TEZ/IVA N = 289	VNZ/TEZ/D-IVA N = 284
Baseline				
n	197	192	282	280
Mean (SD)	82.9 (15.7)	85.8 (14.7)	85.6 (13.2)	85.7 (13.2)
Absolute change through Week 24				
n	192	186	270	268
LS mean (SE)	-1.7 (1.0)	0.5 (1.1)	-1.2 (0.8)	-1.2 (0.8)
95% CI of LS mean	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	--	**2.3 (-0.6, 5.2)**	--	**-0.1 (-2.3, 2.1)**

Key: CFQ-R: Cystic Fibrosis Questionnaire – Revised; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; RD: Respiratory Domain; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (99)

CFQ-R RD results through 52 weeks of treatment with VNZ/TEZ/D-IVA were also consistent with results through Week 24.

B.3.6.1.5 CFQ-R-8D

The Cystic Fibrosis Questionnaire-Revised 8 dimensions (CFQ-R-8D) is the first disease-specific preference-based scoring algorithm for CF (118). It estimates disease-specific utilities based on the CFQ-R. To develop the CFQ-R-8D, nine items from the CFQ-R were used to derive eight domains: physical functioning, vitality, emotion, role functioning, cough, breathing difficulty, abdominal pain, and body image. The CFQ-R-8D was valued using time trade-off with a representative sample of the United Kingdom (UK) general population (n = 400) via face-to-face interviews. The model algorithm has a predicted range for health state utility values of 0.236 to 1 (118).

The magnitude of the treatment-specific utility increment for VNZ/TEZ/D-IVA was derived from a post-hoc analysis in which the CFQ-R-8D preference-based scoring algorithm was used to calculate health state utilities from the CFQ-R data collected in both SKYLINE 102 and 103. Results based on a pooled analysis of SKYLINE 102 and 103 showed that VNZ/TEZ/D-IVA improved CFQ-R-8D utility values, with participants in the VNZ/TEZ/D-IVA group having higher CFQ-R-8D utility values when compared with ELX/TEZ/IVA ([redacted] vs. ELX/TEZ/IVA, P = [redacted]) (119).

The meaningful improvements in CFQ-R-8D utility values with VNZ/TEZ/D-IVA were consistent with superiority observed on SwCl concentration in the SKYLINE 102 and 103 trials. Overall, the utility data suggest that restoration of CFTR function (as measured by reductions in SwCl levels) with VNZ/TEZ/D-IVA leads to benefits in QoL compared to ELX/TEZ/IVA, further supporting the benefit of VNZ/TEZ/D-IVA in the treatment of CF.

B.3.6.1.6 Nutritional parameters

In both studies, nutritional parameters in the VNZ/TEZ/D-IVA group were similar to those in the ELX/TEZ/IVA group at Week 52 (Table 17).

Table 17 Nutritional parameters at Week 52 (SKYLINE studies; FAS)

	SKYLINE 102		SKYLINE 103	
	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196	ELX/TEZ/IVA N = 202	VNZ/TEZ/D-IVA N = 196
Absolute change from baseline in BMI at Week 52 (kg/m^2)				
n				
LS mean (SE)				
95% CI of LS mean				
LS mean difference, 95% CI				
Absolute change from baseline in BMI z-score at Week 52 (subjects ≤20 years of age at baseline)				
n				
LS mean (SE)				
95% CI of LS mean				
LS mean difference, 95% CI				
Absolute change from baseline in weight at Week 52 (kg)				
n				
LS mean (SE)				
95% CI of LS mean				
LS mean difference, 95% CI				

Key: BMI: body mass index; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100)

B.3.6.2 Efficacy in patients aged 6 to 11 years (RIDGELINE 105; Cohort B1)

Note: All subjects were on stable ELX/TEZ/IVA treatment for at least 4 weeks prior to receiving VNZ/TEZ/D-IVA in the Treatment Period; efficacy endpoints summarised as within-group changes are relative to ELX/TEZ/IVA baseline.

Safety was the primary endpoint in Part B of this study. Secondary efficacy endpoints were not controlled for multiplicity.

B.3.6.2.1 SwCl

Treatment with VNZ/TEZ/D-IVA resulted in reductions in SwCl with a mean absolute change through Week 24 of -8.6 mmol/L compared to ELX/TEZ/IVA baseline (Table 18).

Table 18 Absolute change from baseline in SwCl through Week 24 (RIDGELINE 105; MMRM analysis; FAS)

	VNZ/TEZ/D-IVA N = 78
Baseline	
n	77
Mean (SD)	40.4 (20.9)
Absolute change through Week 24	
n	77
LS mean (SE)	-8.6 (1.2)
95% CI of LS mean	(-11.0, -6.3)

Key: CI, confidence interval; D-IVA: deutivacaftor; FAS: full analysis set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SD, standard deviation; SE, standard error of the mean; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al, 2025 (102)

Treatment with VNZ/TEZ/D-IVA led to increases in the proportions of participants with SwCl <60 mmol/L and <30 mmol/L through Week 24 compared to ELX/TEZ/IVA baseline (Table 19). Ninety-five percent of participants achieved SwCl levels below 60 mmol/L and more than half achieved normal levels of CFTR function as measured by SwCl levels below 30 mmol/L.

Table 19 Proportion of participants with SwCl <60 mmol/l or <30 mmol/l through Week 24 (RIDGELINE 105; FAS)

	VNZ/TEZ/D-IVA N = 78	
	Proportion (n/N1 [%])	**95% CI**
SwCl <60 mmol/L		
Baseline	65/77 (84.4%)	--
Average through Week 24	74/78 (94.9%)	87.4%, 98.6%
SwCl <30 mmol/L		
Baseline	30/77 (39.0%)	--
Average through Week 24	41/78 (52.6%)	40.9%, 64.0

Key: D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: number of subjects with SwCl <30 mmol/L; N: total sample size; N1: number of subjects with non-missing SwCl at Week 16 or Week 24; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al , 2025 (102)

B.3.6.2.2 ppFEV$_1$

Participants maintained their ELX/TEZ/IVA baseline level of lung function at 99.7%, with a within group mean absolute change from baseline at Week 24 of 0.0 percentage points (Table 20).

Table 20 Absolute change from baseline in ppFEV$_1$ through Week 24 (RIDGELINE 105; MMRM analysis; FAS)

	VNZ/TEZ/D-IVA N = 78
Baseline	
n	77
Mean (SD)	99.7 (15.1)
Absolute change through Week 24	
n	74
LS mean (SE)	0.0 (1.0)
95% CI of LS mean	(-2.0, 1.9)

Key: CI, confidence interval; D-IVA: deutivacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation; SE, standard error of the mean; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al, 2025 (102)

B.3.6.2.3 PEx

Table 21 shows a summary of PEx through Week 24. There were six PEx, one of which required hospitalization.

Table 21 Summary of PEx through Week 24 (RIDGELINE 105; FAS)

	VNZ/TEZ/D-IVA N = 78
Total number of days (years) in the PEx analysis period	[redacted]
PEx overall	
Number of subjects with events, n (%)	6 (7.7)
Number of events	6
Observed event rate per year	0.15
PEx requiring hospitalization	
Number of subjects with events, n (%)	[redacted]
Number of events	[redacted]
Observed event rate per year	[redacted]
PEx requiring IV antibiotic therapy	
Number of subjects with events, n (%)	[redacted]
Number of events	[redacted]
Observed event rate per year	[redacted]
PEx requiring hospitalization or IV antibiotic therapy	
Number of subjects with events, n (%)	[redacted]
Number of events	[redacted]
Observed event rate per year	[redacted]

Key: D-IVA: deutivacaftor; FAS: Full Analysis Set; IV: intravenous; PEx: pulmonary exacerbation; TEZ: tezacaftor; VNZ: vanzacaftor
Source: RIDGELINE 105 interim clinical study report (101); Hoppe et al, 2025 (102)

B.3.6.2.4 CFQ-R RD

Despite the apparent ceiling effect for $ppFEV_1$, treatment with VNZ/TEZ/D-IVA resulted in improvements in CFQ-R RD scores, with an increase of 3.9 points from ELX/TEZ/IVA baseline through Week 24 (Table 22).

Table 22 Absolute change from baseline in CFQ-R RD score through Week 24 (RIDGELINE 105; MMRM; FAS)

	VNZ/TEZ/D-IVA N = 78
Baseline	
n	75
Mean (SD)	84.8 (16.1)
Absolute change through Week 24	
n	75
LS mean (SE)	3.9 (1.2)
95% CI of LS mean	(1.5, 6.3)

Notes: Child's version of the CFQ-R RD was used
Key: CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; D-IVA: deutivacaftor; FAS: full analysis set; LS: least squares; MMRM: mixed-effects model for repeated measures; SD, standard deviation; SE, standard error; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al, 2025 (102)

B.3.6.2.5 Growth parameters

Treatment with VNZ/TEZ/D-IVA resulted in similar values for growth parameters compared with ELX/TEZ/IVA baseline (Table 23).

Table 23 Absolute change from baseline in BMI, height, weight and associated z-scores (RIDGELINE 105; MMRM; FAS)

Parameter	VNZ/TEZ/D-IVA N = 78
BMI (kg/m^2)	
Baseline	
n	78
Mean (SD)	16.8 (2.1)
Absolute change at Week 24	
n	78
LS mean (SE)	**0.22 (0.08)**
95% CI of LS mean	(0.05, 0.38)
BMI z-score	
Baseline	
n	78
Mean (SD)	0.07 (0.87)
Absolute change at Week 24	
n	78
LS mean (SE)	**-0.05 (0.03)**
95% CI of LS mean	(-0.12, 0.02)
Weight (kg)	
Baseline	
n	78
Mean (SD)	30.21 (7.48)
Absolute change at Week 24	
n	78
LS mean (SE)	**1.67 (0.17)**

Parameter	VNZ/TEZ/D-IVA N = 78
95% CI of LS mean	(1.34, 2.00)
Weight z-score	
Baseline	
n	78
Mean (SD)	0.00 (0.89)
Absolute change at Week 24	
n	78
LS mean (SE)	**-0.02 (0.03)**
95% CI of LS mean	(-0.07, 0.03)
Height (cm)	
Baseline	
n	78
Mean (SD)	133.0 (10.5)
Absolute change at Week 24	
n	78
LS mean (SE)	**2.7 (0.1)**
95% CI of LS mean	(2.5, 3.0)
Height z-score	
Baseline	
n	78
Mean (SD)	-0.03 (0.94)
Absolute change at Week 24	
n	78
LS mean (SE)	**0.01 (0.02)**
95% CI of LS mean	(-0.03, 0.05)

Key: BMI: body mass index; CI, confidence interval; D-IVA: deutivacaftor; FAS: full analysis set; LS: least squares; MMRM: mixed-effects model for repeated measures; SD, standard deviation; SE, standard error; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al, 2025 (109)

B.3.6.2.6 Other efficacy endpoints

The lung clearance index (LCI) measures how well air moves through a person's lungs. It is more sensitive than $ppFEV_1$ in detecting response to treatment, especially in the early stage of lung function abnormalities. In RIDGELINE 105, there were numerical improvements in $LCI_{2.5}$ (the number of lung clearance turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value) (Table 24). A *post-hoc* analysis showed that 7 out of 8 children with abnormal $LCI_{2.5}$ (i.e. >7.5) at baseline achieved normal $LCI_{2.5}$ (≤7.5) at Week 24 (109).

Overall, numerical improvements were seen in faecal elastase-1 (FE-1; a measure of exocrine pancreatic function) (Table 24). Of the 41 children with baseline FE-1 <200 mg/kg (i.e. below the threshold for pancreatic sufficiency), two had FE-1 ≥200

mg/kg at Week 24 (102). In addition, of the 23 children with baseline FE-1 <15 mg/kg (i.e. definitive pancreatic insufficiency and below the detectable limit), three had detectable FE-1 levels at Week 24 (102). There were also numerical improvements in immunoreactive trypsinogen (IRT; another measure of pancreatic function) and faecal calprotectin (a marker of GI inflammation) (Table 24). These results demonstrate the extrapulmonary effects of VNZ/TEZ/D-IVA and the potential to prevent the development and/or progression of CF manifestations by further restoration of CFTR function with VNZ/TEZ/D-IVA vs. ELX/TEZ/IVA.

Table 24 Absolute change from baseline in $LCI_{2.5}$, FE-1, IRT, and faecal calprotectin at Wek 24 (RIDGELINE 105; FAS)

Analysis	Statistic	Total N = 78
Absolute change from baseline in $LCI_{2.5}$ through Week 24	Baseline	
	n	72
	Mean (SD)	6.63 (0.74)
	Absolute change through Week 24	
	n	67
	LS mean (SE)	**-0.08 (0.05)**
	95% CI of LS mean	(-0.18, 0.02)
Absolute change from baseline in FE-1 (mg/kg) at Week 24	Baseline	
	n	53
	Mean (SD)	133.9 (188.6)
	Change at Week 24	
	n	45
	Mean (SD)	**19.5 (54.1)**
Absolute change from baseline in serum levels of IRT (µg/L) at Week 24a	Baseline	
	n	37
	Mean (SD)	119.6 (271.3)
	Change at Week 24	
	n	35
	Mean (SD)	**-51.5** [redacted]
Absolute change from baseline in faecal calprotectin (mg/kg) levels at Week 24	Baseline	
	n	54
	Mean (SD)	94.89 (142.18)
	Change at Week 24	
	n	46
	Mean (SD)	**-31.00** [redacted]

Key: FAS: full analysis set; FE-1: faecal elastase-1; IRT: immunoreactive trypsinogen; $LCI_{2.5}$: number of lung clearance turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; SD, standard deviation; SE, standard error
Source: RIDGELINE 105 interim clinical study report (101); Hoppe et al, 2024 (109); Hoppe et al, 2025 (102)

B.3.7 Subgroup analysis

In SKYLINE 102 and SKYLINE 103, subgroup analyses of the primary endpoint were performed in a manner similar to that of the primary analysis; the results are

presented in Appendix E. In summary, the results of the preplanned subgroup analyses were consistent with the results of the primary analysis, i.e. regardless of differences in age, baseline ppFEV$_1$, baseline SwCl, sex and geographic region, participants receiving VNZ/TEZ/D-IVA had similar ppFEV$_1$ values to those receiving ELX/TEZ/IVA (108).

There was no subgroup analysis in RIDGELINE 105.

B.3.8 Meta-analysis

As no further phase 3 RCTs studying the efficacy and safety of VNZ/TEZ/D-IVA in people with CF were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

In patients aged ≥12 years, SKYLINE 102 and 103 provide head-to-head data against the comparator ELX/TEZ/IVA, so an indirect comparison was not required.

In patients aged 6 to 11 years there are no head-to-head data, as RIDGELINE 105 was a single arm study. However, an indirect treatment comparison was not carried out for the following reasons:

- In RIDGELINE 105, participants received a stable ELX/TEZ/IVA regimen for at least 4 weeks before starting treatment with VNZ/TEZ/D-IVA, meaning that any change from baseline was effectively comparing VNZ/TEZ/D-IVA with ELX/TEZ/IVA.

- The underlying aetiology of CF is consistent between younger and older patients. Pharmacokinetic data from RIDGELINE 105 show that the exposures of VNZ, TEZ, D-IVA and their metabolites in 6 to 11-year-olds were within the range of exposure seen in patients aged ≥12 years and were consistent with those seen in previous clinical trials of IVA, TEZ/IVA and ELX/TEZ/IVA. Trials of other CFTRms in 6 to 11-year olds have shown consistent efficacy and safety with patients aged ≥12 years (84, 120).

- Per the principles of efficacy extrapolation to the paediatric population established by the International Council for Harmonization (ICH) (121), VNZ/TEZ/D-IVA is expected to have comparable efficacy in the population enrolled in RIDGELINE 105 to the observed in SKYLINE 102 and 103, with the non-inferiority assumption deemed appropriate for the CF population aged 6 to 11 years. Based on the results from RIDGELINE 105, an ITC was deemed unnecessary to provide a clinical efficacy estimation for VNZ/TEZ/D-IVA vs. ELX/TEZ/IVA.

B.3.10 Adverse reactions

Overall, the safety and tolerability profile of VNZ/TEZ/D-IVA was comparable to ELX/TEZ/IVA in patients 12 years and older

- In SKYLINE 102 and 103, most AEs were mild to moderate and generally consistent with the manifestations of CF
- The incidence of SAEs and AEs leading to treatment discontinuation was low and balanced between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups

The safety profile of VNZ/TEZ/D-IVA in children aged 6 to 11 years was similar to that in people aged ≥12 years

- In RIDGELINE 105, most AEs were mild to moderate and generally consistent with the manifestations of CF
- The incidence of AEs was low
- The incidence and nature of AEs was similar to that seen in previous CFTRm studies in this age group

B.3.10.1 Safety and tolerability vs ELX/TEZ/IVA (patients aged ≥12 years)

B.3.10.1.1 Summary of AEs

During the treatment periods of SKYLINE 102 and 103, the overall AE profile was similar between VNZ/TEZ/D-IVA and ELX/TEZ/IVA. Most AEs were mild or moderate in severity. The incidence of serious AEs (SAEs) and AEs leading to treatment

interruption or discontinuation was low and comparable between treatment groups (Table 25).

Table 25 Summary of AEs during the treatment period (SKYLINE studies; treatment period safety set)

	SKYLINE 102		SKYLINE 103		Pooled SKYLINE 102 & 103	
	ELX/TEZ/IVA N = 202 n (%)	VNZ/TEZ/D-IVA N = 196 n (%)	ELX/TEZ/IVA N = 289 n (%)	VNZ/TEZ/D-IVA N = 284 n (%)	ELX/TEZ/IVA N = 491 n (%)	VNZ/TEZ/D-IVA N = 480 n (%)
Number of AEs (total)	[redacted]	[redacted]	[redacted]	[redacted]	3795	3551
Subjects with any AEs	[redacted]	[redacted]	[redacted]	[redacted]	469 (95.5)	459 (95.6)
AEs by strongest relationship						
Not related	[redacted]	[redacted]	[redacted]	[redacted]	182 (37.1)	151 (31.5)
Unlikely related	[redacted]	[redacted]	[redacted]	[redacted]	112 (22.8)	140 (29.2)
Possibly related	[redacted]	[redacted]	[redacted]	[redacted]	162 (33.0)	159 (33.1)
Related	[redacted]	[redacted]	[redacted]	[redacted]	13 (2.6)	9 (1.9)
AEs by maximum severity						
Mild	[redacted]	[redacted]	[redacted]	[redacted]	145 (29.5)	166 (34.6)
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	269 (54.8)	239 (49.8)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	54 (11.0)	54 (11.3)
Life-threatening	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	0
Death	[redacted]	[redacted]	[redacted]	[redacted]	0	0
AEs leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	18 (3.7)	18 (3.8)
AEs leading to study drug interruption	[redacted]	[redacted]	[redacted]	[redacted]	12 (2.4)	20 (4.2)
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	81 (16.5)	68 (14.2)
Related SAEs[a]	[redacted]	[redacted]	[redacted]	[redacted]	12 (2.6)	7 (1.5)
AEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	0	0

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. [a]When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted
Key: AE: adverse event; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100); Keating et al, 2024 (108); Keating et al, 2025 (99)

B.3.10.1.2 Most common AEs

The incidence of the most common AEs (those occurring in ≥10% of patients in either treatment group) was generally similar between the VNZ/TEZ/D-IVA and ELX-TEZ-IVA groups (Table 26). Overall, the most common AEs were generally consistent with common manifestations of CF or with common illnesses in people with CF aged ≥12 years.

Table 26 AEs occurring in ≥10% of patients in either treatment group (SKYLINE studies; treatment period safety set)

	SKYLINE 102		SKYLINE 103		Pooled SKYLINE 102 & 103		
	ELX/TEZ/IVA N = 202 n (%)	VNZ/TEZ/D-IVA N = 196 n (%)	ELX/TEZ/IVA N = 289 n (%)	VNZ/TEZ/D-IVA N = 184 n (%)	ELX/TEZ/IVA N = 491 n (%)	VNZ/TEZ/D-IVA N = 480 n (%)	Δ in % (VNZ/TEZ/D-IVA - ELX/TEZ/IVA)
Infective PEx of CF					158 (32.2)	133 (27.7)	-4.5%
COVID-19					127 (25.9)	107 (22.3)	-3.6%
Cough					101 (20.6)	108 (22.5)	1.9%
Nasopharyngitis					95 (19.3)	102 (21.3)	2.0%
Headache					63 (12.8)	76 (15.8)	3.0%
Oropharyngeal pain					60 (12.2)	69 (14.4)	2.2%
Pyrexia					50 (10.2)	52 (10.8)	0.6%
Diarrhoea					59 (12.0)	58 (12.1)	0.1%
Nasal congestion					47 (9.6)	48 (10.0)	0.4%
Blood creatinine phosphokinase increased					-	-	-
Sputum increased					50 (10.2)	45 (9.4)	-0.8
Upper RTI					67 (13.6)	72 (15.0)	1.4%
Fatigue					46 (9.4)	51 (10.6)	1.2%
Influenza					26 (5.3)	52 (10.8)	5.5%

Key: AE: adverse event; CF: cystic fibrosis; COVID-19: coronavirus disease-2019; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; RTI, respiratory tract infection; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100) Keating et al, 2024 (108); Keating et al, 2025 (99)

B.3.10.1.3 SAEs

In SKYLINE 102, [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group reported SAEs. The most common SAE was infective PEx of CF, which was reported by [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group.

In SKYLINE 103, [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group reported SAEs. Again, the most common SAE was infective PEx of CF, which was reported by [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group.

In both studies, most SAEs were considered not related or unlikely related to study treatment.

B.3.10.1.4 Discontinuations owing to AEs

In SKYLINE 102, [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group had AEs that led to treatment discontinuation. No AE leading to treatment discontinuation was reported by more than [redacted] patients in either treatment group.

In SKYLINE 103, [redacted] participants ([redacted]%) in the ELX/TEZ/IVA group and [redacted] ([redacted]%) in the VNZ/TEZ/D-IVA group had AEs that led to treatment discontinuation. The most common AEs leading to discontinuation were increased ALT (reported by [redacted] patients [[redacted]%] in the ELX/TEZ/IVA group and [redacted] [[redacted]%] in the VNZ/TEZ/D-IVA group) and increased AST (reported by [redacted] patients [[redacted]%] in the ELX/TEZ/IVA group and [redacted] [[redacted]%] in the VNZ/TEZ/D-IVA group).

B.3.10.1.5 AEs of special interest

AEs of special interest (AESIs) included elevated transaminases, rash, cataracts and neuropsychiatric events (Table 27).

Elevated transaminases

In SKYLINE 102, [redacted] participants [redacted]%) in the VNZ/TEZ/D-IVA group and [redacted] ([redacted]%) in the ELX/TEZ/IVA group had at least one elevated transaminase event. All events in the VNZ/TEZ/D-IVA group and most events in the ELX/TEZ/IVA group were mild

or moderate in intensity. One participant in each group had elevated transaminase events that led to treatment discontinuation.

In SKYLINE 103, [redacted] ([redacted] %) participants in the VNZ/TEZ/D-IVA group had at least one elevated transaminase event, compared with [redacted] ([redacted] %) in the ELX/TEZ/IVA group. Most events in the VNZ/TEZ/D-IVA group and all events in the ELX/TEZ/IVA group were mild or moderate. [redacted] participants ([redacted] %) in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had elevated transaminase events that led to treatment discontinuation.

Overall, the incidence of elevated transaminase was slightly higher with VNZ/TEZ/D-IVA than with ELX/TEZ/IVA; however, imbalances were observed early (only in the first 3 months of treatment) and the incidence was balanced between the two treatments thereafter. This observation is consistent with the fact that drug-related transaminase events tend to occur early (typically within 3 months) following initiation of a new treatment (i.e. VNZ/TEZ/D-IVA), whilst the transaminase events in the ELX/TEZ/IVA group are reflective of experience in participants who have tolerated ELX/TEZ/IVA.

Rash

In SKYLINE 102, [redacted] ([redacted] %) participants in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had at least one rash event. All rash events were mild or moderate. One participant (0.5%) in the VNZ/TEZ/D-IVA group discontinued treatment because of a rash event. There were no discontinuations owing to rash events in the ELX/TEZ/IVA group.

In SKYLINE 103, [redacted] ([redacted] %) participants in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had at least one rash event. Most events in the VNZ/TEZ/D-IVA group and all events in the ELX/TEZ/IVA group were mild or moderate. No patients in either group had rash events that led to treatment discontinuation.

Overall, the incidence of rash events was slightly higher with VNZ/TEZ/D-IVA than with ELX/TEZ/IVA during the first 3 months of treatment but was balanced between

the two treatments thereafter. This can be explained by the early reaction to a new treatment (i.e. VNZ/TEZ/D-IVA) vs prior tolerance with ELX/TEZ/IVA in the ELX/TEZ/IVA group.

Cataracts

There were no cataract events in SKYLINE 102. In SKYLINE 103, [redacted] participants ([redacted] %) in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had at least one cataract event. All cataract events were mild or moderate and none led to treatment discontinuation.

Neuropsychiatric events

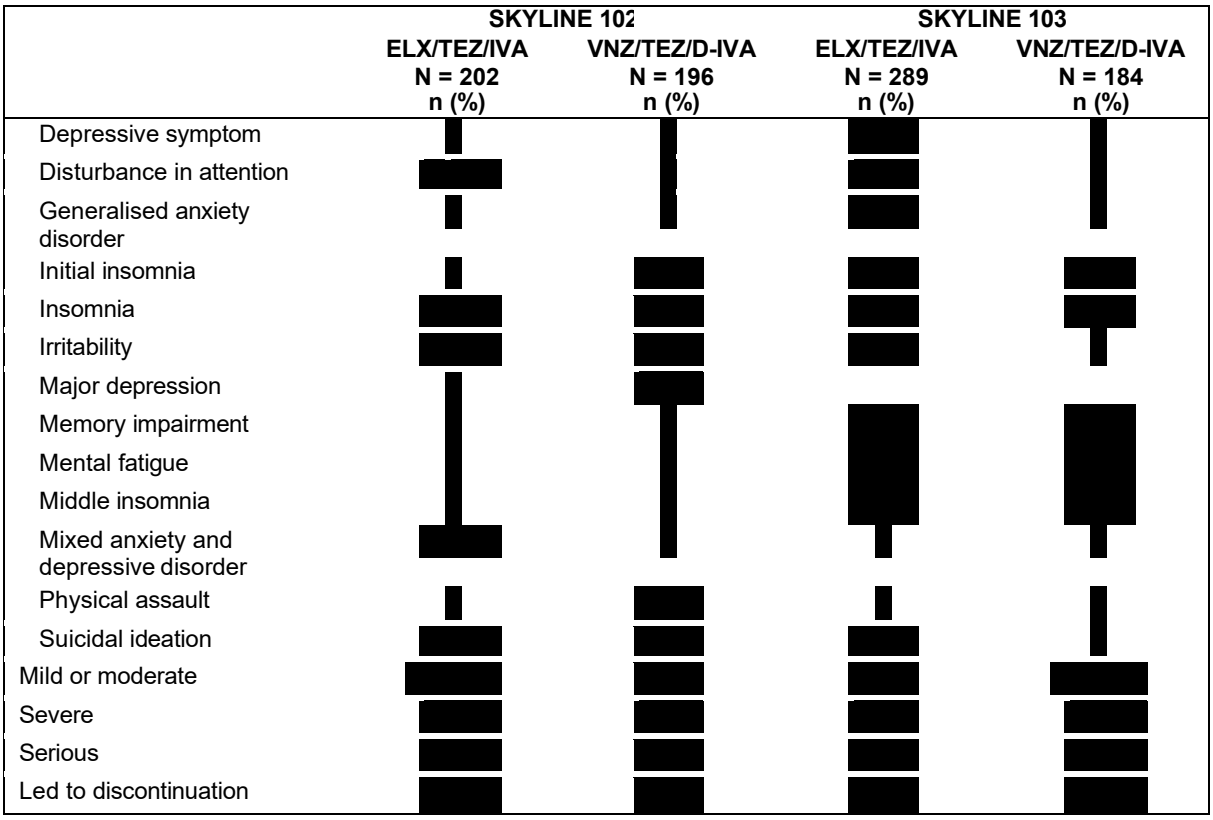
In SKYLINE 102, [redacted] ([redacted] %) participants in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had at least one neuropsychiatric event. Most events were mild or moderate. [redacted] in each group discontinued treatment because of a neuropsychiatric event.

In SKYLINE 103, [redacted] ([redacted] %) participants in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group had at least one neuropsychiatric event. Most events were mild or moderate. [redacted] participants ([redacted]%) in the VNZ/TEZ/D-IVA group and [redacted] ([redacted] %) in the ELX/TEZ/IVA group discontinued treatment because of a neuropsychiatric event.

Table 27 Summary of AESIs (SKYLINE studies; treatment period safety set)

	SKYLINE 102		SKYLINE 103	
	ELX/TEZ/IVA N = 202 n (%)	VNZ/TEZ/D-IVA N = 196 n (%)	ELX/TEZ/IVA N = 289 n (%)	VNZ/TEZ/D-IVA N = 184 n (%)
Elevated transaminases				
Any event	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Hypertransaminasaemia	[redacted]	[redacted]	[redacted]	[redacted]
Mild or moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]	[redacted]
Led to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Any event	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis allergic	[redacted]	[redacted]	[redacted]	[redacted]

	SKYLINE 102		SKYLINE 103	
	EL X/TEZ/IVA N = 202 n (%)	VNZ/TEZ/D-IVA N = 196 n (%)	ELX/TEZ/IVA N = 289 n (%)	VNZ/TEZ/D-IVA N = 184 n (%)
Drug eruption				
Drug hypersensitivity				
Lichen planus				
Perioral dermatitis				
Periorbital dermatitis				
Pityriasis rosea				
Rash				
Rash erythematous				
Rash follicular				
Rash maculo-papular				
Rash papular				
Rash pruritic				
Rash pustular				
Rash vesicular				
Urticaria				
Mild or moderate				
Severe				
Serious				
Led to discontinuation	0	1 (0.5)	0	0
Cataracts				
Any event	0	0		
Cataract	0	0		
Cataract congenital	0	0		
Cataract cortical	0	0		
Mild or moderate	0	0		
Severe	0	0		
Serious	0	0		
Led to discontinuation	0	0	0	0
Neuropsychiatric events				
Any event				
Adjustment disorder with anxiety				
Adjustment disorder with depressed mood				
Anger				
Anhedonia				
Anxiety				
Attention deficit hyperactivity disorder				
Behaviour disorder				
Brain fog				
Depressed mood				
Depression				
Depression suicidal				



Key: D-IVA: deutivacaftor; ELX; elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor
Source: SKYLINE 102 clinical study report (98); SKYLINE 103 clinical study report (100)

B.3.10.2 Safety and tolerability of VNZ/TEZ/D-IVA in patients aged 6 to 11 years (RIDGELINE 105)

Safety and tolerability were the primary objectives of RIDGELINE 105. Overall, the safety profile of VNZ/TEZ/D-IVA was similar in children aged 6 to 11 years to people aged ≥12 years. The incidence and nature of AEs was also similar to those seen in previous CFTRm studies of children aged 6 to 11 years.

B.3.10.2.1 Summary of AEs

During the treatment period of RIDGELINE 105, 75 participants (96.2%) had at least one AE. All AEs were mild or moderate in severity, the incidence of both SAEs and AEs leading to treatment discontinuation was low (Table 28).

Table 28 Summary of AEs during the treatment period (RIDGELINE 105; treatment period safety set)

	VNZ/TEZ/D-IVA N = 78 n (%)
Number of AEs (total)	[redacted]
Subjects with any AEs	75 (96.2)
Subjects with AEs by strongest relationship	
Not related	[redacted]
Unlikely related	[redacted]
Possibly related	[redacted]
Related	[redacted]
Subjects with AEs by maximum severity	
Mild	39 (50.0)
Moderate	36 (46.2)
Severe	0
Life-threatening	0
Death	0
Subjects with AEs leading to study drug discontinuation	1 (1.3)
Subjects with AEs leading to study drug interruption	1 (1.3)
Subjects with Grade 3 or higher AEs	0
Subjects with related AEs[a]	[redacted]
Subjects with SAEs	6 (7.7)
Subjects with related SAEs[a]	1 (1.3)
Subjects with AEs leading to death	0

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. [a]When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted
Key: AE: adverse event; D-IVA: deutivacaftor; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor
Source: RIDGELINE 105 interim clinical study report (101); Hoppe et al, 2024 (109); Keating et al, 2025 (99)

B.3.10.2.2 Most common AEs

Table 29 shows the most common AEs (those occurring in ≥10% of patients).

Overall, the most common AEs were generally consistent with common manifestations of CF or with common illnesses in people with CF aged 6 to 11 years.

Table 29 AEs occurring in ≥10% of patients (RIDGELINE 105; treatment period safety set)

PT	VNZ/TEZ/D-IVA N = 78 n (%)
Subjects with any AEs	75 (96.2)
Cough	36 (46.2)
Pyrexia	16 (20.5)
Headache	14 (17.9)
Infective PEx of CF	13 (16.7)
Oropharyngeal pain	13 (16.7)
Abdominal pain	9 (11.5)
Nasal congestion	9 (11.5)
Rhinorrhoea	9 (11.5)
Vomiting	8 (10.3)

Key: AE: adverse event; CF: cystic fibrosis; D-IVA: deutivacaftor; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Hoppe et al, 2024 (109); Hoppe et al, 2025 (102)

B.3.10.2.3 SAEs

Six participants (7.7%) reported seven SAEs: infective PEx of CF (n = 2), failure to thrive (n = 1), adenovirus infection (n = 1), constipation (n = 1), pulmonary function test decreased (n = 1), cough (n = 1). The SAE of constipation was considered possibly related to treatment.

B.3.10.2.4 Discontinuations owing to AEs

One participant (1.3%) had AEs of cough and fatigue that led to treatment discontinuation. These events were mild and considered [redacted] related to treatment.

B.3.10.2.5 AEs of special interest

The incidence of AESIs was low (Table 30); all AESIs were mild or moderate in intensity.

Elevated transaminases

Four participants (5.1%) had at least one elevated transaminase event; all four had increased alanine transaminase (ALT) and two also had increased aspartate transaminase (AST). None of these events led to treatment discontinuation.

Rash

Four participants (5.1%) had at least one rash event; none of these events led to treatment discontinuation.

Cataracts

[redacted] ([redacted]%) had a cortical cataract, which was not visually significant and did not lead to treatment discontinuation.

Neuropsychiatric events

Four participants (5.1%) had at least one neuropsychiatric event: two had initial insomnia, one had aggression and one had anxiety. None of the events led to treatment discontinuation.

Table 30 Summary of AESIs (RIDGELINE 105; treatment period safety set)

	VNZ/TEZ/D-IVA N = 78 n (%) of participants
Elevated transaminases	
Any event	4 (5.1)
ALT increased	4 (5.1)
AST increased	2 (2.6)
Mild or moderate	4 (5.1)
Severe	0
Serious	0
Led to discontinuation	0
Rash	
Any event	4 (5.1)
Rash	4 (5.1)
Mild or moderate	4 (5.1)
Severe	0
Serious	0
Led to discontinuation	0
Cataracts	
Any event	[redacted]
Cataract cortical	[redacted]
Mild or moderate	[redacted]
Severe	0
Serious	0
Led to discontinuation	0
Neuropsychiatric events	
Any event	4 (5.1)
Aggression	1 (1.3)
Anxiety	1 (1.3)

	VNZ/TEZ/D-IVA N = 78 n (%) of participants
Initial insomnia	2 (2.6)
Mild or moderate	4 (5.1)
Severe	0
Serious	0
Led to discontinuation	0

Key: D-IVA: deutivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor
Source: RIDGELINE 105 interim clinical study report (101); Hoppe et al 2014 (102)

B.3.11 Conclusions about comparable health benefits and safety

VNZ/TEZ/D-IVA was as effective as the standard of care, ELX/TEZ/IVA, on lung function and superior at restoring normal CFTR function

In both SKYLINE 102 and SKYLINE 103, the primary endpoint of absolute change from baseline in ppFEV$_1$ through Week 24 was met and showed that treatment with VNZ/TEZ/D-IVA was non-inferior to treatment with ELX/TEZ/IVA.

Head-to-head against ELX/TEZ/IVA in patients aged ≥12 years, VNZ/TEZ/D-IVA was superior in improving CFTR function, as measured by reduction in SwCl through 24 weeks. Nearly a third of patients on VNZ/TEZ/D-IVA achieved normal levels of CFTR function (SwCl <30 mmol/L) and over 80% reached levels below the CF diagnostic threshold (SwCl <60 mmol/L).

Patients treated with VNZ/TEZ/D-IVA had comparable rates of PEx, similar QoL (CFQ-R RD), and similar nutritional outcomes compared to patients on ELX/TEZ/IVA. In addition, the results at Week 52 were consistent with the results at Week 24.

VNZ/TEZ/D-IVA enabled over half of paediatric patients to achieve normal CFTR function with 95% of patients under the diagnostic threshold for CF

The primary endpoint in the RIDGELINE 105 study in 6 to 11 year-olds was safety. On the secondary endpoint of SwCl levels through Week 24, VNZ/TEZ/D-IVA resulted in reductions in SwCl with a mean absolute change through Week 24 of -8.6 mmol/L compared to a below diagnostic threshold baseline on ELX/TEZ/IVA. Ninety-five percent of children achieved SwCl <60 mmol/L and 53% achieved normal levels of CFTR function as measured by SwCl levels <30 mmol/L. Paediatric patients receiving VNZ/TEZ/D-IVA maintained ppFEV$_1$, showed improvements in CFQ-R RD and nutritional measures and maintained a low rate of PEx.

The safety and tolerability profile observed with VNZ/TEZ/D-IVA was comparable to ELX/TEZ/IVA in patients 12 years and older

Treatment with VNZ/TEZ/D-IVA was well tolerated in all three studies, and overall safety was similar between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups in SKYLINE 102 and 103. The safety profile of VNZ/TEZ/D-IVA in children aged 6 to 11 years was similar to that in people aged ≥12 years.

Greater restoration of CFTR function with VNZ/TEZ/D-IVA is projected to further improve long-term outcomes

VNZ/TEZ/D-IVA is the next generation of CFTRm, developed with the deep understanding of CF biology that brought IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA to people with CF. It has been tested against ELX/TEZ/IVA in a robust Phase 3 pivotal program that enrolled and dosed 1,049 participants with CF. The superior improvement in CFTR function (as measured by reduction in SwCl) with VNZ/TEZ/D-IVA vs ELX/TEZ/IVA has a potential positive impact on patients' outcomes in the long term. The once-daily dosing and flexibility in time of administration may also improve patient experience by reducing treatment burden. VNZ/TEZ/D-IVA therefore provides an additional treatment option for people aged 6 years and over with CF who have at least one *F508del* mutation in the *CFTR* gene, offering greater or at least similar health benefits than the comparator ELX/TEZ/IVA.

B.3.12 Ongoing studies

No studies will provide further evidence within 12 months of this submission. An open-label extension of SKYLINE 102 and 103 (Study VX20-121-104; NCT05444257) is due to complete in October 2026. Results from other cohorts in RIDGELINE 105 are expected in January 2026 (patients aged 2 to 5 years) and June 2026 (patients aged 1 to 2 years). An open-label extension of RIDGELINE 105 (Study VX22-121-106; NCT05844449) is due to complete in October 2030.

B.4 Cost-comparison analysis

As summarised in Section B.3.11, VNZ/TEZ/D-IVA has demonstrated positive results in its efficacy outcomes (non-inferiority in the primary endpoint in SKYLINE 102 and SKYLINE 103 [ppFEV$_1$], and superiority in its secondary endpoints [SwCI]) and similar safety profile to ELX/TEZ/IVA in the treatment of CF. As the efficacy outcomes for VNZ/TEZ/D-IVA are likely to provide similar or greater overall health benefits to patients than the comparator, a CCA is appropriate to determine whether VNZ/TEZ/D-IVA is likely to result in similar or reduced overall costs to the NHS, relative to ELX/TEZ/IVA.

A CCA is used to identify differences in costs that are directly associated with alternative treatment options. Therefore, it is anticipated that this comparison should only include costs that are expected to change as a result of the introduction of VNZ/TEZ/D-IVA, excluding any costs that remain constant compared to ELX/TEZ/IVA. This ensures that an accurate and focused assessment of the cost impact of VNZ/TEZ/D-IVA is conducted.

The CCA incorporates acquisition costs, posology, and administration costs. Additional costs associated with observed/expected differences between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, including treatment of adverse events, were also included. Further details of the costs included in the CCA can be found in Section B.4.2.

B.4.1 Changes in service provision and management

B.4.1.1 Place of administration

CFTRm treatment can only be initiated by physicians with experience in the treatment of CF working within NHS commissioned CF services. As these are oral treatments, no additional infrastructure is required and no additional costs are expected to arise in relation to administering VNZ/TEZ/D-IVA compared to current requirements for ELX/TEZ/IVA. Therefore, costs associated with treatment initiation were not included within the CCA.

B.4.1.2 Administration-related resource use

Patients receiving CFTRms require regular liver function tests (LFTs) and ophthalmologist visits as recommended in the SmPC. These requirements are not expected to differ between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, therefore were not included in the CCA.

Due to both treatments being self-administered orally, ongoing administration-related resource use is not expected to differ between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatments, with neither treatment expected to incur administration costs.

B.4.1.3 Posology

B.4.1.3.1 VNZ/TEZ/D-IVA

VNZ/TEZ/D-IVA is available as an oral tablet administered once-daily containing either VNZ 4mg/ TEZ 20mg/ D-IVA 50mg (for patients weighing <40 kg) or VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg (for patients weighing ≥40 kg).

Patients weighing <40 kg
Three tablets, each containing VNZ 4 mg/ TEZ 20mg/ D-IVA 50mg.

Patients weighing ≥40 kg
Two tablets, each containing VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg.

Once initiated, treatment with VNZ/TEZ/D-IVA is intended to be lifelong.

Dose can be taken at any time of the day, with fat-containing food, but should be taken at approximately the same time each day.

B.4.1.3.2 ELX/TEZ/IVA

<u>Patients aged 6 to <12 years weighing <30 kg</u>
Two tablets, each containing ELX 50 mg/TEZ 25 mg/IVA 37.5 mg in the morning and one tablet containing IVA 75 mg in the evening, to be taken with fat-containing food.

<u>Patients aged 6 to <12 years weighing ≥30 kg, and patients ≥ 12 years</u>
Two tablets, each containing ELX 100 mg/TEZ 50 mg/IVA 75 mg in the morning and one tablet containing IVA 150 mg in the evening, to be taken with fat-containing food.

Once initiated, treatment with ELX/TEZ/IVA is intended to be lifelong.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The objective of the CCA was to evaluate the costs associated with using VNZ/TEZ/D-IVA or ELX/TEZ/IVA to treat patients aged 6 years and over with CF who have at least one *F508del* mutation in the CFTR gene from a UK NHS perspective.

To perform this comparison, a CCA model was developed in Microsoft Excel®. The general features of the CCA are summarised in Table 31.

Table 31 Features of the cost-comparison model

Parameter	Approach
Population	Patients aged 6 years and over with cystic fibrosis who have at least one *F508del* mutation in the CFTR gene
Intervention	Oral administration Patients weighing <40 kg Three tablets, each containing VNZ 4 mg/ TEZ 20mg/ D-IVA 50mg. Patients weighing ≥40 kg Two tablets, each containing VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg
Comparator	Oral administration Patients aged 6 to <12 years weighing <30 kg Two tablets, each containing ELX 50 mg/TEZ 25 mg/IVA 37.5 mg in the morning and one tablet containing IVA 75 mg in the evening Patients aged 6 to <12 years weighing ≥30 kg, and ≥ 12 years Two tablets, each containing ELX 100 mg/TEZ 50 mg/IVA 75 mg in the morning and one tablet containing IVA 150 mg in the evening
Outcome	Total costs per patient Incremental costs per patient
Perspective	UK NHS healthcare perspective
Time horizon	5 years

Discounting	No discounting

Key: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

B.4.2.1.1 Time horizon

The base-case time horizon used in the CCA is five years. Five years was selected as an adequate time horizon to demonstrate differences in the costs associated with VNZ/TEZ/D-IVA and ELX/TEZ/IVA given that key aspects of resource use are either time-invariant (e.g., AE treatment requirements) or are likely to be the same across treatments (e.g., administration costs). Time horizons of 2 and 10 years were assessed during scenario analyses.

B.4.2.1.2 Discounting

In the NICE user guide for submitting single technology cost-comparison assessments, it is stated that discounting of costs is not normally required for CCA. Accordingly, and given the relatively short model time horizon, the discount rate was set to 0% in the base-case. A scenario exploring the impact of an annual 3.5% discount on costs was included.

B.4.2.2 Intervention and comparator acquisition costs

A summary of the acquisition costs for VNZ/TEZ/D-IVA and ELX/TEZ/IVA is provided in Table 32.

Table 32 Acquisition costs of the intervention and comparator technologies.

	VNZ/TEZ/D-IVA	**ELX/TEZ/IVA**
Pharmaceutical formulation	VNZ 4mg/ TEZ 20mg/ D-IVA 50mg film-coated tablet **OR** VNZ 10mg/ TEZ 50mg/ D-IVA 125mg film-coated tablet	ELX 50 mg/TEZ 25 mg/IVA 37.5 mg film-coated tablet **AND** IVA 75 mg film-coated tablet **OR** ELX 100 mg/TEZ 50 mg/IVA 75 mg film-coated tablet **AND** IVA 150 mg film-coated tablet

(Anticipated) care setting	Initiated by healthcare professionals with experience in the treatment of CF. Subsequent doses to be taken at home.	Initiated by healthcare professionals with experience in the treatment of CF. Subsequent doses to be taken at home.
Acquisition cost (excluding VAT)	<u>VNZ 4mg/ TEZ 20mg/ D-IVA 50mg</u> List price: £16,110.00 PAS price: [redacted] (price per 84 tablet [28-day] pack) <u>VNZ 10mg/ TEZ 50mg/ D-IVA 125mg</u> List price: £16,110.00 PAS price: [redacted] (price per 56 tablet [28-day] pack)	<u>ELX 50 mg/TEZ 25 mg/IVA 37.5 mg</u> List price: £8,346.30 PAS price: [redacted] (price per 56 tablet [28-day] pack) <u>ELX 100 mg/TEZ 50 mg/IVA 75 mg</u> List price: £8,346.30 PAS price: [redacted] (price per 56 tablet [28-day] pack) <u>IVA 75mg</u> List price: £7,000.00 PAS price: [redacted] (price per 28 tablet [28-day] pack) <u>IVA 150mg</u> List price: £7,000.00 PAS price: [redacted] (price per 28 tablet [28-day] pack)
Method of administration	Oral	Oral
Doses	Patients weighing <40 kg Three tablets (VNZ 4mg/ TEZ 20mg/ D-IVA 50mg) Patients weighing ≥40 kg Two tablets (VNZ 10mg/ TEZ 50mg/ D-IVA 125mg)	<u>Patients aged 6 to <12 years weighing <30 kg</u> Morning dose: Two ELX/TEZ/IVA (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) tablets Evening dose: One IVA (IVA 75 mg) tablet <u>Patients aged 6 to <12 years weighing ≥30 kg, and ≥ 12 years</u>

		Morning dose: Two ELX/TEZ/IVA (ELX 100 mg/TEZ 50 mg/IVA 75 mg) tablets Evening dose: One IVA (IVA 150 mg) tablet
Dosing frequency	Once daily	Twice daily
Average cost of a course of treatment (acquisition costs only)	[redacted] annually	[redacted] annually

Key: CF, cystic fibrosis; D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; VAT, value added tax; VNZ, vanzacaftor

B.4.2.3 Intervention and comparator healthcare resource use and associated costs

The model does not account for monitoring costs related to CFTRm administration or CF disease management, as these are assumed to be equivalent across both treatments in the model. Therefore, their inclusion is not anticipated to impact incremental costs between the treatments.

As VNZ/TEZ/D-IVA and ELX/TEZ/IVA are administered orally, and frequency of prescribing requirements is not expected to differ (i.e. each pack consists of 28 days of treatment), the cost of administration was assumed null for both technologies in line with the MTA for ELX/TEZ/IVA (TA988).

Where other potential healthcare resource use differences between the treatments in the clinical trials arose, the conservative assumption of comparability was used in the model base case. For example, VNZ/TEZ/D-IVA showed improvements in CFTR function (as indicated by lower SwCl levels; Section B.3.6), and numerically fewer PEx requiring IV antibiotics or hospitalisations, based on post-hoc analysis of pooled data from SKYLINE 102 and SKYLINE 103 through week 52 (Appendix J).

PEx requiring IV antibiotics or hospitalisation related costs were explored in the CCA scenario analysis in order to account for the high economic burden PEx treatment has on the healthcare service. Further detail of the PEx treatment costs used in the scenario analysis can be found in Appendix J.

A summary of the methods used to identify relevant cost and healthcare resource data can be found in Appendix G.

B.4.2.4 Adverse reaction unit costs and resource use

The model includes any treatment-related serious adverse events (TRSAEs) occurring in at least one subject in either treatment arm up to the trial end-point (week 52) for SKYLINE 102 and SKYLINE 103 (Table 33). These were subsequently weighted based on trial size to determine the weighted annual TRSAE rate for patients receiving VNZ/TEZ/D-IVA or ELX/TEZ/IVA.

TRSAE were selected as the most appropriate trial outcomes for use in the CCA due to them being identified as likely related to the treatments received, but also severe enough to have required hospital intervention, thereby incurring costs to the healthcare service. Additional scenario analysis was conducted to identify how changing the source of AEs (e.g. using any SAE [not necessarily treatment related] occurring in ≥ 2 patients in any trial arm [Appendix K]) impacts the model results.

Unit costs applied to the incidence rates for each TRSAE were identified through a three-step process:

1. TRSAEs identified from the clinical trials were classified using their associated code from the international classification of diseases, tenth revision (ICD-10), identified via a desktop search
2. ICD-10 codes were subsequently mapped to healthcare resource group 4+ (HRG4+) codes using the NHS Digital HRG4+ 2023/24 National Costs Grouper “Code to Group” workbook
3. HRG4+ codes were then used to obtain the associated weighted average non-elective inpatient (short-stay and long-stay) cost of hospitalisation using the NHS national cost collection 2023/24

Unit costs associated with the treatment of each TRSAE are summarised in Table 34.

Table 33 Treatment-related serious adverse event incidence from SKYLINE 102 and SKYLINE 103

TRSAE	VNZ/TEZ/D-IVA			ELX/TEZ/IVA		
	SKYLINE 102 (N=196)	SKYLINE 103 (N=284)	Weighted annual rate	SKYLINE 102 (N=202)	SKYLINE 103 (N=289)	Weighted annual rate
Abdominal pain						
ALT increased						
AST increased						
Blood bilirubin increased						
Cholestasis						
CPK increased						
DIOS						
Disturbance in attention						
Epilepsy						
Faecaloma						
GGT increased						
Hyperphosphatasaemia						
Hypersensitivity						
Meningitis aseptic						
MADD						
Pancreatitis						
Psychomotor hyperactivity						
Seizure						
Serotonin syndrome						
Small intestinal obstruction						
Suicidal ideation						

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, deutivacaftor; DIOS, distal intestinal obstruction syndrome; ELX, elexacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; MADD, mixed anxiety and depressive disorder; TEZ, tezacaftor; TRSAE, treatment-related serious adverse event; VNZ, vanzacaftor

Table 34 Serious adverse event unit costs

TRSAE	Unit cost	Source
Abdominal pain	£737.21	ICD-10: R10.4 - Other and unspecified abdominal pain HRG4: FD05 - Abdominal pain, with/without interventions
ALT increased	£681.62	ICD-10: R74.01 - Elevation of levels of liver transaminase HRG4: WH13 - Abnormal findings without diagnosis
AST increased	£681.62	ICD-10: R74.01 - Elevation of levels of liver transaminase HRG4: WH13 - Abnormal findings without diagnosis
Blood bilirubin increased	£2,434.76	ICD-10: E80.7 - Disorder of bilirubin metabolism, unspecified HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Cholestasis	£2,434.76	ICD-10: K71.0 - Toxic liver disease with cholestasis HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
CPK increased	£681.62	ICD-10: R74.8 - Abnormal levels of other serum enzymes HRG4: WH13 - Abnormal findings without diagnosis
DIOS	£6,353.31	ICD-10: E84.19 - Cystic fibrosis with other intestinal manifestations HRG4: DZ13 - Cystic Fibrosis with CC Score 0-1+
Disturbance in attention	£2,546.97	ICD-10: R41.8 - Other and unspecified symptoms and signs involving cognitive functions and awareness HRG4: WH09 - Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions. Weighted average of without/single/multiple interventions and with CC score 0-6+
Epilepsy	£2,138.55	ICD-10: G40.9 - Epilepsy, unspecified HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Faecaloma	£2,047.59	ICD-10: K56.4 - Other impaction of intestine HRG4: FD10 - Non-Malignant Gastrointestinal Tract Disorders. Weighted average of without/single/multiple interventions and with CC score 0-11+
GGT increased	£2,434.76	ICD-10: R94.5 - Abnormal results of liver function studies HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Hyperphosphatasaemia	£2,258.03	ICD-10: E83.3 - Disorders of phosphorus metabolism and phosphatases HRG4: KC04 - Inborn Errors of Metabolism with CC score 0-3+

Hypersensitivity	£2,138.55	ICD-10: R20.3 - Hyperesthesia HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Meningitis aseptic	£3,786.06	ICD-10: G03.0 - Nonpyogenic meningitis HRG4: AA22 - Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-14+
MADD	£1,504.17	ICD-10: F41.2 - Mixed anxiety and depressive disorder HRG4: WD05Z - Neurotic, Stress-Related or Somatoform Disorders, treated by a Non-Specialist Mental Health Service Provider
Pancreatitis	£2,434.76	ICD-10: K85.9 - Acute pancreatitis, unspecified HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Psychomotor hyperactivity	£2,546.97	ICD-10: R41.8 - Other and unspecified symptoms and signs involving cognitive functions and awareness HRG4: WH09 - Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions. Weighted average of without/single/multiple interventions and with CC score 0-6+
Seizure	£2,138.55	ICD-10: R56.8 - Other and unspecified convulsions HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Serotonin syndrome	£1,273.51	ICD-10: T50.9 - Poisoning: Other and unspecified drugs, medicaments and biological substances HRG4: WH04 - Poisoning Diagnosis. Weighted average of without/single/multiple interventions and with CC score 0-2+
Small intestinal obstruction	£2,047.59	ICD-10: K56.6 - Other and unspecified intestinal obstruction HRG4: FD10 - Non-Malignant Gastrointestinal Tract Disorders. Weighted average of without/single/multiple interventions and with CC score 0-11+
Suicidal ideation	£1,795.75	ICD-10: R45.851 - Suicidal ideations HRG4: WH12 - Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 0-2+

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CC, complication and comorbidity; CPK, creatine phosphokinase; DIOS, distal intestinal obstruction syndrome; GGT, gamma-glutamyl transferase; HRG, healthcare resource group; ICD-10, 10th revision of the International Classification of Diseases; MADD, mixed anxiety and depressive disorder; TRSAE, treatment-related serious adverse event

After combining TRSAE incidence and unit costs for both treatments, Table 35 summarises the estimated annual costs of treating TRSAEs associated with VNZ/TEZ/D-IVA and ELX/TEZ/IVA.

Table 35 Summary of annual cost of TRSAEs

	VNZ/TEZ/D-IVA	ELX/TEZ/IVA
Annual cost of TRSAEs	[redacted]	[redacted]

Key: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; TRSAE, treatment-related serious adverse event; VNZ, vanzacaftor

B.4.2.5 Miscellaneous unit costs and resource use

No additional costs are captured within the CCA.

B.4.2.6 Clinical expert validation

The model method was designed to align with NICE's preferred methods. All of the parameters and assumptions applied in the CCA were validated by clinicians. Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. Once the model was finalised it was validated by internal modellers. A programmer (different to the programmer who built the model) reviewed all formulae and labelling in the model to ensure accuracy.

B.4.2.7 Uncertainties in the inputs and assumptions

Due to the simplicity and short time-horizon of the CCA, and the sourcing of model inputs from the recent NICE technology appraisal TA988 and direct head-to-head randomized controlled trials of SKYLINE 102 and SKYLINE 103, there is a low level of uncertainty within the model.

Given the nature of a cost-comparison analysis, the assumption of equivalent treatment effect between VNZ/TEZ/D-IVA and ELX/TEZ/IVA was used based on head-to-head trial data from SKYLINE 102 and SKYLINE 103. This assumption is considered conservative given VNZ/TEZ/D-IVA showed a reduction in SwCl levels (Section B.3.6.1.2), i.e. further restoring CFTR function towards normal levels leading to benefits in QoL (Section B.3.6.1.5), and the potential to prevent the development and/or progression of CF manifestations. Additionally, post hoc analysis using pooled data from SKYLINE 102 and SKYLINE 103 showed

VNZ/TEZ/D-IVA provides a reduction in PEx events requiring hospitalization or IV antibiotics (Appendix J).

The inputs used in the CCA are summarised in Table 36 and key model assumptions are presented in Table 37.

Table 36 Summary of model inputs

Parameter	Parameter value	Source
General		
Time horizon	5 years	Assumption
Annual discount rate	0%	NICE cost-comparison guidelines
Acquisition costs		
PAS price: cost per pack (VNZ/TEZ/D-IVA)	[redacted]	-
PAS price: cost per pack (ELX/TEZ/IVA)	[redacted]	-
PAS price: cost per pack (IVA)	[redacted]	-
Treatment-related serious adverse events		
Weighted annual TRSAE rate (VNZ/TEZ/D-IVA)		
Abdominal pain	[redacted]	Annual TRSAE rate from SKYLINE 102 & 103, weighted based on number of patients in each trial
ALT increased	[redacted]	
AST increased	[redacted]	
Blood bilirubin increased	[redacted]	
Cholestasis	[redacted]	
CPK increased	[redacted]	
DIOS	[redacted]	
Disturbance in attention	[redacted]	
Epilepsy	[redacted]	
Faecaloma	[redacted]	
GGT increased	[redacted]	
Hyperphosphatasaemia	[redacted]	
Hypersensitivity	[redacted]	
Meningitis aseptic	[redacted]	
MADD	[redacted]	
Pancreatitis	[redacted]	

Psychomotor hyperactivity	[redacted]		
Seizure			
Serotonin syndrome			
Small intestinal obstruction			
Suicidal ideation			
Weighted annual TRSAE rate (ELX/TEZ/IVA)			
Abdominal pain	[redacted]		Annual TRSAE rate from SKYLINE 102 & 103, weighted based on number of patients in each trial
ALT increased			
AST increased			
Blood bilirubin increased			
Cholestasis			
CPK increased			
DIOS			
Disturbance in attention			
Epilepsy			
Faecaloma			
GGT increased			
Hyperphosphatasaemia			
Hypersensitivity			
Meningitis aseptic			
MADD			
Pancreatitis			
Psychomotor hyperactivity			
Seizure			
Serotonin syndrome			
Small intestinal obstruction			
Suicidal ideation			
Unit costs			
Abdominal pain	£737.21		ICD-10: R10.4 - Other and unspecified abdominal pain HRG4: FD05 - Abdominal pain, with/without interventions
ALT increased	£681.62		ICD-10: R74.01 - Elevation of levels of liver transaminase HRG4: WH13 - Abnormal findings without diagnosis

AST increased	£681.62	ICD-10: R74.01 - Elevation of levels of liver transaminase HRG4: WH13 - Abnormal findings without diagnosis
Blood bilirubin increased	£2,434.76	ICD-10: E80.7 - Disorder of bilirubin metabolism, unspecified HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Cholestasis	£2,434.76	ICD-10: K71.0 - Toxic liver disease with cholestasis HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
CPK increased	£681.62	ICD-10: R74.8 - Abnormal levels of other serum enzymes HRG4: WH13 - Abnormal findings without diagnosis
DIOS	£6,353.31	ICD-10: E84.19 - Cystic fibrosis with other intestinal manifestations HRG4: DZ13 - Cystic Fibrosis with CC Score 0-1+
Disturbance in attention	£2,546.97	ICD-10: R41.8 - Other and unspecified symptoms and signs involving cognitive functions and awareness HRG4: WH09 - Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions. Weighted average of without/single/multiple interventions and with CC score 0-6+
Epilepsy	£2,138.55	ICD-10: G40.9 - Epilepsy, unspecified HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Faecaloma	£2,047.59	ICD-10: K56.4 - Other impaction of intestine HRG4: FD10 - Non-Malignant Gastrointestinal Tract Disorders. Weighted average of without/single/multiple interventions and with CC score 0-11+
GGT increased	£2,434.76	ICD-10: R94.5 - Abnormal results of liver function studies HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Hyperphosphatasaemia	£2,258.03	ICD-10: E83.3 - Disorders of phosphorus metabolism and phosphatases HRG4: KC04 - Inborn Errors of Metabolism with CC score 0-3+
Hypersensitivity	£2,138.55	ICD-10: R20.3 - Hyperesthesia HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Meningitis aseptic	£3,786.06	ICD-10: G03.0 - Nonpyogenic meningitis HRG4: AA22 - Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-14+
MADD	£1,504.17	ICD-10: F41.2 - Mixed anxiety and depressive disorder HRG4: WD05Z - Neurotic, Stress-Related or Somatoform Disorders, treated by a Non-Specialist Mental Health Service Provider

Pancreatitis	£2,434.76	ICD-10: K85.9 - Acute pancreatitis, unspecified HRG4: GC17 - Non-Malignant, Hepatobiliary or Pancreatic Disorders. Weighted average of without/single/multiple interventions and with CC score 0-9+
Psychomotor hyperactivity	£2,546.97	ICD-10: R41.8 - Other and unspecified symptoms and signs involving cognitive functions and awareness HRG4: WH09 - Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions. Weighted average of without/single/multiple interventions and with CC score 0-6+
Seizure	£2,138.55	ICD-10: R56.8 - Other and unspecified convulsions HRG4: AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+
Serotonin syndrome	£1,273.51	ICD-10: T50.9 - Poisoning: Other and unspecified drugs, medicaments and biological substances HRG4: WH04 - Poisoning Diagnosis. Weighted average of without/single/multiple interventions and with CC score 0-2+
Small intestinal obstruction	£2,047.59	ICD-10: K56.6 - Other and unspecified intestinal obstruction HRG4: FD10 - Non-Malignant Gastrointestinal Tract Disorders. Weighted average of without/single/multiple interventions and with CC score 0-11+
Suicidal ideation	£1,795.75	ICD-10: R45.851 - Suicidal ideations HRG4: WH12 - Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 0-2+

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CC, complication and comorbidity; D-IVA, deutivacaftor; DIOS, distal intestinal obstruction syndrome; ELX, elexacaftor; GGT, gamma-glutamyl transferase; HRG, healthcare resource group; ICD-10, 10th revision of the International Classification of Diseases; IVA, ivacaftor; MADD, mixed anxiety and depressive disorder; TEZ, tezacaftor; TRSAE, treatment related serious adverse event; VNZ, vanzacaftor

Table 37 Key assumptions of the analysis

Assumption	Rationale for assumption
VNZ/TEZ/D-IVA and ELX/TEZ/IVA are assumed to have comparable treatment effect	Given the nature of a cost-comparison analysis, the assumption of equivalent treatment effect between VNZ/TEZ/D-IVA and ELX/TEZ/IVA was made based on head-to-head trial data from SKYLINE 102 and SKYLINE 103. This assumption is considered conservative given VNZ/TEZ/D-IVA showed a reduction in SwCl levels (Section B.3.6.1.2), i.e. further restoring CFTR function towards normal levels leading to benefits in QoL (Section B.3.6.1.5), a potential to prevent the development and/or progression of CF manifestations, and pooled trial results indicating VNZ/TEZ/D-IVA provides a reduction in PEx events (Appendix J).
Patients are assumed to remain on treatment indefinitely	The rates of discontinuation from AEs observed in SKYLINE 102 and SKYLINE 103 were low and appeared broadly similar across the two treatment arms (Table 25). Therefore, for simplicity, treatment discontinuation due to AEs was not incorporated into the model as it was not expected to have a meaningful impact on the incremental costs between VNZ/TEZ/D-IVA and ELX/TEZ/IVA.

Administration costs, including administration related resource use, are equivalent between VNZ/TEZ/D-IVA and ELX/TEZ/IVA	As CFTRm treatments require regular LFTs and ophthalmologist visits, as recommended in the SmPC, these costs are not expected to differ between VNZ/TEZ/D-IVA and ELX/TEZ/IVA. Both treatments are also self-administered orally, therefore are not expected to incur incrementally different associated costs.
Wastage is not accounted for in the analysis	Due to their oral route of administration, the cost of wastage is expected to be negligible. Therefore, for simplicity in the model, wastage was not included.
Only TRSAEs incur costs for healthcare payers	Only at this severity are patients expected to require hospitalization for their adverse events. For lower grade AEs the burden is assumed to be largely borne by the patient, through the use of over-the-counter treatments or a GP visit, which for simplicity was not captured within the CCA.

Key: AE, adverse event; CCA, cost-comparison analysis; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, CFTR modulator; D-IVA, deutivacaftor; ELX, elexacaftor; GP, general practitioner; IVA, ivacaftor; LFT, liver function test; PEx, pulmonary exacerbation; QoL, quality of life; SmPC, summary of product characteristics; SwCl, sweat chloride; TEZ, tezacaftor; TRSAE, treatment-related serious adverse event; VNZ, vanzacaftor

B.4.3 Base-case results

Table 38 and Table 39 present base case summary and disaggregated results for a 5-year time horizon with VNZ/TEZ/D-IVA and ELX/TEZ/IVA at PAS price.

Table 38 Base case - total costs

Cost component	VNZ/TEZ/D-IVA	ELX/TEZ/IVA	Incremental
Acquisition costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
HCRU costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: D-IVA, deutivacaftor; ELX, elexacaftor; HCRU, health care resource use; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Table 39 Base case - disaggregated incremental cost differences

Cost component	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCRU costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: HCRU, health care resource use

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Deterministic sensitivity analysis

Parameter uncertainty was tested using deterministic sensitivity analysis (DSA), in which key model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or ±20% where no estimates of precision were available.

The results of the DSA for the comparison of VNZ/TEZ/D-IVA against ELX/TEZ/IVA are presented in Figure 6 and Table 40. As anticipated, due to the model only including drug costs (excluded from DSA due to the expectation that drug prices and dosing will not be subject to uncertainty in clinical practice), administration costs (assumed £0 in both arms), and adverse event costs, the most influential parameters in the model were TRSAE related parameters (unit costs and incidence).

Figure 6. DSA tornado diagram

Key: AE, adverse event; D-IVA, deutivacaftor; DIOS, distal intestinal obstruction syndrome; DSA, deterministic sensitivity analysis; ELX, elexacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Table 40 DSA outcomes

Parameter	Lower output	Upper output	Delta
Number of AEs - SKYLINE 102 - DIOS - ELX/TEZ/IVA (0.65, 1.43)	[redacted]	[redacted]	[redacted]
AE unit cost - DIOS (£4,112, £9,075)	[redacted]	[redacted]	[redacted]
Number of AEs - SKYLINE 102 - Meningitis aseptic - ELX/TEZ/IVA (0.65, 1.43)	[redacted]	[redacted]	[redacted]
AE unit cost - Meningitis aseptic (£2,450, £5,408)	[redacted]	[redacted]	[redacted]
AE unit cost - Suicidal ideation (£1,162, £2,565)	[redacted]	[redacted]	[redacted]
Number of AEs - SKYLINE 103 - Disturbance in attention - ELX/TEZ/IVA (0.65, 1.43)	[redacted]	[redacted]	[redacted]
Number of AEs - SKYLINE 103 - Psychomotor hyperactivity - ELX/TEZ/IVA (0.65, 1.43)	[redacted]	[redacted]	[redacted]
AE unit cost - Disturbance in attention (£1,648, £3,638)	[redacted]	[redacted]	[redacted]
AE unit cost - Psychomotor hyperactivity (£1,648, £3,638)	[redacted]	[redacted]	[redacted]
Number of AEs - SKYLINE 102 - Cholestasis - VNZ/TEZ/D-IVA (0.65, 1.43)	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; D-IVA, deutivacaftor; DIOS, distal intestinal obstruction syndrome; DSA, deterministic sensitivity analysis; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

B.4.4.2 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied.

Six scenarios were explored within the model, including:

1. Extend the time horizon from 5 years to 10 years
2. Shorten the time horizon from 5 years to 2 years
3. 3.5% annual discount rate on costs over the full time-horizon
4. Remove adverse event costs from the model

5. Include PEx requiring hospitalization or IV antibiotics costs based on SKYLINE 102 and SKYLINE 103 pooled analysis
6. Use of any SAE occurring in ≥ 2 patients to define AEs

The results of scenario analyses are presented in Table 41.

Table 41 Scenario analyses

Scenario	Total incremental costs	Absolute change from base case
Base case	[redacted]	[redacted]
10-year time horizon	[redacted]	[redacted]
2-year time horizon	[redacted]	[redacted]
3.5% discounting of costs	[redacted]	[redacted]
AEs excluded	[redacted]	[redacted]
PEx included	[redacted]	[redacted]
Any SAE occurring in ≥ 2 patients	[redacted]	[redacted]

Key: AE, adverse event; PEx, pulmonary exacerbation; SAE, serious adverse event

B.4.5 Subgroup analysis

No sub-group analyses were explored as part of the CCA as there are no additional cost differences anticipated between patient subgroups.

B.4.6 Interpretation and conclusions of economic evidence

The aim of this analysis was to compare total costs associated with VNZ/TEZ/D-IVA and ELX/TEZ/IVA in the treatment of patients aged 6 years and older with CF who have at least one *F508del* mutation in the CFTR gene.

In the base case, VNZ/TEZ/D-IVA is shown to result in a cost saving of [redacted] per patient over the next five years, when using PAS prices. Due to the conservative nature of the CCA, the model base case does not capture additional benefits of VNZ/TEZ/D-IVA, including it being a more convenient treatment option for CF patients due to its once-daily dosing and flexibility in timing of administration, pooled trial results indicating a reduction in PEx events (Appendix J), reduction in SwCl levels (Section B.3.6.1.2), i.e. further restoring CFTR function towards normal levels leading to benefits in QoL (Section B.3.6.1.5), and potential to prevent the development and/or progression of CF manifestations.

The approach taken in this analysis expands upon the recent (July 2024) positive recommendation from NICE for the use of ELX/TEZ/IVA in CF patients aged 2 years and older who have at least 1 *F508del* mutation in the CFTR gene (TA988), which demonstrated ELX/TEZ/IVA is a more cost-effective use of constrained NHS resources compared to established clinical management. Therefore, the results of the CCA, combined with the comparative efficacy analysis, help illustrate that VNZ/TEZ/D-IVA is also expected to be a cost-effective use of constrained NHS resources, and result in similar or reduced overall costs to the NHS whilst providing similar or greater overall health benefits compared to ELX/TEZ/IVA.

B.5 References

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B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse events

Appendix G: Cost and healthcare resource use identification, measurement and validation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

Appendix J: Pulmonary exacerbation costs

Appendix K: Serious adverse event incidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more *F508del* mutation in the *CFTR* gene in people aged 6 years and over [ID6372]

Summary of Information for Patients (SIP)

January 2025

File name	Version	Contains confidential information	Date
ID6732 VNZ CF NICE SIP_Final [noCON]	1.0	No	31 January 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

The company has submitted a cost-comparison analysis for the technology (vanzacaftor/tezacaftor/deutivacaftor; VNZ/TEZ/D-IVA) vs elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor (ELX/TEZ/IVA). The company believes the cost-comparison approach is appropriate for the following reasons:

- ELX/TEZ/IVA, is NICE approved following the publication of TA988 in 2024 (1) and is currently by far the most commonly used cystic fibrosis transmembrane conductance regulator modulator (CFTRm) treatment in England (2)
- There is evidence from head-to-head clinical trials that VNZ/TEZ/D-IVA maintains the lung function improvement achieved with ELX/TEZ/IVA and is better than ELX/TEZ/IVA in improving the function of the defective CFTR protein (see Section 3e)
- VNZ/TEZ/D-IVA is likely to provide greater or at least similar overall health benefits to patients than ELX/TEZ/IVA at similar or reduced overall costs to the NHS

There is an opportunity to build on the successful MTA for the existing CF medicines (TA988) 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

1a) Name of the medicine (generic and brand name):

Generic name: Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA)

Brand name: ALYFTREK™

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

People with cystic fibrosis (CF) aged 6 years and older with at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

VNZ/TEZ/D-IVA is currently pending approval by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The anticipated dates for approval are confidential and are given in Section B.1.2 of the manufacturer's submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

No collaborations / engagement / activities have taken place in relation to the medicine. Nor has any financial support been provided to UK patient groups.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Clinical presentation

CF is a rare, life-shortening genetic disease. People with CF have mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that result in production of defective CFTR protein. When this protein doesn't work properly, it can't help move chloride ions (a component of salt) and water to the surface of cells. This causes mucus in a number of organs to become thick and sticky. In the lungs, a build-up of thick, sticky mucus leads to long-term lung infections and lung damage that gets worse over time and can eventually lead to death (3). In the pancreas, the thick, sticky mucus stops the enzymes needed for digestion from reaching food in the gut (3). This means that people with CF don't absorb nutrients properly and need a high-calorie diet and vitamin supplements to achieve normal growth and development.

People with CF may also develop diabetes, liver problems, constipation, weakened bones and reduced fertility.

In 2023, there were 9,364 people with CF in England (4).

Impact of CF

The symptoms of CF have a significant impact on quality of life and mental health for both people with CF and their families/caregivers (5-8). Anxiety and depression are common among people with CF, and parents of children with CF are two to three times more likely to experience anxiety and depression than the general population (9, 10).

People with CF can experience periods when their lung symptoms get worse, known as pulmonary exacerbations (PEx). PEx often require a stay in hospital and treatment with an infusion of antibiotics, which can be challenging for patients and their carers.

Day-to-day care (such as physiotherapy to clear the airways) and nutritional support also place a substantial burden on people with CF and their carers. Caregivers of children with CF provide, on average, nearly 75 hours of informal care per week (5).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In the UK, all newborn babies are screened for CF via the newborn blood spot test (11). If this test suggests the child may have CF, they will also have a genetic test to look for CF-causing mutations and a sweat chloride (SwCl) test, which measures the level of salt in sweat (and is a measure of how well the CFTR protein is working). A diagnosis of CF is made if SwCl levels are 60 mmol/L or above, while levels between 30-59 mmol/L indicate that CF is possible and further testing may be needed. SwCl levels below 30 mmol/L are considered normal and that CF is unlikely.

No additional diagnostic tests are needed with VNZ/TEZ/D-IVA.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There is currently no cure for CF. Existing treatment consists of long-term, uninterrupted use of medicines called CFTR modulators (CFTRms), which target the faulty CFTR protein and restore its function (see Section 3a). Alongside CFTRms, people with CF receive supportive care to treat the symptoms. Supportive care may include:

- medicines to make mucus less thick and sticky (mucolytics or inhaled hypertonic saline)
- antibiotics (to combat infection)
- nutritional supplements (to aid growth and development)
- tube feeding (to aid growth and development when oral supplements are not enough)
- pancreatic enzyme replacement (to aid digestion)
- antifungals (to combat infection)
- anti-inflammatories (to reduce inflammation in the lungs)
- physiotherapy (to clear mucus from the airways, improve bone health and muscle strength, help with leaking from the bladder and help with inhaled therapies)

In 2024, NICE approved several CFTRms (elexacaftor/tezacaftor/ivacaftor [ELX/TEZ/IVA], tezacaftor/ivacaftor [TEZ/IVA] and lumacaftor/ivacaftor [LUM/IVA]) for treatment of CF (1). Another CFTRm, IVA, is also available via commissioning (an access agreement between NHS England and the manufacturer). The CFTRms are positioned alongside each other on the treatment pathway and the choice of modulator depends on the patient's age and CFTR mutation.

ELX/TEZ/IVA is the most effective among the currently available CFTRms and is recommended by ECFS to be the preferred treatment option for eligible patients (6). For patients aged 6 years and over with at least one *F508del* mutation, ELX/TEZ/IVA is the most commonly used CFTRm (4), and it is proposed that VNZ/TEZ/D-IVA will be positioned as an alternative to ELX/TEZ/IVA in this patient group.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Jamieson and colleagues reviewed 43 articles that described the experience and perspectives of children and adolescents (≤21 years of age) with CF (12). Across the articles, participants said that:

- their treatment is unrelenting and serves as a constant reminder of their illness. They described treatment as intensive, invasive and physically strenuous;
- they need to take their condition into account when setting career and relationship goals. Some said they feel the need to take risks because they had nothing to lose with their limited time;
- they felt like a burden to family and friends. Many had increased self-consciousness owing to their small stature and having to take medications in public;
- being listed for transplant is a confirmation of disease severity, and that the wait for a transplant was marked by uncertainty and anxiety;
- they had needed to mature faster than their peers without CF, and some said they had to accept differences in physical appearance and capabilities in order to make the most of their life;
- they felt socially isolated with limited independence owing to poor health and time-consuming treatments.

A survey of 294 adults with CF carried out in the US revealed the average time spent on CF treatments was 108 minutes per day (13). Respondents reported taking an average of three inhaled and three oral therapies. Using two or more inhaled therapies and performing airway clearance techniques for 30 minutes or more per day was associated with increased treatment burden.

An international survey of 431 people with CF who were not receiving a CFTRm revealed a high burden of disease in this patient group (14). Two-thirds said that CF affected their mental health. Most (86.1%) said that CF has a moderate or significant impact on their life or the life of a family member. The most burdensome aspects of CF were treatment burden/time required for daily therapies, avoiding germs, feeling isolated or a burden on others, and disruption to daily life caused by hospital admissions.

As treatments improve and people with CF are living longer into adulthood, they may face a new set of challenges associated with getting older. These include balancing work and relationships with managing their CF and developing other health conditions that come with age (15).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

VNZ/TEZ/D-IVA is a new, once-daily, highly effective CFTRm. It contains three active substances: vanzacaftor (VNZ), tezacaftor (TEZ) and deutivacaftor (D-IVA), which act together to correct the defective CFTR protein, thereby addressing the root cause of CF.

VNZ and TEZ are known as correctors and help fix flaws in the CFTR protein so that it can form the right shape and move to the cell surface. D-IVA is known as a potentiator and binds to the CFTR protein at the cell surface, helping it to stay open longer so that chloride ions can flow through. The combination of these three drugs helps restore CFTR protein function better than other existing modulator treatments.

Research has shown that the earlier and greater the improvement in CFTR protein function, the better the outcomes such as lung function, body mass index and survival for patients. By restoring CFTR protein function towards normal levels, VNZ/TEZ/D-IVA has the potential to prevent development and/or worsening of CF symptoms, leading to better long-term outcomes in people with CF.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

VNZ/TEZ/D-IVA will be used alongside various symptom-based treatments for CF, as described in Section 2c.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

VNZ/TEZ/D-IVA is available as an oral tablet and is taken once a day with fat-containing food. It can be taken at any time of the day, but should be taken at approximately the same time each day.

The dose depends on the weight of the patient.

As a once-daily treatment, VNZ/TEZ/D-IVA offers a more convenient dosing schedule than ELX/TEZ/IVA which requires twice-daily dosing (one ELX/TEZ/IVA tablet in the morning plus one IVA tablet in the evening), each with a fat-containing meal.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The table below summarises the clinical trials that are relevant to the NICE appraisal of VNZ/TEZ/D-IVA: SKYLINE 102, SKYLINE 103 and RIDGELINE 105.

Clinical trial name and number	**SKYLINE 102** (VX20-121-102; NCT05033080) (16) **SKYLINE 103** (VX20-121-102; NCT05076149) (17)	**RIDGELINE 105** (VX21-121-105; NCT05422222) (18)
Location	North America, Europe (including UK), Israel, Australia, New Zealand	North America, Europe (including UK), Australia
Population	SKYLINE 102: People aged ≥12 years of age with CF who have one *F508del* mutation and one minimal function mutation SKYLINE 103: People aged ≥12 years with CF who have either: • two *F508del* mutations • one *F508del* mutation and one gating or residual function mutation, • at least one other CFTR mutation that is responsive to triple combination therapy and no *F508del* mutation	People aged 6 to 11 years of age (inclusive) with CF who have at least one mutation that is responsive to triple combination therapy Note this represents one cohort (Cohort B1) in this study, which is still ongoing on other age groups
Length of treatment with VNZ/TEZ/D-IVA	52 weeks	24 weeks
Number of patients	SKYLINE 102: 405 SKYLINE 103: 574	78
Comparators	ELX/TEZ/IVA The studies were double-blind, which means that neither the patients nor the people running the study knew which treatment each patient was allocated to. Allocation to treatment was done randomly.	None This was a single-arm study, meaning that VNZ/TEZ/D-IVA was the only treatment given
Key inclusion criteria	• CFTR mutations as listed under 'Population' • FEV_1 value* ≥40% and ≤90% of predicted mean for age, sex and height for participants currently receiving a CFTR modulator or	• Stable disease and at least one CFTR mutation that is responsive to triple combination therapy

	≥40% and ≤80% for those not currently receiving a CFTR modulator	
Key exclusion criteria	• Lung infection likely to lead to a rapid decline in lung function • History of organ or bone marrow transplant • Liver cirrhosis with high blood pressure in the portal vein (the vein running through the liver) • Moderate or severe impairment of liver function • Respiratory tract infection, pulmonary exacerbation (flare-up of respiratory symptoms) or changes in medication for sinopulmonary disease (disease affecting both the sinuses and the lungs) in the last month • A short-term illness not related to CF in the last 2 weeks • Intolerance to study drug	• Lung infection likely to lead to a rapid decline in lung function • History of organ or bone marrow transplant • Liver cirrhosis with high blood pressure in the portal vein • Moderate or severe impairment of liver function • Intolerance to study drug
Trial completion date	November 2023	November 2023 (Cohort B1)†

*A definition of FEV_1 is provided in the glossary. †Results from other cohorts in RIDGELINE 105 are expected in January 2026 (patients aged 2 to 5 years) and June 2026 (patients aged 1 to 2 years)

There are also two ongoing long-term studies:

- VX20-121-104 (NCT05444257): a study to evaluate the long-term efficacy and safety of VNZ/TEZ/D-IVA. Patients who completed SKYLINE 102 and SKYLINE 103 were eligible to enrol. All patients will receive VNZ/TEZ/D-IVA for up to 144 weeks. The study is due to complete in October 2026 (19).
- VX22-121-106 (NCT05844449): a study to evaluate the long term safety and efficacy of VNZ/TEZ/D-IVA in people with CF aged 1 year and older. Patients who complete RIDGELINE 105 are eligible to enrol. All patients will receive VNZ/TEZ/D-IVA for up to 100 weeks. The study is due to complete in October 2030 (20).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

VNZ/TEZ/D-IVA vs ELX/TEZ/IVA (patients aged ≥12 years)

Patients with CF in this trial received ELX/TEZ/IVA for 4 weeks before being randomly allocated to either VNZ/TEZ/D-IVA or ELX/TEZ/IVA.

The key outcome of the SKYLINE 102 and SKYLINE 103 trials was the change in patients' lung function. This was assessed using a test called percentage predicted forced expiratory volume in 1 second ($ppFEV_1$). An explanation of the $ppFEV_1$ test is given in the glossary. Improvements in lung function achieved during the 4-week ELX/TEZ/IVA run-in were maintained with both treatments for up to 52 weeks of treatment (21).

Another important outcome in the SKYLINE 102 and 103 trials was the change in SwCl levels. Over 24 weeks of treatment, VNZ/TEZ/D-IVA was better than ELX/TEZ/IVA in reducing SwCl levels in both trials. A reduction in SwCl levels indicates an improvement in function of the CFTR protein. These results were statistically significant (which means they were very unlikely to have happened by chance and much more likely to have happened due to receiving treatment with VNZ/TEZ/D-IVA). Reductions in SwCl levels were maintained up to 52 weeks of treatment (21).

After 24 weeks of treatment, 86% of people with CF across both trials who received VNZ/TEZ/D-IVA had SwCl levels below the diagnostic threshold for CF (i.e. below 60 mmol/L) compared with 77% who received ELX/TEZ/IVA; this difference was statistically significant. In addition, 31% of people with CF across both trials who received VNZ/TEZ/D-IVA achieved normal CFTR function (i.e. had SwCl levels below 30 mmol/L) compared with 23% who received ELX/TEZ/IVA; again, this difference was statistically significant (21).

VNZ/TEZ/D-IVA in children aged 6 to 11 years

The key outcome in the RIDGELINE 105 trial was safety (see Section 3g).

Children with CF in this trial received ELX/TEZ/IVA for at least 4 weeks before switching to VNZ/TEZ/D-IVA. After 24 weeks of treatment with VNZ/TEZ/D-IVA, it was found that they maintained normal lung function (measured using $ppFEV_1$) as achieved during the initial ELX/TEZ/IVA treatment period. In addition, VNZ/TEZ/D-IVA improved CFTR function (as measured by SwCl levels) to a greater extent than ELX/TEZ/IVA. 95% of children in the study achieved SwCl levels below the diagnostic threshold for CF (i.e. below 60 mmol/L) and 53% achieved normal CTFR function (SwCl levels below 30 mmol/L) (22, 23).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In all three trials, quality of life was measured using the Cystic Fibrosis Questionnaire-Revised, which is the most commonly-used disease-specific quality of life instrument in CF. Specifically, the studies used the respiratory domain of the questionnaire, which measures patient-reported improvements in respiratory symptoms such as waking up from coughing, wheezing, coughing, congestion, difficulty breathing, and mucus production (24, 25).

In SKYLINE 102 and 103, patients in both treatment groups reported similar improvements in respiratory symptoms (21). In RIDGELINE 105, children aged 6 to 11 years with CF also reported improvements in respiratory symptoms (23).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had

treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In SKYLINE 102 and SKYLINE 103, the side effects seen with VNZ/TEZ/D-IVA were similar to those seen with ELX/TEZ/IVA (21). The following side effects were seen in 10% or more of patients who received VNZ/TEZ/D-IVA across the two studies: infective PEx of CF, cough, COVID-19, nasopharyngitis (inflammation of the nasal passages and throat), headache, infection in the upper airways, pain in the oropharynx (the middle part of the throat behind the mouth), diarrhoea, influenza, pyrexia (fever), fatigue, nasal congestion (21). Most side effects were mild or moderate and there were low numbers of serious side effects or side effects that meant the patient had to stop treatment. Overall, the safety profiles of VNZ/TEZ/D-IVA and ELX/TEZ/IVA were similar.

Safety results from RIDGELINE 105 showed that the overall safety of VNZ/TEZ/D-IVA was similar in 6- to 11-year-olds to that seen in people aged 12 years and older. The type of side effects seen were similar to those seen in trials of other CFTRms in children aged 6 to 11 years (23).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

VNZ/TEZ/D-IVA restores CFTR function to normal levels in more people than ELX/TEZ/IVA
Despite the clear benefits of currently-available CFTRms, most people with CF do not achieve normal CFTR function, even with ELX/TEZ/IVA. As described in Section 3e, more people treated with VNZ/TEZ/D-IVA in the SKYLINE trials achieved normal CFTR function (i.e. SwCl levels below 30 mmol/L) compared with ELX/TEZ/IVA. In addition, 53% of children with CF in RIDGELINE 105 achieved normal CFTR function. Further restoration of CFTR function towards normal levels has the potential to allow people to live a longer and healthier life being less affected by the disease, particularly if treatment is started early in life before significant organ damage has occurred.

VNZ/TEZ/D-IVA has a simple dosing schedule
VNZ/TEZ/D-IVA is taken once a day, compared with ELX/TEZ/IVA, which is taken twice a day (one ELX/TEZ/IVA tablet in the morning and one IVA tablet in the evening). It can be taken at any time of day (as long as it is taken around the same time each day). Once-daily dosing with VNZ/TEZ/D-IVA means only one fat-containing meal per day is needed, which is more convenient and flexible for patients and caregivers. People with CF rely on supportive care alongside CFTRms, which adds to the burden of treatment. Research has shown that people with CF often prioritise treatments that fit better into their daily routine.

VNZ/TEZ/D-IVA offers an alternative treatment option when ELX/TEZ/IVA is not suitable
Some people have to stop treatment with ELZ/TEZ/IVA, either because of side effects or because they feel it is not working for them. VNZ/TEZ/D-IVA offers these patients an alternative highly effective modulator treatment.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Given the similarity in the way the two medicines work, their similar effect in improving lung function, the greater effect of VNZ/TEZ/D-IVA in restoring CFTR function, and their similar safety profiles, there is no reason to expect that VNZ/TEZ/D-IVA will have any specific disadvantages compared with ELX/TEZ/IVA.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction

A cost-comparison model was developed to compare the costs associated with using VNZ/TEZ/D-IVA with the costs associated with using ELX/TEZ/IVA.

ELX/TEZ/IVA was considered the relevant comparator as it is recommended for use in the same population for which VNZ/TEZ/D-IVA is being positioned, and it is by far the most commonly used CFTRm.

As described in Sections 3e and 3g, VNZ/TEZ/D-IVA and ELX/TEZ/IVA have a similar effect on improving lung function and a similar safety profile, with VNZ/TEZ/D-IVA also having a greater effect on improving CFTR function and offering a more convenient once-daily dosing option. Therefore, it is likely that VNZ/TEZ/IVA will provide greater or at least similar overall health benefits to ELX/TEZ/IVA. This means that an analysis that only compares the costs associated with each treatment is an appropriate way to determine whether VNZ/TEZ/D-IVA is likely to result in similar or reduced overall costs to the NHS, relative to ELX/TEZ/IVA.

Costs included in the model

The cost-comparison model included the following costs:

- Cost of the medicine (drug acquisition)
- Cost of giving the treatment to people (drug administration)
- Costs of treating pulmonary exacerbations and side-effects (healthcare resource use)

Cost-comparison results
The analysis showed that VNZ/TEZ/D-IVA is expected to result in similar or reduced overall costs to the NHS compared with ELX/TEZ/IVA.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

VNZ/TEZ/D-IVA is the next generation of CFTRm, developed with the deep understanding of CF that brought IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA to people with CF.

In clinical trials, VNZ/TEZ/D-IVA was at least as effective as the standard of care, ELX/TEZ/IVA, at improving lung function and better at restoring normal CFTR function (see Section 3e). Greater restoration of CFTR function with VNZ/TEZ/D-IVA is projected to further improve long-term outcomes and deliver quality-adjusted life year (QALY) gains (one QALY is equal to one year in perfect health). Note that given the cost-comparison approach taken for this appraisal, QALYs were not considered in the economic model.

Once-daily dosing with VNZ/TEZ/D-IVA means only one fat-containing meal per day is needed, which is more convenient and flexible for patients and caregivers, and has the potential to reduce treatment burden.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are no potential equality issues that need to be taken into account. People who have non-*F508del* mutations that are responsive to VNZ/TEZ/D-IVA and are not covered by this appraisal will be able to access the medicine through NHS commissioning.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Information on CF:

- Cystic Fibrosis Trust: https://www.cysticfibrosis.org.uk/

- NHS: https://www.nhs.uk/conditions/cystic-fibrosis/
- Patient.info: https://patient.info/chest-lungs/cystic-fibrosis-leaflet

VNZ/TEZ/D-IVA clinical trial results:

- SKYLINE 102 and SKYLINE 103 : Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials - The Lancet Respiratory Medicine
- RIDGELINE 105 : Vanzacaftor–tezacaftor–deutivacaftor for children aged 6–11 years with cystic fibrosis (RIDGELINE Trial VX21-121-105): an analysis from a single-arm, phase 3 trial - The Lancet Respiratory Medicine
- Vertex press release : https://news.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-pivotal-trials

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Term	Definition
CFTR protein	A type of protein that is found in the membrane of cells in several organs of the body. It is a channel that allows salt to move from the inside of cells to the outside. Once outside the cell, the salt attracts water. In CF, the CFTR protein is absent or does not work properly. This means that less salt is transported across the cell membrane and less water is attracted, resulting in thick, sticky mucus
Double-blind	Neither the study participants nor the study staff know which treatment is given to which person

Inhaled hypertonic saline	Hypertonic saline is a strong solution of salt water. It is turned into a fine mist by a device called a nebuliser and breathed in by the patient. Hypertonic saline "pulls" water from the walls of the airways into the mucus, making it less sticky and easier to cough up (26)
Mucolytic	A medicine that breaks up mucus and makes it easier to cough up. Like hypertonic saline, they are often given via a nebuliser
Nasopharyngitis	Inflammation of the nasal passages and throat
Newborn blood spot test	Previously known as the heel prick test. Usually done when a baby is around 5 days old. A small amount of blood is taken from the baby's heel and is tested for nine rare but serious conditions, including CF
Oropharynx	The middle part of the throat, behind the mouth. The oropharynx includes the soft palate, the side and back walls of the throat, the tonsils and the back third of the tongue
Pancreatic enzyme replacement	Most people with CF do not produce enough enzymes in the pancreas for proper digestion of food. Every time they eat food that contains fat, protein or carbohydrate, they must take a capsule containing enzymes to ensure the food is digested properly.
Portal vein	The vein that runs through the liver
$ppFEV_1$	A measure of how well a person's lungs work. The person blows out the air in their lungs hard and fast for as long as possible. The amount of air that comes out in the first second is measured – this is the forced expiratory volume in 1 second (FEV_1). The FEV_1 is then compared to expected values for the person's height, gender and age to give the percentage predicted forced expiratory volume in 1 second ($ppFEV_1$). This should be close to 100% if the lungs are working properly (27)
Pulmonary exacerbation (PEx)	A short-term increase in respiratory symptoms, such as cough, sputum production and shortness of breath, that is accompanied by a decrease in lung function. PEx generally require a stay in hospital and treatment with antibiotics
Pyrexia	Fever
Single-arm	All participants in the study get the same treatment
Sinopulmonary	Affecting the sinuses and the lungs
Sputum	A thick mucus produced in the lungs. If not cleared regularly, it can cause irritation and increase the risk of infection
Supportive care	Treatments aimed at treating the symptoms of CF, rather then the cause. Examples include physiotherapy, antibiotics and anti-inflammatories
Triple combination therapy	A medicine made up of three active substances. VNZ/TEZ/D-IVA and ELX/TEZ/IVA are triple combination therapies in CF

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. National Institute for Health and Care Excellence. *Ivacaftor-tezacaftor-elexacaftor, tezacaftor-ivacaftor and lumacaftor-ivacaftor for treating cystic fibrosis (TA988). Final guidance.* 2024.
2. Vertex. *Commercial data*. 2024.
3. NHS. Overview. Cystic fibrosis, https://www.nhs.uk/conditions/cystic-fibrosis (2021, accessed 23 September 2024).
4. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry 2023 annual data report*. 2024.
5. Angelis A, Kanavos P, Lopez-Bastida J, et al. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. *BMC health services research* 2015; 15: 428. 2015/09/30. DOI: 10.1186/s12913-015-1061-3.
6. Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018; 17: 153-178. 2018/03/07. DOI: 10.1016/j.jcf.2018.02.006.
7. Chevreul K, Berg Brigham K, Michel M, et al. Costs and health-related quality of life of patients with cystic fibrosis and their carers in France. *J Cyst Fibros* 2015; 14: 384-391. 2015/01/27. DOI: 10.1016/j.jcf.2014.11.006.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

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

Clarification questions - company response

April 2025

File name	Version	Contains confidential information	Date
ID6372 vanzacaftor Clarification Response [CON]	1	Yes	16/04/2025

Section A: Clarification on effectiveness data (Heading 1)

Clinical effectiveness evidence

A 1. Priority question. The company did not perform the subgroup analyses specified in the NICE scope i.e. by number of copies of the CFTR gene with F508del mutations. However, there might be an issue of generalisability of the trial populations to clinical practice in England and Wales in terms of the mix of genotypes.

a) **Please provide a comparison between the trial populations (SKYLINE 102 and 103, and RIDGELINE 105), and patients in England and Wales in terms of mix of genotypes.**

Please perform these subgroup analyses in order to test for equivalence or at least similarity in all efficacy and safety outcomes.

b) **Please discuss the implications of any differences in mix of genotypes between the trials and the population in clinical practice in England and Wales in terms of equivalence or similarity in efficacy and safety.**

Company response:

(a) Table 1 shows the mix of *F*/Any genotypes among people with CF in England and Wales (according to the UK CF Registry[1]). This is presented alongside the distribution of participants in the SKYLINE 102 and 103, and RIDGELINE 105 trials, as well as LONGITUDE, an observational, retrospective, registry-based cohort study evaluating real-world outcomes in people with CF in the UK with an *F*/Any genotype treated with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)[2]. The LONGITUDE study informed a Data Collection Agreement, that was assessed as part of the recent NICE CF Multiple Technology Appraisal (TA988). The LONGITUDE patient population is included here, as this is representative of the patients likely to be treated with vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) in clinical practice.

SKYLINE 102 enrolled 398 CF subjects, all of which had the *F*/MF (minimal function) genotype, and SKYLINE 103 enrolled 531 CF subjects who are *F*/*F*

(*F508del* homozygous), *F*/G (Gating), *F*/RF (residual function) or have at least 1 other triple combination responsive (TCR) *CFTR* mutation and no *F508del* mutation (TCR/non-*F*). In total, the SKYLINE trials included 929 people with CF aged 12 years and older aligned the population in scope, and the proportion of genotypes are shown in Table 1.

The combined SKYLINE 102 and SKYLINE 103 population included a similar proportion of F/F patients (48%) relative to the age-matched UK CF Registry population and LONGITUDE ([redacted] % and [redacted] %, respectively). Although there are some differences in distribution of genotypes between registry data and the VNZ/TEZ/D-IVA clinical trials, for instance proportion with the *F*/MF genotype (Table 1), the clinical trials for VNZ/TEZ/D-IVA included participants with genotypes representing over 90% of the *F/*any population in England and Wales.

Table 1 Distribution of *F/any* genotypes in the UK CF registry, the LONGITUDE observational study, and the VNZ/TEZ/D-IVA clinical trials

	Total	N (%)				
	***F508del* on ≥1 allele**	***F*/*F***	***F*/MF**	***F*/G + *F*/*R117H***	***F*/RF**	***F*/other**
UK CF registry data (2023)						
England 12+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales 12+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
England 6-11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales 6-11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LONGITUDE observational study (August 2019 – December 2023)						
Aged 12+ years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aged 6 to 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SKYLINE 102 and 103 & RIDGELINE trials*						

*The SKYLINE and RIDGELINE trials included participants with non-*F508del* mutations; these are not included in this table as they fall outside of the scope of the appraisal.

Source: Vertex data on file, 2024[1]; Vertex data on file, 2025[2]; Keating et al, 2025[3]; Hoppe et al, 2025[4]

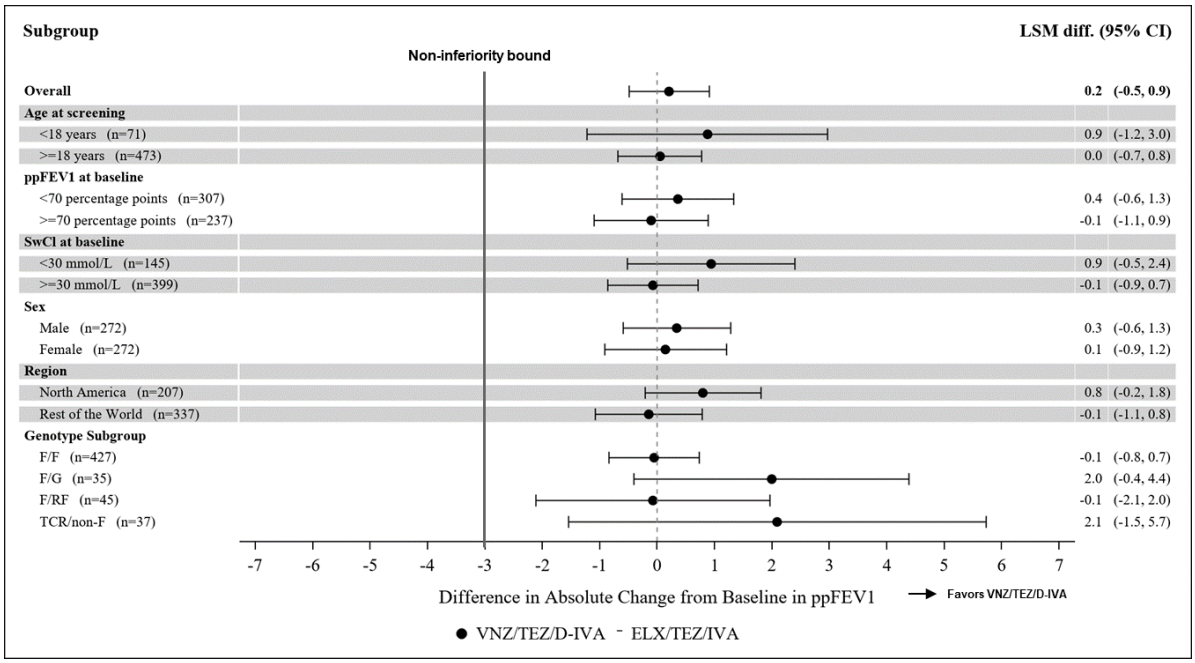
(b) For SKYLINE 102, all patients had the F/MF genotype, therefore subgroup analysis by genotype is relevant only for SKYLINE 103. Furthermore, 77.8% of patients (446 of 573) in SKYLINE 103 were *F*/*F* genotype, with the two other relevant genotypes (*F*/G, *F*/RF) accounting for between 6.8% and 8.0% of the SKYLINE 103 population each (39-46 patients). As such, interpretation

of subgroup data for these genotypes should be made with caution due to small sample size.

For efficacy endpoints, we focus herein on the primary and key secondary endpoint to support the assessment of similarity across genotypes. Subgroup analysis by genotype for other endpoints presented in our submission are not provided here. The rationale for this – as briefly mentioned during the clarification questions call on 9th April – is the available sample sizes. Furthermore, for event-based endpoints (pulmonary exacerbations, AEs), where only a proportion of patients experienced the event, the issue of small sample size by genotype is further compounded. For instance, in SKYLINE-103, only 21.5% of patients experienced a pulmonary exacerbation. This analysis is therefore not considered informative.

Subgroup analyses by genotype for SKYLINE 103 are presented below for the primary and key secondary efficacy endpoint, demonstrating consistent results across genotypes. A prespecified subgroup analysis by genotype was carried out for the absolute change from baseline in ppFEV$_1$ through Week 24 (Figure 1). Data relating to genotype are presented at the bottom of the forest plot.

Figure 1 Forest plot of absolute change from baseline in ppFEV$_1$ through Week 24 by subgroup (SKYLINE 103; FAS)



Treatment effect through Week 24 is estimated by averaging Weeks 16 and 24.
D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LSM: least squares mean; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor
Source: Keating et al, 2025[3]

In addition, a *post-hoc* subgroup analysis by genotype was carried out on the key secondary endpoint, absolute change from baseline in sweat chloride (SwCl) levels through Week 24 (Table 2). In general, the results were consistent with the overall population, with VNZ/TEZ/D-IVA demonstrating numerically greater reductions in SwCl vs ELX/TEZ/IVA. For the *F*/G subgroup, despite the numerically higher $ppFEV_1$ (Figure 1) in favour of VNZ/TEZ/D-IVA, there was a non-significant increase in SwCl of 3.6 mmol/L in the VNZ/TEZ/D-IVA arm, although both confidence intervals are wide and cross zero (Table 2). These results should be interpreted with caution, with this subgroup comprising only a small number of participants (n = 36; 5.5%). Therefore, as already stated, clinical inference is confounded by small patient numbers.

Table 2 *Post-hoc* absolute change in sweat chloride levels from baseline through Week 24 by genotype (SKYLINE 103; FAS)

Genotype subgroup	**ELX/TEZ/IVA**	**VNZ/TEZ/D-IVA**
	n = 289	**n = 284**
Overall, n = 546		
LS mean change (SE)	-2.3 (0.7)	-5.1 (0.7)
LS mean difference, 95% CI		-2.8 (-4.7, -0.9)
***F508del/F508del*, n = 427**	214	213
LS mean change (SE)	-2.5 (0.8)	-5.7 (0.8)
LS mean difference, 95% CI		-3.2 (-5.3, -1.1)
***F508del*/gating, n = 36**	19	17
LS mean change (SE)	-2.4 (2.6)	3.6 (2.8)
LS mean difference, 95% CI		5.9 (-1.9, 13.7)
***F508del*/residual function, n = 46**	23	23
LS mean change (SE)	-1.0 (1.8)	-4.4 (1.8)
LS mean difference, 95% CI		-3.4 (-8.5, 1.6)
ELX/TEZ/IVA-responsive-non-*F508del*, n = 37	20	17
LS mean change (SE)	-2.1 (4.1)	-3.7 (4.5)
LS mean difference, 95% CI		-1.6 (-14.2, 11.2)

CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; SE, standard error; TEZ, tezacaftor; VNZ, vanzacaftor
Source: Keating et al, 2025[3]

(c) Experience with ELX/TEZ/IVA suggests that efficacy from the clinical trials translates to UK clinical practice, regardless of genotype.

LONGITUDE is a non-interventional, observational, retrospective, registry-based cohort study evaluating real-world outcomes in people with CF with an F/Any genotype treated with ELX/TEZ/IVA using data from the UK Cystic Fibrosis Registry. The analysis of LONGITUDE below relates to a large sample size of 6,874 patients aged six years and older in the UK. Comparison of the genotype distribution in LONGITUDE with that in the ELX/TEZ/IVA Phase 3 clinical trials also shows some differences in genotype distribution (Table 3). Change from baseline in $ppFEV_1$ by genotype in the LONGITUDE study is presented in Table 4.

Notably, the improvements in $ppFEV_1$ seen in this study were broadly consistent with what has been reported in ELX/TEZ/IVA Phase 3 clinical trials (Table 5), though it should be noted that the sample size for the 6-11 and 12+ open-label extensions is small, particularly relative to LONGITUDE.[5-7] Further, in the AURORA 6-11 open-label extension (OLE) study, [redacted] had received a prior CFTR modulator at baseline, compared to [redacted] in LONGITUDE [2,8]. The higher proportion of patients with CFTR modulator exposure in the LONGITUDE study may explain the numerically lower improvement in $ppFEV_1$ observed (Table 5).

Table 3 Distribution of F-Any genotypes in LONGITUDE and pivotal ELX/TEZ/IVA studies

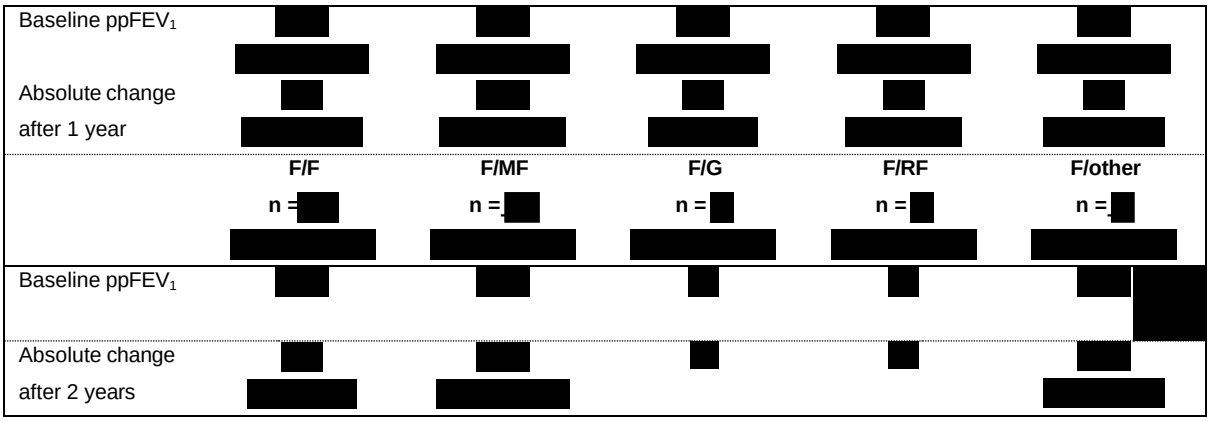
	Total	N (%)				
	***F508del* on ≥1 allele**	**F/F**	**F/MF**	**F/G**	**F/RF**	**F/other**
LONGITUDE observational study						
Aged 12+ years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aged 6 to 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pivotal AURORA trials*						
Aged 12+ years	768	107 (13.9)	403 (52.5)	95 (12.4)	163 (21.2)	-
Aged 6 to 11 years**	187	29 (15.5)	158 (84.5)	-	-	-

*NCT03525444; NCT03525548; NCT04058353; NCT03691779; NCT04353817. **includes data from the Galileo study

Source: Vertex data on file, 2025[2]; Middleton et al, 2019[9]; Heijerman et al, 2019[7]; Barry et al, 2021[5]; Zemanick et al, 2021[10]

Table 4 Change from baseline in $ppFEV_1$ after 1 and 2 years by genotype, LONGITUDE

	F/F	F/MF	F/G	F/RF	F/other
	n = [redacted]	n = [redacted]	n = [redacted]	n = [redacted]	n = [redacted]
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)



CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; NR, not reported (owing to small sample size); $ppFEV_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.

Note: $ppFEV_1$ data breakdown by genotype is only available for the December 2022 data cut.

Source: Vertex data on file, 2023[11]

Table 5: Change from baseline in $ppFEV_1$ after 1 and 2 years - comparison between ELX/TEZ/IVA trial data and LONGITUDE

	Age 6-11 LONGITUDE N=		Age 6-11 ELX/TEZ/IVA OLE N=		Age 12+ LONGITUDE N=		Age 12+ ELX/TEZ/IVA OLE N	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Baseline $ppFEV_1$								
Absolute change after 1 year								
Baseline $ppFEV_1$								
Absolute change after 2 years								

[a]Mean (SD). Value only provided for the parent study baseline.

[b]Week 48 used as this was the closest timepoint to 1 year.

[c]Week 96 used as this was the closest timepoint to 2 years.

CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; NR, not reported (owing to small sample size); $ppFEV_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor

Source: Vertex data on file, 2025[2]; AURORA 6-11 OLE CSR[8]; AURORA 12+ OLE CSR[12]

Given the similarities between ELX/TEZ/IVA and VNZ/TEZ/D-IVA in terms of mode of action, and demonstrated direct evidence of non-inferiority in improving $ppFEV_1$ in the pivotal trials, we would also expect the clinical trial outcomes seen with VNZ/TEZ/D-IVA to be generalisable to UK clinical practice, regardless of genotype distribution.

A 2. Priority question. No RCT evidence was included in the company submission for the population between 6 and 11 with the only clinical evidence being from RIDGELINE 105.

a) **Please confirm that there is no comparative evidence for this age group, or include it.**

b) **If it is the case that there is no comparative evidence for this age group, then please provide evidence for the comparator i.e. ELX/TEZ/IVA in this age group in order to demonstrate equivalence or at least similarity in efficacy and safety.**

Company response:

(a) Vertex can confirm that there is no comparative evidence for VNZ/TEZ/D-IVA in children with CF aged 6 to 11 years. However, it is important to note that, although RIDGELINE 105 was a single-arm study, it included a 4-week run-in period during which participants received ELX/TEZ/IVA to establish an on-treatment baseline before receiving VNZ/TEZ/D-IVA, with the run-in period waived for participants already stable on ELX/TEZ/IVA. Consequently, improvements observed during treatment with VNZ/TEZ/D-IVA were calculated as change from a baseline of ELX/TEZ/IVA. On this basis, the stable ppFEV$_1$ and numerical improvement in SwCl demonstrated in RIDGELINE 105 further reinforce that baseline efficacy measures on ELX/TEZ/IVA were either maintained or improved over time with VNZ/TEZ/D-IVA, as was demonstrated in the 12+ years clinical trials directly comparing VNZ/TEZ/D-IVA and ELX/TEZ/IVA.

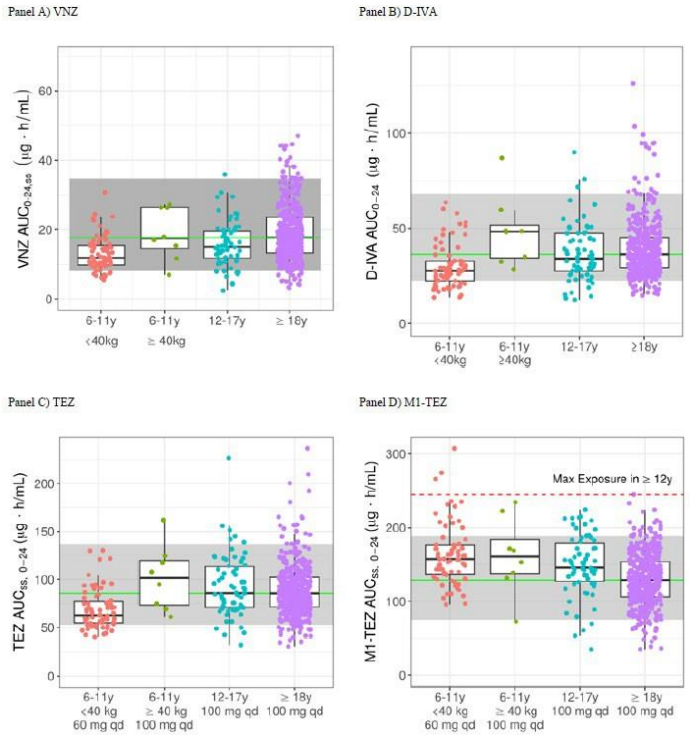
RIDGELINE 105 was conducted as a single-arm study because the primary objective was to assess safety and tolerability of VNZ/TEZ/D-IVA in 6 to 11-year-olds, rather than efficacy vs ELX/TEZ/IVA. Efficacy endpoints such as lung function (ppFEV$_1$) and CFTR function (measured by SwCl levels) were included as secondary endpoints. Per the principles of efficacy extrapolation to the paediatric population outlined in the International Conference on Harmonisation guideline E11,[13] VNZ/TEZ/D-IVA is expected to have comparable efficacy in the RIDGELINE 105 study population to that observed in the SKYLINE trials in people with CF aged 12+ years. The non-inferiority assumption is deemed appropriate for the CF population aged 6 to 11 years:

- The underlying aetiology of CF is consistent between younger and older patients

- Pharmacokinetic data from RIDGELINE 105 show that the exposures of VNZ, TEZ, D-IVA and their metabolites in 6 to 11-year-olds were within the range of exposure seen in patients aged ≥12 years (see Figure 2) and were consistent with those seen in previous clinical trials of IVA, TEZ/IVA and ELX/TEZ/IVA. Trials of other CFTR modulators in 6- to 11-year-olds have shown consistent efficacy and safety with patients aged ≥12 years.[10,14]

- Safety data of VNZ/TEZ/D-IVA in age 6-11 from RIDGELINE 105 were generally consistent with that observed in the patients aged 12 years and older in SKYLINE 102 and 103.

Figure 2: Drug exposure versus Age Group for VNZ, D-IVA, TEZ, and M1-TEZ



$AUC_{0\text{-}24h}$, area under the concentration versus time curve at steady state; D-IVA, deutivacaftor, EBE: empirical Bayes estimate; IQR: interquartile range; qd, once daily; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor
Source: Hoppe et al (2025)[4]

This approach of extrapolating efficacy from older to younger populations has been accepted by the CF clinical community and HTAs for previous CFTR

modulators (for example, TA988). Furthermore, the indication is the same in the paediatric population as in adults, with the comparability of efficacy and safety therefore deemed acceptable by the MHRA.

(b) Direct side-by-side comparison of the efficacy and safety between VNZ/TEZ/D-IVA and ELX/TEZ/IVA in the 6-11 age group is not possible. In RIDGELINE 105, participants were stable on ELX/TEZ/IVA for at least 4 weeks before receiving VNZ/TEZ/D-IVA, therefore the improvements seen with VNZ/TEZ/D-IVA were additional to the ELX/TEZ/IVA baseline, whereas ELX/TEZ/IVA studies (AURORA 6-11 and GALILEO) did not include an active run-in period. Therefore, the change from baseline cannot be directly compared across the studies. As requested, we provide the summary of the safety and efficacy of ELX/TEZ/IVA in children aged 6 to 11 years from the following studies:

- AURORA 6-11: 24-week open-label, phase 3 study (Study VX18-445-106)[10]
- AURORA 6-11 OLE: 192-week open-label extension (Study VX19-445-107)[15]
- GALILEO: 24-week randomised, double blind, placebo-controlled phase 3 study (Study VX19-445-116)[16]
- LONGITUDE: a non-interventional, observational, retrospective, registry-based cohort using data from the UK Cystic Fibrosis Registry[2]

<u>AURORA 6-11 and AURORA 6-11 OLE</u>

Sixty-six children with CF with *F*/*F* or *F*/MF genotypes were enrolled in AURORA 6-11. Participants weighing <30 kg received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h, and those weighing ≥30 kg received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Table 6 shows the participants' baseline characteristics.

Table 6 Baseline characteristics: AURORA 6-11

	ELX/TEZ/IVA (n = 66)

Sex, n (%)	
Female	39 (59.1)
Age (years), mean (SD)	
Race, n (%)	
White	58 (87.9)
Asian	1 (1.5)
Not collected per local regulations	8 (12.1)
Region, n (%)	
North America	47 (71.2)
Europe & Australia	19 (28.8)
Genotype, n (%)	
F/F	29 (43.9)
F/MF	37 (56.1)
$ppFEV_1$, mean (SD)	88.8 (17.7)
SwCl, mmol/L	102.2 (9.1)
CFQ-R respiratory domain score, mean (SD) points	80.3 (15.2)
$LCI_{2.5}$, mean (SD) units	9.77 (2.68)
Weight, mean (SD) kg	30.0 (7.7)
<30 kg, n (%)	36 (54.5)
≥30 kg, n (%)	30 (45.5)
Height, mean (SD), cm	134.1 (12.3)
BMI, mean (SD) kg/m^2	16.39 (1.69)

BMI, body mass index; CFQ-R RD, Cystic Fibrosis Questionnaire – Revised ; ELX, elexacaftor ; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; ppFEV1, percent predicted forced expiratory volume in 1 second; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor

Source: Zemanick et al, 2021[10]

The primary endpoint was safety and tolerability, and the safety profile of ELX/TEZ/IVA was consistent with that seen in older patients. The most common adverse events were consistent with manifestations of CF or common childhood infections.

Efficacy was assessed as secondary endpoints. Key efficacy results are summarised in Table 7. Rapid and sustained improvements were seen in $ppFEV_1$, CFQ-R respiratory domain scores and SwCl levels. BMI, BMI-for-age z-score, weight, weight-for-age z score and height increased over the 24-week treatment period without reaching a plateau, whereas height-for-age score was maintained.

After completion of the 24-week study, participants could enter a 192-week open-label extension (AURORA 6-11 OLE; the longest such study ever conducted in CF in this age group).[15] This study consisted of two parts (Part A and Part B), each with a 96-week treatment period followed by a 4-week safety follow-up period. Participants who completed Part A had the opportunity to take part in Part B. Sixty-four participants entered Part A and 48 entered Part B.

The final analysis of efficacy data showed sustained, robust and clinically meaningful improvements that were consistent with the efficacy data observed in the parent study (Table 7). There was no evidence of clinically meaningful decline in mean $ppFEV_1$ over the 4.5 years of treatment in AURORA 6-11 and AURORA 6-11 OLE.

Table 7 Key efficacy endpoints: AURORA 6-11 and AURORA 6-11 OLE

	Absolute change from baseline, LS mean (95% CI)		
	AURORA 6-11 (n = 66) Through Week 24	**AURORA 6-11 OLE (n=64)**	
		At OLE Week 96	**At OLE Week 192**
ppFEV, percentage points	10.2 (7.9, 12.6)	11.2 (8.3, 14.2)	9.6 (5.4, 13.7)
SwCl, mmol/L	-60.9 (-63.7, -58.2)	-62.3 (-65.8, -58.8)	-57.9 (-63.3, -52.5)
CFQ-R respiratory domain score, points	7.0 (4.7, 9.2)	13.3 (11.4, 15.1)	10.0 (6.9, 13.0)
$LCI_{2.5}$, units	-1.71 (-2.11, -1.30)	-2.00 (-2.45, -1.55)	-2.33 (-2.87, -1.79)
BMI z-score*	0.37 (0.26, 0.48)	0.24 (0.11, 0.37)	0.39 (0.19, 0.59)

*At Week 24 in VX18-445-106. BMI, body mass index; CI, confidence interval; CFQ-R, Cystic Fibrosis Questionnaire – Revised ; $LCI_{2.5}$, lung clearance index 2.5; LS, least squares; $ppFEV_1$, percent predicted forced expiratory volume in 1 second
Source: Wainwright et al, 2024[15]

The final analysis of safety data revealed no new safety concerns (Table 8).

Table 8 Safety results: AURORA 6-11 and AURORA 6-11 OLE

	Number (%) of patients	
	AURORA 6-11	**AURORA 6-11 OLE**
	(n = 66)	**(n=64)**
All TEAEs	65 (98.5)	64 (100.0)
AEs by maximum severity		
Mild	36 (54.5)	20 (31.3)
Moderate	28 (42.4)	41 (64.1)
Severe	1 (1.5)	3 (4.7)
Life-threatening	0	0
AEs by strongest relationship		
Not related	16 (24.2)	18 (28.1)
Unlikely related	16 (24.2)	18 (28.1)
Possibly related	29 (43.9)	28 (43.8)
Related	4 (6.1)	0
SAEs	1 (1.5)	7 (10.9)
Related SAEs	0	2 (3.1)
AEs leading to discontinuation	1 (1.5)	2 (3.1)
AEs leading to interruptions	1 (1.5)	4 (6.3)
Most common AEs (≥20%)*		
Cough	28 (42.4)	40 (62.5)
Pyrexia	14 (21.2)	28 (43.8)
Headache	16 (24.2)	26 (40.6)
Oropharyngeal pain	12 (18.2)	24 (37.5)
Nasal congestion	10 (15.2)	23 (35.9)
Rhinorrhoea	8 (12.1)	21 (32.8)
Upper RTI	11 (16.7)	19 (29.7)
COVID-19	0	18 (28.1)
Vomiting	7 (10.6)	17 (26.6)
Abdominal pain	8 (12.1)	14 (21.9)

*Based on AURORA 6-11 OLE. AE, adverse event; OLE, open-label extension; RTI, respiratory tract infection; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Source: Wainwright et al, 2024[15]

GALILEO

Children with CF with the *F*/MF genotype were randomised to receive either ELX/TEZ/IVA (n = 60) or placebo (n = 61).[16] Participants weighing <30 kg received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h, and those weighing ≥30 kg received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Table 9 shows participants' baseline characteristics.

Table 9 Baseline characteristics: GALILEO

	Placebo (n=61)	ELX/TEZ/IVA (n = 60)
Sex, n (%)		
Female	35 (57.4)	35 (58.3)
Age (years), mean (SD)	9.2 (1.7)	9.1 (1.8)
Race, n (%)		
White	42 (68.9)	45 (75.0)
Black or African American	0 (0)	1 (1.7)
Asian	0 (0)	1 (1.7)
American Indian or Alaska Native	0 (0)	1 (1.7)
Other	1 (1.6)	0 (0)
Not collected per local regulations	18 (29.5)	11 (18.3)
Region, n (%)		
Europe	49 (80.3)	43 (71.7)
Other (Australia, Canada, Israel)	12 (19.7)	17 (28.3)
Genotype, n (%)		
F/MF	61 (100.0)	60 (100.0)
$ppFEV_1$, mean (SD)	87.2 (15.8)	91.4 (13.8)
SwCl, mmol/L	102.6 (8.6)	102.8 (10.0)
CFQ-R respiratory domain score, mean (SD) points	82.7 (14.1)	85.7 (11.7)
$LCI_{2.5}$, mean (SD) units	9.75 (1.95)	10.26 (2.22)
Weight, mean (SD) kg	29.8 (8.6)	29.1 (7.6)
<30 kg, n (%)	38 (62.3)	39 (65.0)
≥30 kg, n (%)	23 (37.7)	21 (35.0)
Height, mean (SD), cm	134.6 (13.3)	132.3 (11.7)
BMI, mean (SD) kg/m^2	16.11 (2.32)	16.33 (1.84)

BMI, body mass index; CFQ-R RD, Cystic Fibrosis Questionnaire – Revised ; ELX, elexacaftor ; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; ppFEV1, percent predicted forced expiratory volume in 1 second; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor

Source: Mall et al, 2022[16]

The primary endpoint was absolute change in $LCI_{2.5}$ from baseline through Week 24. Secondary endpoints were absolute change in SwCl from baseline through Week 24 and safety and tolerability. Other endpoints included absolute changes in $ppFEV_1$ and CFQ-R respiratory domain score from baseline through Week 24.

Treatment with ELX/TEZ/IVA resulted in significant improvements in $LCI_{2.5}$ as well as robust improvements in SwCl, $ppFEV_1$ and CFQ-R RD scores compared with placebo (Table 10).

Table 10 Efficacy results: GALILEO

	Placebo n = 61	**ELX/TEZ/IVA n = 60**
$LCI_{2.5}$, units		
Baseline, mean (SD)*	9.75 (1.95)	10.26 (2.22)
Absolute change through Week 24, LS mean (95%CI)	-0.02 (-0.34 to 0.29)	-2.29 (-2.60 to -1.97)
Between group difference (95% CI)	-2.26 (-2.71 to -1.81) P<0.0001	
SwCl, mmol/L		
Baseline, mean (SD)	102.6 (8.6)	102.8 (10.0)
Absolute change through Week 24, LS mean (95%CI)	-0.9 (23.8 to 2.0)	-52.1 (-55.0 to -49.2)
Between group difference (95% CI)	-51.2 (-55.3 to -47.1) P<0.0001†	
$ppFEV_1$, percentage points		
Baseline, mean (SD)	87.2 (15.8)	91.4 (13.8)
Absolute change through Week 24, LS mean (95%CI)	-1.5 (-4.4 to 1.4)	9.5 (6.6 to 12.4)
Between group difference (95% CI)	11.0 (6.9 to 15.1) P<0.0001†	
CFQ-R respiratory domain score, points		
Baseline, mean (SD)	82.7 (14.1)	85.7 (11.7)
Absolute change through Week 24, LS mean (95%CI)	0.5 (-2.7 to 3.6)	5.9 (2.8 to 9.1)
Between group difference (95% CI)	5.5 (1.0 to 10.0) P=0.0174†	

*Baseline defined as the most recent non-missing measurement before the first dose of study medication in the treatment period. †P values are considered to be nominal. CI, confidence interval; CFQ-R, Cystic Fibrosis Questionnaire – Revised ; ELX, elexacaftor ; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; LS, least squares; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation; TEZ, tezacaftor

Source: Mall et al, 2022[16]

Post-hoc analyses showed that 49 of 60 children (81.7%) treated with ELX/TEZ/IVA had SwCl concentrations <60 mmol/L (the diagnostic threshold for CF), and 2 of 60 children (3.3%) had SwCl concentrations <30 mmol/L (normal levels of CFTR function) through Week 24; no children who received placebo had sweat chloride concentrations <60 mmol/L through Week 24.

Safety data were consistent with the established safety profile for ELX/TEZ/IVA, with no new safety concerns observed (Table 11).

Table 11 Safety results: GALILEO

	Number (%) of patients	
	Placebo (n = 61)	**ELX/TEZ/IVA (n=60)**
All TEAEs	57 (93.4)	48 (80.0)
AEs by maximum severity		
Mild	26 (42.6)	30 (50.0)
Moderate	29 (47.5)	16 (26.7)
Severe	2 (3.3)	2 (3.3)
SAEs	9 (14.8)	4 (6.7)
Related SAEs	1 (1.6)	1 (1.7)*
AEs leading to discontinuation	0	1 (1.7)*
AEs leading to death	0	0
Most common AEs (≥10%)		
Headache	12 (19.7)	18 (30.0)
Cough	26 (42.6)	14 (23.3)
Nasopharyngitis	9 (14.8)	7 (11.7)
Productive cough	6 (9.8)	7 (11.7)
Rhinorrhoea	7 (11.5)	7 (11.7)
Rash	3 (4.9)	6 (10.0)
Abdominal pain	17 (27.9)	5 (8.3)
Oropharyngeal pain	12 (19.7)	3 (5.0)
Infective PEx of CF	16 (26.2)	1 (1.7)

*One child had an SAE of rash that was considered possibly related to ELX/TEZ/IVA and resolved after study discontinuation.

AE, adverse event; CF, cystic fibrosis; ELX, elexacaftor ; IVA, ivacaftor; PEx, pulmonary exacerbation; SAE, serious adverse event; TEZ, tezacaftor

Source: Mall et al, 2022[16]

LONGITUDE

Baseline characteristics for patients aged 6-11 enrolled in the LONGITUDE study are presented in Table 12.[2]

Table 12: Baseline Characteristics: LONGITUDE 6-11

	ELX/TEZ/IVA (n = [redacted])
Sex, n (%)	
Female	[redacted]
Age (years), mean (SD)	[redacted]
Race, n (%)	
White	[redacted]
Genotype, n (%)	
F/F	[redacted]
F/MF	[redacted]
F/RF	[redacted]
F/G	[redacted]
F/other	[redacted]
$ppFEV_1$, mean (SD)	[redacted]

Source: Vertex data on file, 2025[2];

Clinical efficacy data for LONGITUDE 6-11 are summarised for $ppFEV_1$ in Table 4. Data on rate of pulmonary exacerbations for the 6-11 population are captured below (Table 13).

Table 13: Rate of PEx: LONGITUDE 6-11

	ELX/TEZ/IVA 6-11 years cohort (N=[redacted])	
	12 months pre-ELX/TEZ/IVA initiation	**Post-ELX/TEZ/IVA initiation**
Follow-up time (months); mean (SD)	[redacted]	[redacted]
Annualized PEx rate[a] (in hospital and/or at home) 95% CI	[redacted] [redacted]	[redacted] [redacted]
Number of patients with at least one episode in hospital and/or at home, n (%)	[redacted]	[redacted]
For patients with at least one-episode, cumulative days on IV antibiotics (at home and in hospital), per patient year[b]; mean (SD)	[redacted]	[redacted]
For patients with at least one-episode, days in hospital per treatment episode [c]; mean (SD)	[redacted]	[redacted]

[a] Proxied by IV antibiotic episodes, calculated for all patients in the cohort; [b] Cumulative duration of days on IV antibiotics (at home and in hospital); [c] Number of days in hospital per treatment with IV antibiotics; mean (SD). Note: 95% confidence interval (CI) represents an exact 95% Poisson confidence interval.
Source: Vertex data on file, 2025[2];

SwCl decreased post-ELX/TEZ/IVA initiation, however a low number of patients in the registry had a recorded SwCl value (<5%).[2]

- 6-11 years (n=[redacted]): [redacted] (95% CI: [redacted] reduction in SwCl after 2-years on ELX/TEZ/IVA
- ≥12 years (n=[redacted]): [redacted] (95% CI: [redacted] reduction in SwCl after 2-years on ELX/TEZ/IVA

Though safety data are not presented for LONGITUDE, with a mean exposure time of [redacted] months, a total of [redacted] ([redacted]%) patients aged 6-11 years discontinued treatment with ELX/TEZ/IVA.[2]

Section B: Cost-effectiveness evidence

No questions.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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

About you

1.Your name	[redacted]
2. Name of organisation	Cystic Fibrosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cystic Fibrosis Trust is the only UK charity dedicated to uniting for a life unlimited by cystic fibrosis (CF) for everyone affected by the condition. CF is a rare genetic condition that affects over 11,000 people in the UK. The Trust funds vital and impactful research that accelerates breakthrough science and therapeutics, improves care and the way its delivered and provides essential advice, support, and information to people affected by CF so they can live a life unlimited.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Cystic Fibrosis Trust has received the following funding:

	<table><tr><th></th><th>Date</th><th>Total exc VAT</th></tr><tr><td>Sponsorship of CTAP conference on 6th March 2024</td><td>25/01/2024</td><td>£20,000</td></tr><tr><td>CF workforce survey – securing the future of excellence for CF healthcare</td><td>16/05/2024</td><td>£14,301</td></tr><tr><td>CTAP feasibility study</td><td>15/08/2024</td><td>£3,000</td></tr><tr><td>CF Registry data extraction</td><td>25/07/2024</td><td>£9,375</td></tr><tr><td>UK CF early careers researchers conference</td><td>28/10/2024</td><td>£12,000</td></tr><tr><td>Vertex Pharmaceuticals Inc subtotal</td><td colspan="2">£58,676</td></tr><tr><td>CF Registry data extraction</td><td>30/01/2024</td><td>£9,375</td></tr><tr><td>Attendance for [redacted] at CTAP conference</td><td>18/03/2024</td><td>£350</td></tr><tr><td>Attendance for [redacted] at CTAP conference</td><td>11/03/2024</td><td>£350</td></tr><tr><td>Attendance for [redacted] at CTAP conference</td><td>03/04/2024</td><td>£350</td></tr><tr><td>Attendance for [redacted] at MDT conference</td><td>03/04/2024</td><td>£350</td></tr><tr><td>Attendance for [redacted] at MDT conference</td><td>18/03/2024</td><td>£350</td></tr><tr><td>Lay review of an informed consent form for a clinical trial</td><td>30/09/2024</td><td>£750</td></tr><tr><td>Lay review of an informed consent form for a clinical trial</td><td>30/09/2024</td><td>£795</td></tr><tr><td>ECFS 2024 – Cystic Fibrosis Trust presentation at Vertex meeting</td><td>22/07/2024</td><td>£200</td></tr><tr><td>Vertex Pharmaceuticals Europe subtotal</td><td colspan="2">£12,870</td></tr></table> Cystic Fibrosis Services Limited, a subsidiary of the Cystic Fibrosis Trust, hosts the UK CF Registry and received funding for pharmacovigilance studies and the HTA study agreement as part of TA988.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in	This submission has been informed by our previous submissions as part of TA988, where we ran focus groups for people with CF and their families, as well as a survey seeking experiences which gathered over 1,110 responses. We have additionally utilised insights gained from numerous focus groups run by the Involvement team within Cystic Fibrosis Trust, which have covered a number of topics, including aging with CF, standards of

your submission?	care and experiences of adults with CF who are unable to treated with current CFTR modulators (Kaftrio, Orkambi and Symkevi).

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People with CF experience a wide range of challenging symptoms affecting the whole body, in particular the lungs and gut. They can also develop co-morbidities, including CF diabetes, osteoporosis, infertility in males and liver problems. Although the median age of death has increased over recent years due to advances in treatments and care, CF remains a life-limiting condition with the UK CF Registry reporting a median age at death of 46 in 2023[1]. There is currently no cure for CF. Living with CF has a high treatment burden, requiring medication and physiotherapy to stay well. Reducing the treatment burden of CF has been identified as a top priority for the community as part of the James Lind Alliance priority refresh[2]. Being unwell can interfere with work, education, and social activities – people living with CF describe there being no day off from relentless CF. People with CF have thick and sticky mucus in their lungs which makes it difficult to clear and it is easier for bacteria to colonise. Bacteria builds up in the airways causing infection. The lining of the airways becomes inflamed, causing tissue damage. Repeated infections and inflammation can lead to permanent scarring of the lungs. Looking after the lungs and keeping them clear is extremely important for people with CF. Airway clearance techniques and exercise are used to loosen and clear mucus to prevent infections and lung damage. Physiotherapy, whilst essential, can be a huge daily burden particularly alongside a rigorous regime of medicines and nebulisers. This seriously affects the quality of life for people with CF and their families. Cough swabs and sputum samples are regularly required to check for lung infections so that bacteria can be treated with targeted antibiotics and other medicines. It is common for people with CF to spend weeks in hospital several times a year for intravenous antibiotic treatment and monitoring. In 2023, 22% of people with CF had at least one course of intravenous antibiotics, although some people with CF with their families have told us that hospital stays for intravenous antibiotic treatment have been as frequent as every two months on average and that they have been on antibiotics consistently since birth. Infection can cause the lung function of someone with CF to drop far lower than that expected in someone with fully functioning lungs. People with CF are particularly vulnerable to antimicrobial resistance (AMR). Antimicrobial drugs, such as

[1] https://www.cysticfibrosis.org.uk/sites/default/files/2024-11/CFT_2023_Annual_Data_Report_Oct2024%201.pdf
[2] https://www.cysticfibrosis.org.uk/news/refreshed-top-10-research-priorities-for-cf-revealed

	antibiotics are a crucial part of day-to-day treatment in CF care – often used prophylactically to control existing or colonised bacterial infections as well as treating exacerbations. Early antibiotic intervention has significantly contributed to people with CF living longer. However, with some CF infections becoming increasingly resistant to the treatments available, AMR will ultimately shorten the lives of people with CF. The small tubes that transport enzymes out of the pancreas become blocked with mucus because of CF. The enzymes build up in the pancreas instead of reaching the digestive system, causing the pancreas to become inflamed. As a result, people with CF take supplements to replace these enzymes to help digest their food. Enzyme supplements must be taken with foods containing fat, protein, or carbohydrate and the amount of enzymes is variable to the individual. Not taking enough enzymes will result in undigested food passing through the body, which can cause abdominal pain, bloating, excess wind, and difficulty gaining weight. Parents have described the difficulty that digestive problems can cause their children with CF: *"she'd have oily poos and some faecal incontinence…its dreadfully embarrassing…certainly not something you want to go into the teenage years with."* Parents have also described the difficulty of ensuring their children are a healthy weight and managing the high-calorie diet required*: "It's not been easy…over the years we've been trying so hard"." My son struggled to gain weight from very early on and takes quite a lot of Creon* [pancreatic enzymes] *…we had to mound the cheese…heap on the butter until it's like so gross that you wouldn't want to eat it yourself"* and that they are used to "*chucking food down our children's throats*" to *"maximise fat and calorie intake".* The scarring in the pancreas of people with CF can mean it does not produce insulin as effectively, resulting in CF diabetes, a condition that affects more than 30% of adults with CF[3]. The condition is associated with increased morbidity, mortality, and a faster decline in lung function[4]. CF diabetes cannot be cured but can be managed with insulin and dietary changes – this significantly adds to the already high treatment burden of CF. Some people with CF may need a transplant if standard treatments are no longer working as well as they should. The main transplants that people with CF may need are lungs or liver. For some people with CF, other organs may need to be transplanted because of the damage the condition can inflict on the whole of the body. As CF is a genetic condition, people who receive a transplanted organ will still have CF in the rest of their body and will still require CF treatment, even after a successful transplant. Additionally, special care and treatment must be adhered to after a transplant on top of existing management options.

[3] https://www.cysticfibrosis.org.uk/sites/default/files/2022-10/CFT_2021-Annual-Data-Report-WEB.pdf
[4] https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Trust%20Diabetes%20Consensus%20FINAL.pdf

	Living with CF has significant impacts on mental and emotional wellbeing. This has been recognised within specialist multidisciplinary teams as part of CF care. Parents have described how having children with life-limiting conditions has affected them: the constant *"heartache and concerns about her having CF."* Adults with CF told us: *"It is impossible to comprehend how psychologically difficult it is to cope with CF and the opportunities in life you must give up."* People with CF and their families have frequent visits to specialist CF centres for monitoring and inpatient admissions.. An outpatient appointment for people with CF takes 4 hours and 50 minutes, including the mean travel time[5]. Living with CF has a significant impact on family life. Parents of children with CF and carers have sometimes had to give up work to care for family members. Parents have described the impact a diagnosis of CF can have: *"When he was diagnosed at three weeks old, our whole world fell apart…you hear of young children passing away from this disease"* and the enormous anxiety that living with CF can cause: *"its continual pressure and grind"* to manage to the daily medicines and physiotherapy. This treatment burden is noticeably larger during periods of exacerbations where additional physiotherapy and intravenous antibiotics may be needed, along with hospital admissions. Parents also feel they must *"live a very structured life and the whole family loses spontaneity."* CF also has significant financial implications for those living with the condition. A 2022 report by Cystic Fibrosis Trust found that 69% of people felt they had less money compared to those around them, due to either their own or their child's CF[6]. In January 2023, Cystic Fibrosis Trust and the University of Bristol research found that living with CF costs someone who has the condition an additional £6,800 a year due to the substantial extra costs associated with the condition (such as traveling for regular medical appointments, prescription charges, dietary requirements due to the higher calorie intake needed, and higher energy bills) and reduced income (such as taking unpaid leave to attend appointments and reducing working hours)[7]. Many people with CF incur a 'double hit' to their finances: not just to keep themselves healthy, but potentially also losing income because of poor health, taking leave, and affecting education or employment opportunities, such as working reduced hours

[5] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/CF%20Insight%20Survey%20full%20report%202018.pdf
[6] https://www.cysticfibrosis.org.uk/sites/default/files/2022-06/Cost%20of%20CF%20report.pdf
[7] https://www.cysticfibrosis.org.uk/sites/default/files/2023-01/CFT%20final%20report.pdf

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Whilst not a cure, access to CFTR modulators has profoundly changes the lives of people with CF who are able to benefit from these treatments. Our numerous evidence submissions as part of our participation in TA988, and we strongly encourage NICE to consider these submissions as part of this appraisal. A summary of what the CF community feel about CFTR modulators can be found below: • Increased health stability, reduced hospital admissions and reduced use of antibiotics is seen as a major change to CF care since access to CFTR modulators. • Increased pregnancies – the number of women with CF becoming mothers has risen from 56 in 2020 to 116 in 2023. • Improved opportunities for education and employment, as well as a newfound ability to plan for the future. • Reduced coughing and improved lung function. • Fewer medical interventions. • Weight gain. • Increased energy levels. • Improved quality life. In a survey conducted with the CF community as part of TA988, Cystic Fibrosis Trust found that 6% of survey respondents felt that access to Orkambi/Symkevi/Kaftrio has significantly improved their quality of life, with 25% reporting an improved quality of life. 80% of survey respondents felt significantly more positive about the future of living with CF because of access to CFTR modulators, with 15% reporting feeling slightly more positive
8. Is there an unmet need for patients with this condition?	Kaftrio, Orkambi, Symkevi and Kalydeco were the first disease-modifying treatments for CF. Whilst the majority of people with CF are eligible for these medicines and therefore may be eligible for the vanzacaftor triple therapy, there remains a significant minority of people who are not yet benefitting from a modulator therapy. These groups can be broadly categorised into the following: • People with CF who are not eligible for Kaftrio, but may be eligible for the vanzacaftor triple therapy, • People with CF who are unable to tolerate Kaftrio due to side effects, • People with CF who are taking Kaftrio but seeing little or no clinical benefit.

	For these groups, having a potential treatment option is hugely significant because of the potential for better clinical outcomes, and therefore health stability.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	As the vanzacaftor triple therapy is a once-daily medicine, there is a potential for a reduced treatment burden. This has been identified as a top priority for the community as part of the James Lind Alliance priority refresh as well as identifying options for those not able to take current CFTR modulators (including people with CF with rare mutations, those who are not eligible and those who are unable tolerate current treatments). A once-daily administration may also increase adherence, as Cystic Fibrosis Trust are aware that the requirement to take Kaftrio twice a day with a high-fat meal to aid absorption can be challenging. Simplifying treatments makes it easier for individuals to follow their prescribed therapies consistently, which is essential for managing CF effectively. Streamlining these processes can alleviate stress and improve overall quality of life by making daily routines more manageable.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Cystic Fibrosis Trust has been approached by members of the CF community who are eager to receive vanzacaftor–tezacaftor–deutivacaftor, and early feedback from the US has been positive from clinicians and people with CF.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As Cystic Fibrosis Trust has detailed above, there are groups of people with CF with significant unmet need who may benefit more than others, including: • People with CF who are not eligible for Kaftrio, but may be eligible for the vanzacaftor triple therapy, • People with CF who are unable to tolerate Kaftrio due to side effects, • People with CF who are taking Kaftrio but seeing little or no clinical benefit.

Topic specific questions

12. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	As of 31st December 2023, there were 3,056 people who were not taking Kaftrio (some of these were taking another CFTR modulator). From the data in the UK CF Registry annual report, Cystic Fibrosis Trust cannot determine how many people with CF are not able to tolerate Kaftrio vs those who are not eligible. In people aged 6 and over (n=9316), 7453 people were taking Kaftrio, 1863 not. Of the 1863, 1231 have no record of any CFTR modulator use. 841 of those have a genotype that could be responsive to Kaftrio, and 390 have a genotype Cystic Fibrosis Trust believe is non-responsive to Kaftrio.
13. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (Kaftrio) managed in the NHS?	As Cystic Fibrosis Trust has detailed above, people with CF who are not able to be treated with Kaftrio require an intensive treatment regime, which can be broadly categorised 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. The way people with CF are managed in the NHS has not changed since the introduction of Kaftrio. Regardless of eligibility, care is delivered by a specialist multidisciplinary team.

Equality

14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	A higher proportion of people with CF who are from non-white ethnic backgrounds are currently not eligible for CFTR modulator therapy[8].

Other issues

15. Are there any other issues that you would like the committee to consider?	It is vital this cost-comparison appraisal is conducted swiftly to ensure no delay for people with CF who are not currently benefitting from a CFTR modulator are given the opportunity to access vanzacaftor–tezacaftor–deutivacaftor.

[8] https://www.cysticfibrosis.org.uk/news/shining-a-light-on-those-who-cant-benefit-from-cftr-modulators

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• CF is a rare, genetic condition that causes a wide range of challenging symptoms affecting the whole body. There is no cure, and it is a life-limiting, life-shortening condition. • Living with CF has a significant impact on quality of life. The condition has a high treatment burden, requiring medication and physiotherapy stay well. Reducing the treatment burden of CF has been identified as a top priority for the community. Being unwell can interfere with work, education, and social activities – people living with CF describe there being no day off from the relentless condition. • Access to CFTR modulators has profoundly changed the experience and care of living with CF for those who are eligible and can tolerate the medicines, with a wide range of outcomes transformed, including improved lung function; reduced treatment burden, antibiotic usage and hospital stays; significantly improved quality of life and increased health stability leading to better physical and mental wellbeing. • However, not everyone is eligible for current CFTR modulators, and some people with CF have not been able to tolerate these medicines. For these people, there remains a significant unmet need, with a heavily reduced quality of life.

Thank you for your time.

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Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Chartered Physiotherapist in CF (ACPCF) is a Chartered Society of Physiotherapists (CSP) approved professional network of Physiotherapists and allied professionals working in within the area of physiotherapy in Cystic Fibrosis in the UK and Ireland.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Educational grants received to support annual ACPCF educational study days; Grants received from; Vertex, PARI, Aerogen, Zambon, S-Med and Trudell Medical (£2000 from each company paid between Jan and April 2024). All sponsors in turn received an educational stand for the duration of the event where they could engage and network with the membership. Education grant received to support an ACPCF member place on a Non-Medical Prescribing course: Vertex - £2,000 – 25/04/2024 Zambon - £1,655 – 29/05/24
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent disease progression, Improve life expectancy, function and quality of life. To minimise treatment burden in an already complex medical and therapeutic daily treatment regime. To allow people with CF to live long and fulfilling lives with CF in the background of their life rather than being the main focus.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in the annual rate of FEV1 decline Improvement in BMI and/ or body composition. Reduction in sweat chloride
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**The 10% ineligible** Approximately ~10% of people with CF are ineligible for 'technologies'. Since the 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. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies - ScienceDirect

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Those who are not eligible for current technologies available through the NHS (Ivacaftor, Orkambi, Symkevi and/or Kaftrio) receive multidisciplinary care including: Physiotherapy: · Airway Clearance (twice daily for 10-30 minutes up to multiple times throughout the day as the condition progresses)· Exercise (prescription and support to complete a programme of CV and strengthening exercise) Inhaled therapy (Including inhaled medications to improve clearance of mucus such as Dornase alfa [rhDNase], hypertonic saline, Bronchitol [Mannitol] and bronchodilators, and inhaled antibiotics to suppress

	chronic infection) · Oxygen and Non-Invasive Ventilation (NIV) for respiratory failure · Treatment of musculoskeletal complaints associated with living with CF (such as postural problems and stress incontinence etc.) There is a high treatment burden for people with CF, particularly with respect to their physiotherapy routine, people are often prescribed multiple inhaled/nebulised treatments (report attached) to complete alongside airway clearance, exercise and oral medications1. Part of physiotherapy treatment will be to support the patient with their routine and habit formation. 1. The cost of cystic fibrosis - June 2022 p41Other important aspects of MDT care: · Nutritional repletion (for example, pancreatic enzymes and nutritional supplements); · Treatment of acute infections; · Suppression of chronic infection including use of inhaled antibiotics; · Suppression of inflammation (for example, steroids, high dose ibuprofen) · Organ transplantation, including lung, liver or pancreas. · Psychological support and intervention · Social worker supportThose who are eligible for current technologies available through the NHS:.The appropriate modulator therapy should be offered to all with eligible gene variants once a diagnosis of CF has been confirmed and the person with CF is at the appropriate age (e.g. Ivacaftor from age of 4 months, Orkambi from age of 1, Kaftrio from age of 2).Monitoring should be undertaken to screen for tolerance, side effects and clinical stability..Routine MDT care as outlined above should continue to be reviewed and individualised for each person taken into consideration the multidisciplinary care as outlined above.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis Fourth edition December 2020.pdf • Standards for the clinical care of children and adults with cystic fibrosis in the UK 2024 • Cystic fibrosis (nice.org.uk) • Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis - Journal of Cystic Fibrosis There are various other CF Trust consensus documents followed in the treatment of people with CF.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The 2024 Standards for the clinical care of children and adults with cystic fibrosis in the UK are being implemented by specialist services. The NHSE cystic fibrosis review is currently underway but not yet ready to report.
9c. What impact would the technology have on the current pathway of care?	The introduction of Vanzocaftor – texacaftor – deuticaftor would offer a futher modulator option for those with eligible gene variants. It would offer a modultor option for a futher 31 gene variants in comparison to current options. The trial data also shows when compared to Elexecaftor-Tezacaftor-Ivacaftor:

	- An additional 31 gene variants are responsive to Vanzocaftor – texacaftor – deuticaftor which are not currently indicated for use of modulator therapy available - Vanzocaftor – tezacaftor – deuticaftor showed further reduction in sweat chloride towards diagnostic threshold (<60mmol/L) and closer towards normal levels (<30mmol/L). Reduction in sweat chloride can lead to improved outcomes. - Vanzocaftor – tezacaftor – deuticaftor is to be taken only once a day in comparison to twice a day with other modulator therapies currently approved. - Absolute change in FEV_1 % predicted from baseline has been used as a primary endpoint in trials and a non inferior response was shown Vanzacaftor–tezacaftor–deutivacaftor for children aged 6–11 years with cystic fibrosis (RIDGELINE Trial VX21-121-105): an analysis from a single-arm, phase 3 trial - The Lancet Respiratory Medicine Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials - The Lancet Respiratory Medicine In addition: - The once-a-day dosing regimen of Vanzocaftor – texacaftor – deuticaftor may offer benefit in improved outcomes for those currently struggling to maintain twice daily regime, and reduces the burden of treatment. Some people with CF have had an adverse reaction or suboptimal response to Elexecaftor-Tezacaftor-Ivacaftor and therefore introduction of Vanzocaftor – tezacaftor – deuticaftor allows an opportunity to see if improved tolerance and/or clinical outcomes can be achieved.What does the expanding CFTR modulator programme mean for people with cystic fibrosis? - The Lancet Respiratory Medicine
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The same pathway for initiation and monitoring would be followed as currently used for modulator therapy.
10a. How does healthcare resource use differ between the technology and current care?	Unknown price of Vanzocaftor – tezacaftor – deuticaftor however if similar or lower price then no difference.
10b. In what clinical setting should the technology be used? (For example, primary	Specialist CF centres

or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There would initially be increased blood monitoring when swapping patients stable on Elexecaftor-Tezacaftor-Ivacaftor to Vanzocaftor – texacaftor – deuticaftor and increased workload in facilitating homecare prescriptions and delivery
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The introduction of Vanzocaftor – texacaftor – deuticaftor would offer a further modulator option for those with eligible gene variants. It would offer a modulator option for a further 31 gene variants in comparison to current options. The trial data also shows when compared to Elexecaftor-Tezacaftor-Ivacaftor: - Vanzocaftor – tezacaftor – deuticaftor showed further reduction in sweat chloride towards diagnostic threshold (<60mmol/L) and further towards normal levels (<30mmol/L). Reduction in sweat chloride can lead to improved outcomes. - Vanzocaftor – tezacaftor – deuticaftor is to be taken only once a day in comparison to twice a day with other modulator therapies currently approved.
11a. Do you expect the technology to increase length of life more than current care?	Yes if improved adherence and further reduction of sweat chloride can be achieved
11b. Do you expect the technology to increase health-related quality of life more than current care?	A once daily dosing regimen reduces the burden of treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The introduction of Vanzocaftor – texacaftor – deuticaftor would offer a further modulator option for those with eligible gene variants. It would offer a modulator option for a further 31 gene variants in comparison to current options.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Easier for patients as reduced dosing regime There would initially be increased blood monitoring when swapping patients stable on Elexecaftor-Tezacaftor-Ivacaftor to Vanzocaftor – texacaftor – deuticaftor and increased workload in facilitating homecare prescriptions and delivery
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same criteria as with initiation of current modulator therapy
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not that are aware of
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The introduction of CF modulator therapy has been transformational, offering huge benefits in terms of disease progression, quality of life and the potential to live a normal life expectancy. The addition of Vanzocaftor – texacaftor – deuticaftor would offer a further modulator option for those with eligible gene variants who currently have not access to modulator therapy, and offer an option for improved outcomes in those unable to tolerate and/or having suboptimal response to Elexecaftor-Tezacaftor-Ivacaftor

16a. Is the technology a 'step-change' in the management of the condition?	Data so far has shown Vanzocaftor – texacaftor – deuticaftor is non inferior with respect to key outcomes when compared to Elexecaftor-Tezacaftor-Ivacaftor
16b. Does the use of the technology address any particular unmet need of the patient population?	An additional 31 gene variants are responsive to Vanzocaftor – texacaftor – deuticaftor which are not currently indicated for use of modulator therapy available
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Trial data so far has shown a similar safety profile to Elexecaftor-Tezacaftor-Ivacaftor

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	A reduction in the annual rate of FEV1 decline Improvement in BMI and/ or body composition. Reduction in sweat chloride
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	Not aware of any new evidence
21. How do data on real-world experience compare with the trial data?	There is currently no real-world data on Vanzocaftor – texacaftor – deuticaftor

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	From CF Trust registry data 2023 1,231 individuals age 6 and above were recorded as no record of CFTR modulator use UK Cystic Fibrosis Registry - 2023 Annual Data Report
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	As outlined above in section 9

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	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. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies - ScienceDirect
24b. Consider whether these issues are different from issues with current care and why.	Same as current

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Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Access to Vanzocaftor – texacaftor – deuticaftor would offer a modulator option for a further 31 gene variants in comparison to current options. In addition would offer an option for use with those unable to tolerate Elexecaftor-Tezacaftor-Ivacaftor • The once a day dosing regime of Vanzocaftor – texacaftor – deuticaftor may offer benefit in improved outcomes for those currently struggling to maintain twice daily regime, and reduces the burden of treatment. • Data has shown potential further reduction in sweat chloride with Vanzocaftor – texacaftor – deuticaftor compared to Elexecaftor-Tezacaftor-Ivacaftor – this may lead to improved clinical outcomes and life expectancy • Data so far has shown Vanzocaftor – texacaftor – deuticaftor is non inferior with respect to key outcomes when compared to Elexecaftor-Tezacaftor-Ivacaftor • Trial data so far has shown a similar safety profile to Elexecaftor-Tezacaftor-Ivacaftor

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About you

1. Your name	1 [redacted] and 2 [redacted]
2. Name of organisation	British Dietetic Association (BDA) Cystic Fibrosis (CF) Specialist Group
3. Job title or position	1 [redacted], 2. [redacted].
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** (nutritional evidence) Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BDA CF Specialist Group is the professional group representing dietitians caring for people with CF through all life stages. The group is part funded via individual annual membership fees paid to the BDA, who subsequently provide an annual income for the specialist group. Members are supported through education events, peer support and educational awards and grants.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of CFTR modulators is to reach normal CFTR function. Efficacy outcomes of Vanzacaftor-tezacaftor-deuticaftor (VTD) are likely to provide similar or greater overall health benefits to patients than Elexacaftor-tezacaftor-Ivacaftor (ETI) in terms of improvements in lung function and superiority in terms of further restoration of CFTR function towards normal. In children this may have the potential to prevent development or progression of disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, in those for whom the current CFTR modulators are unsuitable.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	ETI is the current standard of care available for all patients aged 2y and older with at least one DF508 mutation, which is the most common mutation in the UK CF population. Ivacaftor, another highly effective modulator, is available for a limited number of patients with G551D and other class 3 mutations. All modulators have a twice daily dosing schedule and require to be taken with a fat-containing meal. An estimated 10% of patients do not qualify for any of the CFTR modulators currently available.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. Southern *et al.* Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. 2023. 22. 17-30.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In Wales, the Welsh Government require that all patients commencing ETI have a pre and post initiation sweat chloride assessments in order to show efficacy. Post sweat chloride assessment occurs initially at 6 months and then annually thereafter.
9c. What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The proposed CFTR modulator VTD is likely to be used in the same way with the potential to be applicable for a wider CFTR gene variant population.
10a. How does healthcare resource use differ between the technology and current care?	With the introduction of VTD there will be a greater requirement / demand on healthcare resource in the initial phases of monitoring effects of VTD.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care seems to be the most appropriate setting, managed by the specialist CF MDT care teams with the expertise to provide careful monitoring and review.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It is assumed that VTD will use the currently agreed and established use. However, investment will be required in relation to communicating the potential of this new CFTR modulator to patients and carers. Additionally, it is likely that more assessments and reviews will required e.g. blood tests and initially more frequent patient visits to their CF care centre to assess tolerance of the drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. There are several population groups who may have significant clinical improvements to their health from VTD introduction. Those with rare CFTR gene variants not currently supported by ETI might respond to VTD and may potentially be transformative. Those unable to tolerate ETI may tolerate VTD better. Those patients who tolerate ETI but have not experienced significant benefits to their nutritional or respiratory health despite good adherence, may have greater benefit with VTD. As VTD is delivered as a 'once-a-day' dose, those patients who have struggled with adherence to twice daily dosing ETI may benefit from reduced treatment burden.
11a. Do you expect the technology to increase length of life more than current care?	Life expectancy has significantly increased in the era of ETI. The UK CF Registry 2023 identifies that median predicted survival has increased from 50.6 years in the pre ETI era (2016-2020) to 64.1 years (2019-2023). With the introduction of VTD potentially benefiting a greater CFTR gene variant range this might contribute to a further improvement in survival. Longterm impact of VTD on disease progression is not yet known.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. A simpler once daily dosing regimen will reduce treatment burden for patients, which is important when considering quality of life and lifelong treatment burden.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. There are several population groups who may benefit significantly from VTD introduction. VTD may potentially be transformative for a small number of rare CFTR non-DF508 gene variants not currently supported by ETI. Those patients who are eligible for ETI but are unable to tolerate. As VTD is delivered as a 'once-a-day' dose, those people who have struggled with adherence to twice daily dosing ETI may benefit from reduced treatment burden. Those patients who tolerate ETI but have not experienced significant benefits in respiratory or nutritional outcomes.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As VTD is a once-a-day preparation it is anticipated that adherence will improve for those that have struggled with the twice-daily ETI adherence. Initially, on commencing VTD there is likely to be a requirement for additional monitoring, including visits to the individuals respective CF care centre, which will include blood tests amongst other assessments by the CF specialist MDT.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We assume locally agreed guidance regarding starting / stopping medication will be based on tolerance of VTD, adherence and measured outcomes. In Wales it is likely that post VTD annual sweat chloride assessment, identifying efficacy of the modulator will be required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Additional health markers not likely to be captured by the QALY may include an improvement in energy levels, prolonged stability of health, reduced treatment burden.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Although highly effective CFTR modulators are available for most people with CF with the availability of ETI, it is anticipated that introducing a once-a-day therapy will benefit a wider population. Additionally, there is the potential that some effects of the current ETI such as recognised weight gain, may be lessened due to the single dose.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Moving to once-a-day dosing may be seen as a step-change as this improves treatment burden, in addition to being able to be provided to a wider range of genetic mutations.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. It is believed that VTD will be appropriate for a greater number of CFTR gene variants not currently qualifying for ETI.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects or side effects may result in a temporary pause, reduction in dose or complete termination of the provision of VTD-I. Considering the individual, in addition to not experiencing an improvement in QOL and measured outcomes they may well suffer psychologically.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	QOL, lung function, hospitalisation events (exacerbations), IV courses / year, sweat chloride, nutritional status e.g. BMI.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Considering nutritional health, BMI is routinely included as an outcome measure. However, BMI only informs on quantity of weight and is unable to inform on quality of weight, namely body composition (fat mass and fat free mass). Some recent published evidence exploring the effect of ETI on body composition (Proud and Duckers 2023, Boat *et al* 2025) recommend that due to individual variation in response to ETI there is a need to monitor body composition. Treatment burden.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of. Phase 3 studies of VTD indicate it is a non-inferior and safe medication.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatments since the publication of	Yes. Three phase 3 clinical trials: SKYLINE Trial VX20-121-102) and SKYLINE Trial VX20-121-103 testing efficacy and safety of VTD versus ETI in patients aged 12y and older indicate non-inferior and

NICE technology appraisal guidance TA988?	safe comparison for VTD compared to ETI. RIDGELINE Trial VX21-121-105 phase 3 trial evaluated safety and efficacy in children aged 6-11y found non-inferior to ETI and further improvement in CFTR function.
21. How do data on real-world experience compare with the trial data?	

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	Approximately 10%.
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	Usual care, requiring a greater treatment burden, including nutritional support and more frequent hospital admissions.

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Although it is anticipated that VTD may be applicable for a wider CFTR gene variant there are still likely to be a minority of individuals unable to benefit from VTD.
24b. Consider whether these issues are different from issues with current care and why.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Expanded range of CFTR gene variants potentially able to have VTD • Potential to help those currently unable to tolerate or not doing well on ETI • Reduced treatment burden with once-a-day dosing • Clinical trials indicating non-inferior comparison to current ETI •

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Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Society
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	BTS is the professional membership organisation representing respiratory health care professionals.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No funding received from manufacturers.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve health related quality of life, mortality, lung function, reduce respiratory exacerbations (including need for hospitalisation and intravenous antibiotics), improve body mass index of people living with CF. In addition to minimise treatment burden in an already complex medical and therapeutic daily treatment regime.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Published trial data suggests VTD therapy is non inferior to ETI therapy. However *in vitro* data shows an increase in CFTR function and the phase 3 trial showed a greater reduction in sweat chloride in a proportional of individuals, which is likely to be clinically relevant as sweat chloride is an indirect biomarker of CFTR function. .
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Would welcome expansion of available modulators for this patient group as it would make modulators available for some patients previously not eligible and some who cannot tolerate current modulators and those who have not benefitted from current modulators. It may also improve adherence as once a day and MAY improve clinical response in individuals with poorer response to ETI.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Eligible people with CF would be offered ETI therapy from their CF centre as part of their CF Care. CF patients not eligible for modulators receive best supportive care, including airway clearance techniques, inhaled therapies, nutritional support, and antibiotics. Some patients may require lung transplantation due to progressive disease
9a. Are any clinical guidelines used in the	NICE CF guidelines, UK CF Trust Guidelines 2024, European Standards of care 2024, CF toolkit

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is very clearly defined Standard protocols across UK with senior engagement and collaboration Personal experience from Wales as well as feedback from clinical teams in England
9c. What impact would the technology have on the current pathway of care?	Offer treatment options to some people with CF where modulator not currently available/ tolerated or poorer response to ETI and potentially improve adherence as once daily vs twice daily. It may also reduce healthcare utilisation by lowering frequency of exacerbations
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Used in the same way- but once daily with potentially improved adherence There may be benefit for those with higher sweat chloride levels / poorer response to ETI
10a. How does healthcare resource use differ between the technology and current care?	Not changed when patients are on VTD and stable. There would initially be a minimal increase in blood monitoring when swapping patients stable on ETI to VTD and some increased workload in facilitating a switch for homecare prescriptions and delivery. Transitioning stable ETI patients to VTD will require additional clinic visits
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist CF clinics All people with CF attend a regional specialist CF Unit with treatment being delivered through the MDT.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There would initially be increased blood monitoring when swapping patients stable on ETI to VTD and increased workload in facilitating homecare prescriptions and delivery. Additional education/training for CF teams on transitioning patients and managing potential side effects may be required.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes- Would welcome expansion of available modulators for this patient group especially as would make modulators available for some patients previously not eligible and some who cannot tolerate current modulators and those who have not benefitted from current modulators. It may also improve adherence as once a day which may lead to improved long term outcomes
11a. Do you expect the technology to increase length of life more than current care?	No long term evidence that I am aware of but potentially improved sweat chloride in trials which might confer better long term outcomes for patients vs ETI therapy. It will be life changing for those who are able to access treatment and were previously not eligible for ETI. *In vitro* data and increased reduction in sweat chloride suggest the drug may be more effective in the longer term. If improved adherence with once daily regimen, outcomes would improve. Long-term data is not yet available, but improvements in lung function , reduction in sweat chloride and adherence could translate to prolonged survival
11b. Do you expect the technology to increase health-related quality of life more than current care?	No long term evidence that I am aware of but potentially improved sweat chloride in trials which might confer better long term outcomes for patients vs ETI therapy. It will be life changing for those who are able to access treatment and were previously not eligible for ETI. The once daily dosing regimen reduces the burden of treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	May be particularly beneficial for adolescents and younger adults who struggle with treatment burden and adherence to twice-daily ETI

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are	There would initially be increased blood monitoring when swapping patients stable on ETI to VTD and increased workload in facilitating homecare prescriptions and delivery. For people with CF it may result in potential simplification of treatment regimen (once daily vs. twice daily) may increase adherence, especially in younger or working-age populations.

there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	no
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes- offering new therapy to some and potentially a treatment option for those who could not tolerate ETI therapy and once vs twice a day benefits. The longer term aims will be to further increase CFTR expression towards levels of carriers and limit disease progression.

16a. Is the technology a 'step-change' in the management of the condition?	yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes- those not eligible for ETI previously or who didn't respond or could not tolerate
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	VTD therapy appears to have acceptable safety profile

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	na
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes A reduction in the annual rate of FEV1 decline . Improvement in BMI and/ or body composition.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	na
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Possible additional benefit health economics- family/ carers input required to assist patients may be reduced due to health improvements seen for some patients. Patient-reported outcome measures (PROMs) may provide additional insight into adherence, quality of life, and treatment burden reduction
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	no
21. How do data on real-world experience compare with the trial data?	RWE published on ETI has suggested similar clinical benefits to the trial evidence on ETI. I am not aware of RWE on VTD

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	Approximately 10-15% of UK CF Population (of the 11,000)
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	Best supportive care with other non modulator therapies (Symptomatic management with airway clearance, nutritional support, long-term antibiotics, and in severe cases, lung transplantation)

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
24b. Consider whether these issues are different from issues with current care and why.	no

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• VTD may offer a modulator option to some UK CF patients not currently eligible to ETI • Some patients have not been able to tolerate ETI but might tolerate VTD • Some patients have not responded to ETI therapy but might respond to VTD • Once daily dosing of VTD vs twice daily for ETI might show benefit in term of adherence • Improved sweat chloride change on VTD might potentially lead to improved longer term outcomes—but no data to show this yet

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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About you

1. Your name	[redacted] & [redacted]
2. Name of organisation	Cystic Fibrosis Nursing Association
3. Job title or position	[redacted] & [redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Cystic Fibrosis Nursing Association was established in 1988. We are dedicate to providing opportunities for nurses in the cystic fibrosis specialism, and improving the lives of patients, families, and carers.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Vertex provided lunch for our committee meeting (March & Sept 2024). Unknown amount, food/drink only provided.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevent progression, stop progression in those with establish disease
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Prevention/slowing of disease/stability. Reduction in sweat chloride
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	People with CF with genotypes not currently eligible for genetic modifiers

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Kaftrio
9a. Are any clinical guidelines used in the	Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK Cystic Fibrosis Trust Standards of care.pdf

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway well defined
9c. What impact would the technology have on the current pathway of care?	Increased number of patients eligible Reduced treatment burden with once-a-day treatment Improved compliance with once-a-day treatment ?Possible future benefit with further reduced sweat chloride
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	Increased number of patients eligible Reduced treatment burden with once-a-day treatment
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Px by specialist clinic/secondary
10c. What investment is needed to introduce the technology? (For example,	None, roll replacement of current treatment

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Reduction in treatment burden/increased compliance can have clinical benefit. ?Further reductions in sweat chlordie will have clinical impact.
11a. Do you expect the technology to increase length of life more than current care?	Unsure, only short term data currently available, evidence would suggest reduced sweat chloride will reduce complications associated with disease progression.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, Increased number of patients eligible Improved compliance as od regime Long term effects of reduced sweat sodium chloride
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, more beneficial to those that currently don't qualify for genetic modifiers.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Concomitant treatments as per current treatment. Once a day regime easier for people with CF

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Increased blood monitoring (as is in paediatrics only just established)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	QoL with reduced treatment burden
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	For those who aren't currently eligible and will be, yes For those already established on kaftrio, no.
16a. Is the technology a 'step-change' in the	Unsure of 'step change' phrase meaning

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Those that aren't eligible, those struggling with compliance, those that were unable to tolerate Kaftrio
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Same as current treatment

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not currently used so unable to comment
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	No
21. How do data on real-world experience compare with the trial data?	As above not in use so unable to comment.

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	Unable to comment
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	As per guidelines included above.

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
24b. Consider whether these issues are different from issues with current care and why.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Increased number of patients eligible • Reduced treatment burden with once-a-day treatment • Improved compliance with once-a-day treatment • Possible future benefit with further reduction in sweat chloride •

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About you

1. Your name	[redacted]
2. Name of organisation	**Neonatal and Paediatric Pharmacist Group**
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	**Neonatal and Paediatric Pharmacist Group** We are a specialist interest group for Paediatric and Neonatal Pharmacists, operating as a charitable organization primarily funded by our members, although we occasionally receive limited support from pharmaceutical companies. We maintain close collaboration with The Royal College of Paediatrics and Child Health (RCPCH) and the Royal Pharmaceutical Society.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Enhance overall CF health, particularly by reducing CF morbidity and mortality related to respiratory conditions. Increasing evidence supports additional benefits, such as the reversal of pancreatic insufficiency, improved glycemic control, and better management of bowel issues, especially in younger populations.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Change in ppFEV1, rate of pulmonary exacerbations, sweat chloride, CFQ-R scores to assess changes in quality of life and weight/BMI. Ability to go to school with a good school attendance and undertake PE etc.. To continue learning as normal children.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are 2 main unmet needs: 1. Individuals with CF who have certain CFTR variants are not eligible for treatment with highly effective CFTR modulators, which uniquely alter disease progression unlike any other available therapies. 2. Even among those who are eligible, some cannot tolerate these treatments or take the full dose due to adverse effects.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Children with CF receive specialist care at CF centres, where a multidisciplinary team is appropriately staffed to address their specific needs. They attend outpatient clinics at a frequency tailored to their individual requirements, following the CF Trust's Standards of Care. Inpatient care may be required, typically for intravenous antibiotics and intensive multidisciplinary support during a pulmonary exacerbation. CF is widely recognized as a highly burdensome disease, with treatments including nebulized or inhaled antibiotics and mucolytics, CFTR modulators for those who are eligible and can tolerate them, long-term macrolides, daily airway clearance therapy, regular exercise, and nutritional support. Those who progress to severe respiratory disease may need long-term oxygen therapy, non-invasive ventilation, and evaluation for double lung transplant eligibility.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	CF Trust Standards for the clinical care of children and adults with cystic fibrosis in the UK, 2024 NICE Guideline NG78 – Cystic fibrosis: diagnosis and management, 2017
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined with shared care arrangements
9c. What impact would the technology have on the current pathway of care?	Minimal at most as it will be used in the same way as other CFTR modulators

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, similar to other CFTR modulators
10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource use is expected to remain unchanged for people with CF already taking elexacaftor/tezacaftor/ivacaftor, as clinical trials showed the new technology to be non-inferior, providing comparable improvements in lung function, pulmonary exacerbation rates, and quality of life. For those unable to take elexacaftor/tezacaftor/ivacaftor or a less effective CFTR modulator due to intolerance, vanzacaftor/tezacaftor/ivacaftor is likely to reduce healthcare resource use. This is because it enables similar improvements in respiratory function, exacerbation rates, and quality of life as the most effective currently available CFTR modulator.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary specialist CF centres and network centres thereof as per current practice for CFTR modulators
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	For people with CF who are currently taking elexacaftor/tezacaftor/ivacaftor, switching to the new technology is unlikely to result in a clinically meaningful difference, as phase 3 trials showed similar outcomes. However, those struggling with adherence may benefit from the new technology's simpler administration schedule. For those unable to take elexacaftor/tezacaftor/ivacaftor due to intolerance, the new technology is expected to provide a significant clinical benefit, as observed in phase 3 trials of elexacaftor/tezacaftor/ivacaftor, given its comparable effectiveness. These findings are generalizable to the new treatment.
11a. Do you expect the technology to increase length of life more than current care?	Based on current trial data, it is difficult to determine the impact on life expectancy, as the phase 3 trial was designed as a non-inferiority study. However, for people with CF already taking elexacaftor/tezacaftor/ivacaftor, it is unlikely to significantly affect life expectancy due to the similar responses observed. For individuals who are unable to take elexacaftor/tezacaftor/ivacaftor, or cannot tolerate the full dose due to an adverse reaction, the new treatment could have a significant impact on life expectancy. If they can tolerate it, the new technology is equally effective as the current benchmark triple CFTR modulator combination, which is much more effective than dual or single modulator treatments or standard care without CFTR modulators.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Trial data shows that the new technology increased the CFQ-R respiratory domain score by 2.3 after 24 weeks, with a treatment difference of 2.4 compared to elexacaftor/tezacaftor/ivacaftor. While this is a positive outcome, it falls below the minimal clinically important difference of 4 points for this domain. As a result, people with CF who are already taking elexacaftor/tezacaftor/ivacaftor are unlikely to experience a significant change in quality of life. However, for those unable to take elexacaftor/tezacaftor/ivacaftor, or a full dose, due to adverse drug reactions and who are instead on a less effective CFTR modulator or standard care (depending on their CFTR variants), the new treatment would lead to a substantial improvement in quality of life. This aligns with the phase 3 trial

	results for elexacaftor/tezacaftor/ivacaftor, as the new technology is equally effective and these findings are generalizable.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As mentioned previously, children who are unable to take elexacaftor/tezacaftor/ivacaftor, or a full dose, due to adverse drug reactions would benefit more from this new technology compared to those who tolerate elexacaftor/tezacaftor/ivacaftor well. Additionally, people with CF who struggle with adherence to elexacaftor/tezacaftor/ivacaftor may also experience greater benefits from the new treatment due to its simpler dosing regimen—requiring just one tablet once daily rather than multiple doses of different medications.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The new technology will be more convenient for patients, as it consists of two tablets in the morning containing a combination of three CFTR modulators. In contrast, the current benchmark CFTR modulator also requires two tablets in the morning with three CFTR modulators but additionally requires an evening dose of a single CFTR modulator. The effect on healthcare professionals will be neutral as whilst LFT monitoring requirements may increase for vanzacaftor / tezacaftor/ivacaftor following changed to the US license for elexacaftor/tezacaftor/ivacaftor this is equal across both the new technology and elexacaftor/tezacaftor/ivacaftor.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment discontinuation will follow the SPC guidelines for liver function test (LFT) monitoring. In many cases, treatment is reintroduced once LFT levels stabilize, but if they rise above the specified thresholds again, it would be permanently discontinued. This is unlikely to require additional testing beyond the mandated LFT monitoring frequency outlined in the SPC.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Given that elexacaftor/tezacaftor/ivacaftor has demonstrated more health benefits than what was observed in phase 3 clinical trials, it is likely that the new technology will also offer health benefits that may not be fully captured in the QALY calculation. However, this would apply only to individuals who are not currently taking elexacaftor/tezacaftor/ivacaftor due to intolerance, not to those who are already on it, as the treatments appear equally effective in trials. Therefore, this effect would be neutral for those currently taking elexacaftor/tezacaftor/ivacaftor.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No, because the only significant difference between the new technology and elexacaftor/tezacaftor/ivacaftor is the simpler administration schedule, which is likely to improve treatment adherence. However, this change is not clinically innovative.
16a. Is the technology a 'step-change' in the management of the condition?	No, for most people, as elexacaftor/tezacaftor/ivacaftor represented a significant advancement in managing the condition, and they are already taking it. However, the new technology has shown to be

	equally effective in clinical trials and would represent a major breakthrough for those who cannot take elexacaftor/tezacaftor/ivacaftor due to intolerance.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, it provides an alternative treatment for individuals who couldn't tolerate elexacaftor/tezacaftor/ivacaftor due to an adverse drug reaction, and it is equally effective based on trial data.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	If treatment is discontinued due to an adverse drug reaction, a significant decline in lung function, quality of life, and an increase in pulmonary exacerbations can be expected, as CFTR function will quickly return to pre-treatment baseline levels. If treatment is continued despite a mild adverse drug reaction, in accordance with the patient's preferences, they may experience a reduced quality of life, depending on the severity of the reaction. However, the management of the condition will remain unchanged.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, participants in the trial who were not already taking it were given a 4-week run-in period with the current best available care in the UK. The trial design followed the same approach as previous CFTR modulator trials.
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	FEV1, rate of pulmonary exacerbations, CFQ-R scores (especially the respiratory domain to assess quality of life), adverse events, sweat chloride levels, and weight/BMI were all measured and reported, except for weight/BMI, for which only baseline data is available.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	NO
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	NO
21. How do data on real-world experience compare with the trial data?	To my knowledge, real-world data for the new technology is not yet available. However, an increased incidence of mental health side effects has been observed with elexacaftor/tezacaftor/ivacaftor after the

	trials. Lung function improvements in the real world for elexacaftor/tezacaftor/ivacaftor have been similar to those observed in clinical trials.

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	It is estimated that about 8-10% of people with CF are either ineligible for elexacaftor/tezacaftor/ivacaftor due to their CFTR variants or cannot tolerate it. According to the CF registry's 2023 annual data report, 13.5% of individuals aged 6 and older had no record of using any CFTR modulator.
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	This depends on their CFTR variants. Individuals eligible for one or more of the following—tezacaftor/ivacaftor, lumacaftor/ivacaftor, or ivacaftor monotherapy—will be prescribed the most effective, yet tolerable, CFTR modulator for their specific needs. Although these options are less effective than elexacaftor/tezacaftor/ivacaftor, they still provide benefits over best supportive care, which does not include a CFTR modulator. Best supportive care consists of nebulized/inhaled antibiotics, nebulized/inhaled mucolytics, long-term macrolide therapy, regular airway clearance therapy, exercise, nutritional support, and intravenous or oral antibiotics to treat pulmonary exacerbations.

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Based on trial data, the new technology appears to be as effective as the current benchmark highly effective CFTR modulator combinations. • Trial results showed a slight reduction in sweat chloride levels with the new technology compared to the current benchmark. While sweat chloride is an accepted surrogate marker for improved CFTR function, this did not translate into better outcomes in terms of FEV1, exacerbation rates, or quality of life scores in the trials. • An advantage of the new technology over the current benchmark is its once-daily dosing with a single medication, compared to twice-daily dosing with two separate formulations. This is likely to improve adherence to treatment. • The new technology provides an alternative treatment option for individuals who cannot tolerate the current benchmark CFTR modulator combination due to an adverse drug reaction. • In trials, the new technology demonstrated a safety profile comparable to the current benchmark CFTR modulator.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	UK CF Medical Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK CF Medical Association has over 300 members, physicians with an interest in CF. The association is free to join and has no support from pharma or any other commercial agencies The UK CFMA has administrative support from the UK CF Trust, but acts as an independent voice for CF Physicians.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No conflicts of interest for [redacted]
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Vanzacaftor-Tezacaftor-Deutivacaftor (V-T-D) corrects the molecular defect caused by certain CFTR gene variants, including F508del (the commonest variant associated with CF). Historically, CF care has been based on addressing the sequelae of the molecular defect, especially nutritional and respiratory complications. CFTR modulators are the first class of drug that directly correct the underlying molecular defect. The UK CFMA welcomes the expansion of the CFTR modulator programme with the introduction of the new triple therapy, V-T-D.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in key clinical outcomes compared to standard therapy - HRQoL - Respiratory Function (FEV1) - Nutritional parameters - Survival Non-inferiority compared to Elexacaftor-Tezacaftor-Ivacaftor (E-T-I)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	These four patient populations are likely to benefit a. People with CF who have *CFTR* gene variants that are potentially responsive to V-T-D, but are not eligible for E-T-I. b. E-T-I eligible patients that did not tolerate E-T-I because of adverse events, may tolerate V-T-D. c. Patients established on E-T-I, who have experienced minimal or no improvement in clinical outcomes, may benefit from a switch to V-T-D. d. Some patients have struggled with adherence for various reasons and may benefit from a switch to a once-a-day combination.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	People with CF receive specialised multi-disciplinary care. Therapies addressing the sequelae of the molecular defect - PERT - Antibiotics (oral and nebulised) - Mucolytics - Vitamins - ETC Therapies that correct the underlying molecular defect - CFTR modulator therapies
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	ECFS guidelines and standards Recent UK Standards of Care Document
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is clear and there is a consistent approach to management across the UK Patients who are eligible for V-T-D should have access to this therapy
9c. What impact would the technology have on the current pathway of care?	The UK CFMA welcomes expansion of the modulator programme
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used together with other available CFTR modulator therapies, as an adjunct to standard therapy. A national NIHR funded trial is ongoing examining if pwCF established on E-T-I therapy can safely rationalise their standard therapy (the CF STORM study, data lock expected in September 2025).

10a. How does healthcare resource use differ between the technology and current care?	The new V-T-D therapy is a once-a-day dosing regimen. The trial data in adults and older children suggest V-T-D is non-inferior compared to E-T-I with respect to key clinical outcomes.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Four patient groups may benefit significantly (see question 8)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be some additional monitoring needed for the transfer of patients onto V-T-D
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	See question 8 above
11a. Do you expect the technology to increase length of life more than current care?	Yes, survival is predicted by FEV1, which is improved by these therapies (E-T-I and V-T-D). The trial data suggest that V-T-D is non inferior compared to E-T-I
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, same as for E-T-I compared to standard care

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	For patients with non-eligible CFTR gene variants, the intervention will not be appropriate

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No change
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For patients who have had a good clinical response to E-T-I, the evidence to support transfer to V-T-D is less clear. Decisions to transfer should be made jointly with the patient and their family reviewing the evidence.
15. Do you consider that the use of the technology will result in any	Other societal benefits (less time off work/college) and reduced health service utilisation.

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Innovative agents that will require post market surveillance
16a. Is the technology a 'step-change' in the management of the condition?	Not a step change but a significant addition to the CF armamentarium
16b. Does the use of the technology address any particular unmet need of the patient population?	For the four patient groups listed above, V-T-D represents a potentially transformational therapy.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	These agents have a good safety profile. As the trials were undertaken on patients, stable on E-T-I, there will need to be careful post market surveillance for V-T-D

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, on the whole, they are translatable. Patients in the trials were stable on E-T-I so the intervention has not been tested on patients who are not able to tolerate E-T-I
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	HRQoL Change in FEV1 Both measured in the two non-inferiority trials
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Sweat chloride levels were measured. These may predict response, but more information needed on the relevance of this outcome to longer term clinical impact
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Some reporting of mental health issues (see MHRA yellow card scheme and EMA licence warning, (see PMID 39299889))
19. Are you aware of any relevant evidence that might not be found by a	6-11 trial is open label safety trial and so does not provide reassurance of efficacy in this age group

systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	Two papers discussed in this editorial (PMID 39805295)
21. How do data on real-world experience compare with the trial data?	NA

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	About 5-40 % depending on the frequency of F508del in the population
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	About 5-10% (see UK registry data from the UK CF Trust)

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	People with CF from a non-Caucasian background are more likely to have *CFTR* gene variants that are not eligible for V-T-D (or other modulator therapy)
24b. Consider whether these issues are different from issues with current care and why.	V-T-D will cover more variants

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	1) The published trial data suggest that for older children and adults who are stable and established on elexacaftor-tezacaftor-ivacaftor (E-T-I), vanzacaftor-tezacaftor-deuterated ivacaftor (V-T-D) is non inferior (non-inferiority margin, 3% for the primary outcome, change in FEV1). 2) For children (6-11 years), established on E-T-I, V-T-D appears to have an acceptable safety profile. 3) Four patient populations may benefit significantly (see question 8), 4) For people with CF on E-T-I who are stable and have enjoyed good improvement in clinical outcomes, there is less clear evidence to switch to V-T-D. The CF team should work in partnership with these individuals and their families to make a shared decision on any change to V-T-D. 5) The once-a-day dosing for V-T-D is a positive factor for people with CF and their families.

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Cost Comparison Appraisal

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

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About you

1. Your name	[redacted]
2. Name of organisation	Cystic Fibrosis Pharmacy Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	We are the specialist interest group for all CF pharmacy professionals in the UK. We do not charge any membership fees to join our group. We also welcome members from across the world to participate in our meetings and forum discussions. We are the contact for the CF Trust Clinical Advisory Group when they require advice for medication related issues in people with CF. We do not receive any funding for our group, and we do not hold any funds in any form of bank account.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve overall CF health but the majority of this will be from a respiratory perspective given that CF morbidity and mortality is mostly due to respiratory pathology. Then after improving health CFTR modulators should slow the progression of CF respiratory disease. It has not yet been confirmed in long term data if highly effective modulators stop this progression. Initial short term real-world data is positive but long term data is not available yet due to the timescales involved.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	CFTR modulator treatment response is usually assessed on the following parameters: change in ppFEV1, rate of pulmonary exacerbations, sweat chloride, CFQ-R scores to assess changes in quality of life, and in particular the respiratory domain, and weight/BMI A treatment response in the above parameters similar to the results obtained for Symkevi and Orkambi should be viewed as clinically significant. These two CFTR modulator formulations are considered effective treatment and are approved for use in the NHS. However, they are the least effective of the currently available CFTR modulators. A treatment response similar to ivacaftor monotherapy and elexacaftor/tezacaftor/ivacaftor, the current benchmark highly effective CFTR modulators, should therefore be considered as highly significant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, not everyone with CF is eligible for treatment with a highly effective CFTR modulator that can alter disease progression in a way no other current treatments can due to their CFTR variants. Furthermore, not everyone who is eligible can tolerate these treatments, or take full dose, due to adverse effects. These two groups of patients have an unmet need.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	People with CF receive specialist care from CF centres who are suitably staffed with a multidisciplinary team to meet their specific needs. They are reviewed in outpatient clinics at a regular frequency tailored to their individual needs as per the CF Trust's Standards of Care for people with CF and they may receive inpatient care if indicated. This is usually for intravenous antibiotics and intensive MDT support for a pulmonary exacerbation of CF. CF is well documented as a particularly burdensome disease and treatments include nebulised/inhaled

	antibiotics and mucolytics, CFTR modulators for those eligible and can tolerate, long term macrolides, daily airway clearance therapy, regular exercise and nutritional support. People with CF who progress to severe respiratory disease may require long term oxygen therapy, non-invasive ventilation and referral for double lung transplant eligibility assessment.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	CF Trust Standards for the clinical care of children and adults with cystic fibrosis in the UK, 2024 NICE Guideline NG78 – Cystic fibrosis: diagnosis and management, 2017
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined
9c. What impact would the technology have on the current pathway of care?	Minimal at most as it will be used in the same way as other CFTR modulators
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it will be used in the same way as other CFTR modulators
10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource use is unlikely to differ for the people with CF already taking elexacaftor/tezacaftor/ivacaftor as the new technology was non-inferior in trials, giving a similar rate of lung function improvement, reduction in rate of pulmonary exacerbations and improvement in quality of life. For the people with CF not taking elexacaftor/tezacaftor/ivacaftor or a less effective CFTR modulator due to intolerance vanzacaftor/tezacaftor/ivacaftor will decrease their healthcare resource use due to being able to obtain improvements in respiratory function, exacerbation rate and quality of life that will be similar to the most effective CFTR modulator currently available.
10b. In what clinical setting should the technology be	Tertiary specialist CF centres and network centres thereof as per current practice for CFTR modulators

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – the necessary resources are available from the rollout of currently available CFTR modulators
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	For people with CF currently taking elexacaftor/tezacaftor/ivacaftor it is unlikely that they will experience a clinically meaningful difference if switched to the new technology given the similarity of results obtained in the phase 3 trials unless they are struggling with adherence to elexacaftor/tezacaftor/ivacaftor as the new technology has a simpler administration schedule. For people with CF not currently taking elexacaftor/tezacaftor/ivacaftor due to intolerance they will experience a definite clinically meaningful benefit in health as was observed in the phase 3 trials of elexacaftor/tezacaftor/ivacaftor given the new technology is seemingly equally effective. These results are generalisable to the new technology.
11a. Do you expect the technology to increase length of life more than current care?	It is not possible to tell from current trial data as the phase 3 trial was set up as a non-inferiority trial but for the people with CF currently taking elexacaftor/tezacaftor/ivacaftor it is unlikely to have a dramatic effect on life expectancy given the similarity of the response observed. However, for people with CF not currently able to take elexacaftor/tezacaftor/ivacaftor, or at full dose, due to an adverse drug reaction it would have a profound effect on life expectancy if they could tolerate this new treatment as it is equally effective as the current benchmark triple CFTR modulator combination which is significantly more effective than dual or single modulator preparations or standard care without CFTR modulators.
11b. Do you expect the technology to increase health-related quality of life more than current care?	From trial data the new technology increased the CFQ-R respiratory domain score by 2.3 after 24 weeks with a treatment difference of 2.4 when compared to elexacaftor/tezacaftor/ivacaftor. Whilst this is positive it is below the minimal clinically important difference that is known to be a change of 4 points in the score of this domain. Therefore, it is unlikely that people with CF who currently take elexacaftor/tezacaftor/ivacaftor will experience a dramatic change in quality of life.

	However, people with CF who are not currently taking elexacaftor/tezacaftor/ivacaftor, or at full dose, due to an adverse drug reaction and are either on a less effective CFTR modulator or standard care depending on their CFTR variants would receive a dramatic improve in quality of life in keeping with the results seen from the phase 3 trials for elexacaftor/tezacaftor/ivacaftor as this new technology is equally effective and these results are generalisable.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As outlined above people who cannot currently take elexacaftor/tezacaftor/ivacaftor, or at full dose, due to an adverse drug reaction would receive greater benefit from this new technology compared to those who are tolerating treatment with elexacaftor/tezacaftor/ivacaftor well. People with CF who struggle to adhere to treatment with elexacaftor/tezacaftor/ivacaftor may also receive greater benefit from this new technology due to its greater simplicity of once a day dosing with one tablet rather than twice daily dosing with different drugs.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The new technology will be easier for patients to take as it is two tablets in the morning of one preparation containing a combination of 3 CFTR modulators compared to the current benchmark CFTR modulator formulation that is also two tablets in the morning containing 3 CFTR modulators but requires a further evening dose of a single CFTR modulator formulation. The effect on healthcare professionals will be neutral as whilst LFT monitoring requirements may increase for vanzacaftor/tezacaftor/ivacaftor following changed to the US license for elexacaftor/tezacaftor/ivacaftor this is equal across both the new technology and elexacaftor/tezacaftor/ivacaftor.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	In terms of starting treatment the patient in question will need to have an eligible genotype. This will not require additional testing for the vast majority as the test is done during the diagnosis work up. A very small percentage of

include any additional testing?	people with CF have unidentified CFTR variants and they may get tested again as testing has improved over the years and it may now be possible to discover the genotype. In terms of stopping the treatment this will be as per SPC for liver function test monitoring. Treatment often rechallenged at a later date once LFTs settled but if LFT increase above prespecified levels again treatment would be discontinued. This would unlikely be additional testing given the mandated frequency of LFT testing in the SPC.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Given that elexacaftor/tezacaftor/ivacaftor has been shown to have many more health benefits than what was observed in phase 3 clinical trials it is likely that there will be health benefits for the new technology that are unlikely to be included in the QALY calculation. However, this will only be applicable for people not taking elexacaftor/tezacaftor/ivacaftor at the moment due to intolerance, not those already taking it as the treatments seem equally effective in trials so this effect will be neutral for those taking currently elexacaftor/tezacaftor/ivacaftor.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No, as the only key difference between the new technology and elexacaftor/tezacaftor/ivacaftor is the new technology has a simpler administration schedule that will likely lead to improved adherence to treatment, but this is not innovative clinically.
16a. Is the technology a 'step-change' in the management of the condition?	No for the majority of people as elexacaftor/tezacaftor/ivacaftor was the step change in the management of the condition and they now take this. However, the new technology is as effective as this in clinical trials and it would be a step change for the people who cannot take elexacaftor/tezacaftor/ivacaftor due to intolerance.
16b. Does the use of the technology address any	Yes, it offers people who couldn't tolerate elexacaftor/tezacaftor/ivacaftor due to an adverse drug reaction an alternative treatment that is equally effective according to trial data.

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	If treatment has to be stopped due to an adverse drug reaction a significant reduction in lung function and quality of life and an increase in the rate of pulmonary exacerbations will be expected as CFTR function will reduce back to pretreatment baseline soon after treatment has stopped. If treatment is continued in the presence of a mild adverse drug reaction in line with the patient's wishes then they will likely experience a reduced quality of life depending on how much of an impact this reaction has on the life but the management of the condition will be unchanged.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, participants in the trial were given a 4 week run in with current best available care in the UK if they were not already taking it. The trial design was in keeping with previous CFTR modulator trials.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	FEV1, rate of pulmonary exacerbations, CFQ-R scores and in particular the respiratory domain to assess quality of life, adverse events, sweat chloride and weight/BMI. All were measured and reported excluding weight/BMI for which only baseline data is available.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	No, but it was only published in July 2024 and long-term studies are continuing. Further CFTR variants have been added to the eligible for treatment with elexacaftor/tezacaftor/ivacaftor list by the FDA since.
21. How do data on real-world experience compare with the trial data?	Real world data for the new technology is not available yet to my knowledge. Increased incidence of mental health side effects has been noted with elexacaftor/tezacaftor/ivacaftor post trials. Lung function improvements have been similar in the real world for elexacaftor/tezacaftor/ivacaftor.

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	It is believed that approximately 8-10% of people with CF are either not eligible for elexacaftor/tezacaftor/ivacaftor based on their CFTR variants or are not able to take it due to an intolerance. The CF registry annual data report in 2023 reported 13.5% of people aged 6 and over had no record of any CFTR modulator use.
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	This depends on their CFTR variants. Those eligible for one, or more, of either tezacaftor/ivacaftor, lumacaftor/ivacaftor or ivacaftor monotherapy will be prescribed the most effective but tolerable of these CFTR modulators for the individual in question. Whilst they are less effective than elexacaftor/tezacaftor/ivacaftor they do offer benefit over best supportive care which does not consist of a CFTR modulator. This consists of nebulised/inhaled antibiotics, nebulised/inhaled mucolytics, long term macrolide therapy, regular airway clearance therapy, exercise, nutritional support and intravenous or oral antibiotics for treatment of pulmonary exacerbations.

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, though it should be noted that those from ethnic minorities are more likely to not to be eligible for a modulator, but this is the same as for current care.
24b. Consider whether these issues are different from issues with current care and why.	This issue is not different as the same issue exists with current care.

NICE National Institute for Health and Care Excellence

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• From trial data the new technology seems to be as effective as current benchmark highly effective CFTR modulator combinations • Trial data showed the new technology led to a slight decrease in sweat chloride compared to the current benchmark. This is an accepted surrogate marker of increased CFTR function, but it did not lead to improved outcomes in terms of FEV1, exacerbation rates or QoL score in the trials • It has an advantage over this current benchmark in that it is a once-a-day preparation and one medication to take compared to twice a day dosing and two different formulations so it is likely people will find it easier to adhere to treatment • The new technology offers an alternative treatment option to people who can tolerate the current benchmark highly effective CFTR modulator combination due to an adverse drug reaction • The new technology had a comparable safety profile to the current benchmark CFTR modulator in trials

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Cost Comparison Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	UK Psychosocial Professionals in Cystic Fibrosis
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	UKPPCF is a national grouping of Psychologists or Social Workers working in Cystic Fibrosis (CF) who share good practice and learning and consult on psychosocial topics within CF. The group is not funded.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop the progression of Cystic Fibrosis by targeting CFTR function in the most common genes to enable those who have the condition to live longer and healthier lives.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Increase in lung function, or stability and preservation of lung function. Reduction in frequency of exacerbations, hospital admissions, courses of acute treatment & daily treatment burden. Improvements across the majority of domains of the CFQ-R questionnaire indicating an increase in quality of life. From a social work perspective an increased ability to engage in desired social/educational/work/family activities.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Whilst clinical teams understand CF as an illness, there is often a less understanding about how each individual conceptualises the disease. More research is needed to explore the effect that modulators is having on patients' lives beyond just the physical aspects and what support they require in relation to these. Care teams need to gain further understanding of the existential concerns relating to the dramatic change in health status for many in an extremely short time period. The CF Social Worker is uniquely placed to help the rest of the team understand these. According to research carried out by the CF Trust in 2019, only 34% of CF Centres have access to CF social workers and 45% of respondents to the same survey said that other than health, the things most impacted by CF were education and employment. (CF Trust, 2019). CF Registry Data Reports 2021 show that the number of women with CF becoming pregnant post-modulator treatment – this is a wonderful development but throws up many new questions about maternal care, inpatient stays for mothers of small children who are breastfeeding and social supports for the whole family unit to ensure that the adjustment to family life is fully supported alongside medical care. It's worrying that many patients with CF and their families do not have access to crucial support from social workers to help them cope with the practical, emotional and financial issues associated with changes to their condition / social circumstances as a result of treatment. The positive impact of the forerunner of this technology – ETI - on health and lifespan has been life changing for those eligible for the treatment. It is not yet clear whether the technology currently under discussion will have as significant an impact now that ETI is readily available. It is hoped that the new technology will benefit people with CF, whom have not experienced benefits (of increased lung function, fewer exacerbations), or whom have been unable to tolerate Kaftrio. The following was also in the previous submission for kaftrio – I would welcome thoughts on whether or not parts, or the whole of it should be included or excluded: Yes I think still relevant. It has to be acknowledged that for some patients the prospect of a suddenly prolonged life can initially seem intimidating and stressful as it involves changes in all areas of life. CF Teams and care pathways need to focus on future planning and preparing patients for a longer, healthier life. Patients will need

	support with considering and developing skills, and making plans to prepare them for employment, family life and possibly even retirement as survival continues to improve. With improved physical health comes reduced access to sickness benefits or for some their discontinuation altogether. This can be very distressing for both patient and their loved ones who are part of their social support systems and can lead to disruptions in caring roles, the necessity to work after a long period of being unwell and changes in the financial situation for the family unit as a whole. This all comes during a prolonged economic crisis, a cost of living crisis and after 12 years of reduced funding for health and social care services and across the public sector as a whole. This is important as we know already that poor socioeconomic status can impact negatively on physical and mental health and QoL more generally (Taylor Robinson et al, 2015).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Social Work guidelines are being developed with the CF Trust - draft currently under review. Guidelines currently in place: CF Psychology guidelines (2024) CF Trust Standards of Care (2024) European Cystic Fibrosis Symposium Guidelines (2018) Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis (2011 & 2022 Interim addendum) NICE Guidelines (2017)

	The primary legislation that is relevant to social work for children and adults in the UK is: The Children Act 1989, The Mental Capacity Act 2005 and the Care Act 2014.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no current pathway of care that I am aware of. There are also a significant number of CF Centres across the UK and Ireland without social work support despite people with CF advising that they need more support with education and employment. (CF Trust, 2019 & 2021)
9c. What impact would the technology have on the current pathway of care?	Decrease in need for inpatient treatments, overall reduction in treatment burden and perhaps an increase in the use of telemedicine as individuals feel better and don't feel the need to be medically reviewed as frequently as pre-kaftrio. As adults with CF age, their health and social care needs may become more complex, requiring greater coordination between CF care teams and other specialties. Any new pathway of care needs to acknowledge that social needs can become more complex through the process of ageing such as age-related diseases, care in older age, pensions, mortgages, life insurance and other financial and emotional considerations. It is likely that some patients will have less contact with their CF Teams as a result of better health and this may impact on the patient and clinician relationship. It remains critically important to maintain a good relationship with patients and to get to know them as individuals and consider all aspects of who they are and what they value most. Social workers also provide many practical and emotional supports to aid children, young people. parents, carers and adults with CF to continue to engage with treatment despite feeling much better. Treatment in CF is currently preventative as well as responsive and must be carried out daily regardless of how ill or well a patient objectively feels. This has a big impact on motivation to engage in pre-existing treatments with a much more solid evidence base. The introduction of the new technologies is enabling pathways of care to be refocused from eventual decline to maintaining health and enabling patients to make life decisions based on good, and not ill health. Any new pathway needs to run closely alongside existing pathways as patients' needs often jump from one to the other on an

	individual basis. It is also not yet known whether these technologies work better alongside existing treatments or independently of them, or whether the overall treatment burden can be reduced: This means that the need for support around treatment adherence remains – and in my limited experience is currently increasing for some patients: Those who feel better with the advent of the new technologies are less motivated to engage in pre-existing treatments and the longer term consequences of this are unknown, and so enabling maximum adherence to all treatment remains a priority. The technologies under appraisal are having a positive impact for many people who are eligible to take them but there is variation in experience and possible/alleged side effects are reported by some patients. Longitudinal research in years to come will tell us more about any alleged side effects but at present we are still learning. In social work terms these technologies are having a significant impact on quality of life for many people and on the patient's ability to engage in work, education, civic society and social and cultural activities beyond the medial sphere. Having access to social workers who can support patients and intervene in and between these social systems/environments is important to ensure that patients do not meet unexpected barriers to improving their self-determined QoL and to ensure that improvements in health are maximised and complemented by supportive interventions in other areas of life. This is explored fully in the CF Trust leaflet on the emotional and social impacts of the new technologies produced in 2020 with the collaboration of the UKPPCF.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is hoped that the technologies will soon be available to children under 6yrs.
10a. How does healthcare resource use differ between the technology and current care?	Fewer exacerbations and hospitalisations mean less resource is used in hospital. Outpatient work continues.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Further social and emotional support resources to ensure that patients using the technologies can take full advantage of any improvements in physical health and engage fully in society.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Unknown at this juncture. Hopefully it improves outcomes for the subsection of patients eligible for kaftrio who have not greatly benefited.
11a. Do you expect the technology to increase length of life more than current care?	Unknown at this juncture. Hopefully it improves outcomes for the subsection of patients eligible for kaftrio who have not greatly benefited.
11b. Do you expect the technology to increase health-related quality of life more than current care?	For some people with CF - the subsection of patients eligible for Kaftrio who haven't greatly benefited from it.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients must have CF and have the correct genotype for the new technologies to be effective.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For very young children and those with difficulties swallowing tablets (possibly some people with physical or learning disabilities who either don't take medications orally or are unable to manage tablets for physical or sensory reasons) an oral suspension would be needed.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: No psychosocial impacts are being measured with regards to mental health (other than incidence of depression) or the impact of socioeconomic factors. The technologies under appraisal are having a positive impact for many people who are eligible to take them but there is variation in experience and possible/alleged side effects are being reported by some patients. Longitudinal research in years to come will tell us more about any alleged side effects but at present data is still emerging. Support with emotional wellbeing and adjustment to being a more 'well' individual can take time. Alongside the mental health interventions provided by CF psychologists, CF social workers can provide practical and emotional support to aid this adjustment, and support individuals in reviewing their options

	and decision making where their circumstances change. CF Teams without this facility will have to rely on localised services in multiple local authority areas without knowledge of Cystic Fibrosis, with all of the attendant waiting times for support.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It may be for the subsection of people with CF who have not greatly benefited from previous modulator therapies.
16a. Is the technology a 'step-change' in the management of the condition?	No.
16b. Does the use of the technology address any particular unmet need of the patient population?	CF is incurable and chronic, as well as progressive. Modulator technologies appear to press the 'pause' button on CF. The vanzacaftor-tezacaftor-diutivacaftor (VTD) technology will be available to a wider group of people with CF than elexacaftor-tezacaftor-ivacaftor (ETI) technology and may prove effective for those who were eligible for, but unable to tolerate ETI.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is some evidence of mood being affected at a similar incidence to that of ETI but no research is currently in place to look at this. Ensuring patients and their families feel fully heard and supported – particularly around decisions that involve stopping the use of the technologies – need to be carefully considered and psychosocially informed. Any new pathways need to run parallel to the existing ones: points of intersection such as transplant eligibility (in particular with regards to social and psychological determinants of eligibility) also need to be carefully considered.

	Modulator therapy may elicit feelings of anxiety associated with the overwhelming and uncertain future individuals now face in regards to themselves, their identity, and their future. For example, some people with CF have stopped modulators due to body image concerns as a result of weight gain. The high burden of mental health conditions in people with cystic fibrosis, including depression, anxiety, suicidal ideation, insomnia, and other conditions, is well established in the published literature.[31–34] Previous analysis of pooled placebo-controlled elexacaftor–tezacaftor–ivacaftor clinical trials has shown that the incidence of depression-related events was similar between the elexacaftor–tezacaftor–ivacaftor group (3·32 events per 100 person years) and the placebo group (3·24 events per 100 person years).[35] Results from Trials VX20-121-102 and VX20-121-103 showed that the incidence of neuropsychiatric events reported by the investigators in these trials was similar between treatment groups and was consistent with the background rate of these events in people with cystic fibrosis not receiving CFTR modulator therapy. The cumulative review of the elexacaftor–tezacaftor–ivacaftor data, including from clinical trials, post-marketing reports, an ongoing registry-based post authorisation safety study, and peer-reviewed literature, suggests that depression symptoms and depression-related events reported in people with cystic fibrosis treated with elexacaftor–tezacaftor–ivacaftor are generally consistent with background epidemiology of these events in the cystic fibrosis population and do not suggest a causal relationship with CFTR modulator treatment. Ref: Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials - The Lancet Respiratory Medicine

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	From a social work perspective, impacts on mental health and emotional wellbeing are complex and multifactorial and extremely difficult to measure. They dictate how well a person can adjust to a change in health and how they are able to engage in activities that increase quality of life such as work, education, social activities. These are not being measured in trials, nor, to my knowledge, is socioeconomic impact as described by Taylor-Robinson et al (2013 and 2015).
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As an organisation we have no experience of VTD at this point. However, given that Skyline trials have identified a similar response as to ETI in the incidence of depression-related events, CF teams need to remain vigilant and monitor effectively.: 'the incidence of depression-related events was similar between the elexacaftor–tezacaftor–ivacaftor group (3·32 events per 100 person years) and the placebo group (3·24 events per 100 person years).[35] Results from Trials VX20-121-102 and VX20-121-103 showed that the incidence of neuropsychiatric events reported by the investigators in these trials was similar between treatment groups and was consistent with the background rate of these events in people with cystic fibrosis not receiving CFTR modulator therapy' Ref: Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials - The Lancet Respiratory Medicine

	Also of concern is that 'The most common adverse events and serious adverse events were generally consistent with common manifestations in cystic fibrosis' and may not be recognised as being related to use of the new technology. Vanzacaftor–tezacaftor–deutivacaftor versus elexacaftor–tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials - The Lancet Respiratory Medicine
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA988?	No.
21. How do data on real-world experience compare with the trial data?	No real world experience as yet.

Topic specific questions

22. How many people with cystic fibrosis are not able to be treated with elexacaftor/tezacaftor/ivacaftor?	
23. How are people with cystic fibrosis who are not able to be treated with elexacaftor/tezacaftor/ivacaftor (kaftrio) managed in the NHS?	They still require specialised CF MDT care and legacy treatments as before the availability of modulator therapies.

Equality

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Socioeconomic and family/patient specific factors need to be addressed/considered to ensure equitable access to the new technologies given the impact of low socioeconomic status as described by Taylor-Robinson et al (2013 and 2015).
24b. Consider whether these issues are different from issues with current care and why.	Other treatments are well established and more understood with more longitudinal data to provide guidance. Social and emotional issues are complex, dynamic and influences are multifactorial. We are dealing with unknowns and must err on the side of caution until more data emerges. This requires ongoing assessment and psychosocial input and insight.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients and their families need access to social support and advice to navigate family, social, financial, educational and employment systems impacting on socioeconomic status as this is a major indicator of health outcomes (Taylor-Robinson et al, 2013 &2015). • Evidence of low mood as a potential side-effect of the use of the technologies for a minority of patients needs to be addressed/assessed/monitored so that a consensus can be reached about addressing the issue. • Addressing socioeconomic barriers needs to be an integral part of the management of CF care throughout the lifespan. •

Thank you for your time.

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Maastricht University

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

Produced by

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Contributions of authors:

Nigel Armstrong acted as project lead and health economist/reviews manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Kevin McDermott and Xiaoyu Tian acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Mehlika Toy acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang critiqued the company's definition of the decision problem and the network meta-analysis, contributed to the writing of the report and jointly led the project.

Abbreviations

AE	Adverse event
BMI	Body mass index
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFQ-R-8D	Cystic Fibrosis Questionnaire – Revised 8 dimensions
CFTR	Cystic fibrosis transmembrane conductance regulator protein
CFTRm	Cystic fibrosis transmembrane conductance regulator modulator
CI	Confidence interval
CON	Confidential
CS	Company submission
D-IVA	Deutivacaftor
DARE	Database of Abstracts of Reviews of Effects
DP	Decision problem
EAG	External Assessment Group
ELX/TEZ/IVA	Elexacaftor/tezacaftor/ivacaftor
ESHPM	Erasmus School of Health Policy and Management
EUR	Erasmus University Rotterdam
F/F	Homozygous for the F508del-CFTR mutation
F/G	Heterozygous for the F508del mutation and a gating mutation
F/MF	Heterozygous for the F508del-CFTR mutation and another mutation that produces no CFTR protein or is unresponsive to CFTR modulators ('minimal function')
F/RF	Heterozygous for the F508del mutation with a mutation associated with residual CFTR protein
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FEV1	Forced expiratory volume in 1 second
HCRU	Healthcare resource use
HRG	Healthcare resource group
HTA	Health Technology Assessment
ICD-10	International classification of diseases, tenth revision
ICH	International Council for Harmonization
ITC	Indirect treatment comparison
IV	Intravenous
IVA	Ivacaftor
KSR	Kleijnen Systematic Reviews Ltd
LCI	Lung clearance index
LS	Least squares
LUM/IVA	Lumacaftor/ivacaftor
MF	Minimal function
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
NR	Not reported
OLE	Open-label extension
OR	Odds ratio
PAS	Patient Access Scheme
PEx	Pulmonary exacerbation
ppFEV1	Percentage of predicted FEV1

q12h	Every 12 hours
qd	Once daily
RCT	Randomised controlled trial
RF	Residual function
SAE	Serious adverse event
SE	Standard error
SwCl	Sweat chloride
TCR	Triple combination responsive
TEZ	Tezacaftor
TEZ/IVA	Tezacaftor/ivacaftor
TRSAE	Treatment-related serious adverse event
UK	United Kingdom
UMC+	University Medical Center+
VNZ	Vanzacaftor
VNZ/TEZ/D-IVA	Vanzacaftor/tezacaftor/deutivacaftor

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1. Summary of the External Assessment Group's view of the company's cost comparison case

The External Assessment Group (EAG) believes that the company has shown that equivalence in efficacy and safety has been demonstrated between vanzacaftor–tezacaftor–deutivacaftor (VNZ/TEZ/D-IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in patients with cystic fibrosis (CF) with at least 1 F508del mutation (cystic fibrosis transmembrane conductance regulator protein (CFTR) gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein) in the age group 12 and upwards. This is via a direct head-to-head comparison in two randomised controlled trials (RCTs), SKYLINE 102 and SKYLINE 103, as presented in Section 3.:

- In both studies, the primary endpoint of absolute change in percentage of predicted forced expiratory volume in 1 second (FEV1) (ppFEV1) from baseline through Week 24 was met and showed VNZ/TEZ/D-IVA to be non-inferior to ELX/TEZ/IVA (i.e., the lower bound of the 95% confidence interval (CI) for the treatment difference was greater than the pre-specified non-inferiority margin of -3.0 percentage points). There continued to be little difference between the treatments at Week 52.
- In both studies, there was a statistically significant improvement in CFTR function (as assessed by absolute change from baseline in sweat chloride (SwCl) through Week 24 and 52) after treatment with VNZ/TEZ/D-IVA compared with ELX/TEZ/IVA.
- There was a statistically significant advantage in the odds of both SwCl <60 mmol/l and SwCl <30 mmol/l at Week 24 in a pooled analysis of both trials.
- There was no statistically significant difference in the rate of pulmonary exacerbation (PEx) at Week 52 in both trials.
- A pooled analysis of SKYLINE 102 and 103 showed that VNZ/TEZ/D-IVA improved Cystic Fibrosis Questionnaire – Revised 8 dimensions (CFQ-R-8D) utility values ([redacted] versus ELX/TEZ/IVA, P=[redacted]).
- There was no statistically significant difference in change from baseline in BMI or weight in both studies.
- Rates of adverse events (AEs) are similar in the two RCTs.

There is some doubt in patients aged 6 to 11 years given that they were excluded from the RCTs, and data were only available from the single-arm RIDGELINE 105 study, although outcomes were similar to those in the VNZ/TEZ/D-IVA arm of the RCTs. In the request for clarification, the EAG requested evidence for the comparator i.e., ELX/TEZ/IVA in this age group in order to demonstrate equivalence or at least similarity in efficacy and safety. The company responded by providing evidence from trials of ELX/TEZ/IVA, but did not perform an indirect treatment comparison (ITC) or a side-by-side comparison of outcomes by which equivalence might have been demonstrated.

As shown in Section 4., the base-case cost comparison combined with the sensitivity and scenario analyses show that it is likely that treatment with VNZ/TEZ/D-IVA will lead to a modest cost saving compared to ELX/TEZ/IVA.

2. Critique of the decision problem in the company's submission

The population in the National Institute for Health and Care Excellence (NICE) scope is:[1] *People aged 6 years and over with CF with at least 1 F508del mutation*. The population in the company's decision problem (DP), as stated in Table 1 of the company submission (CS), was the same as the scope.[2]

The intervention in the NICE scope is simply described as vanzacaftor–tezacaftor–deutivacaftor (VNZ/TEZ/D-IVA).[1] The intervention in the DP, as stated in Table 1 of the CS, was the same as the scope. VNZ/TEZ/D-IVA is available as an oral tablet that is administered once-daily (qd).[2] The recommended doses are, based on the marketing authorisation, as provided in the company factual accuracy check (FAC):[3]

- for 6-11 years:
    - <40 kg three tablets of VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg, i.e., VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd
    - ≥40 kg two tablets of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg, i.e., VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd
- For 12+ years: two tablets of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg, i.e., VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd

The comparators in the NICE scope are:[1]

- Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)
- Established clinical management including but not limited to: antibiotics, inhaled mucolytics (including mannitol dry powder for inhalation, hypertonic saline and dornase alfa), anti-inflammatory agents, bronchodilators.

For people with specific mutations, treatment may include:

- Tezacaftor/ivacaftor (TEZ/IVA)
- Lumacaftor/ivacaftor (LUM/IVA)
- IVA monotherapy.

The only comparator in the DP, as stated in Table 1 of the CS, is ELX/TEZ/IVA.[2]

EAG comment: The EAG note that there is no discrepancy between scope and DP in either population or intervention. There is only one comparator, but this is appropriate for a cost only comparison.

3. Summary of the EAG's critique of clinical effectiveness evidence submitted

3.1 Systematic literature review methods

3.1.1 Searches

Clinical effectiveness searches were conducted to identify clinical trials and observational studies to identify relevant evidence of clinical efficacy and safety associated with cystic fibrosis transmembrane conductance regulator modulators (CFTRms) for the treatment of patients with CF. The searches combined facets for CF with terms for the intervention and comparators. The Embase and MEDLINE searches were limited using published study design filters.

The CS, Appendix B and the Company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 4, 5] Searches were conducted on 10-12 May 2022, and updated on 5 August 2024 and covered a broad range of resources including MEDLINE, MEDLINE In-Process, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database, all via the OvidSP interface. Searches were limited to data published from 2007 onwards and studies published in English. Grey literature searches were carried out across a wide range of conference proceedings and websites and on ClinicalTrials.gov. These searches were conducted in June 2022 and updated in September 2024 with a date limit of 2015+. For full details please see the CS, Appendix B and response to clarification.[2, 4, 5]

EAG comment: Searches were transparent and reproducible, and comprehensive strategies were used over a wide range of resources. Overall, the EAG has no concerns regarding the literature searches conducted.

3.1.2 Inclusion screening

EAG comment: The EAG has no concerns regarding the identification of studies given that the company has conducted and reported on the only RCT of the intervention versus a comparator that is in scope i.e., VNZ/TEZ/D-IVA compared with ELX/TEZ/IVA.

3.2 Identified randomised controlled trials

3.2.1 Methods

Two RCTs, SKYLINE 102 and SKYLINE 103 were included in the CS, which directly compared VNZ/TEZ/D-IVA at the recommended dose (see Section 2) with ELX/TEZ/IVA at the licensed dose of elexacaftor (ELX) 200 mg qd/TEZ 100 mg qd and IVA 150 mg every 12 hours (q12h) in patients aged at least 12. Note that the company informed the EAG in the FAC that the marketing authorisation states: "in the evening" instead of q12h.[3] Also included in the CS was a single-arm trial of VNZ/TEZ/D-IVA, which included patients aged 6 to 11 (Cohort B1: n=78). The dose of VNZ/TEZ/D-IVA depended on body weight: those of at least 40 kg were treated as recommended (see Section 2). Those lower than 40 kg were treated with a lower dose of D-IVA than recommended i.e., VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 75 mg qd instead of VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd.

SKYLINE 102 (VNZ/TEZ/D-IVA (n=200), ELX/TEZ/IVA (n=205)) and SKYLINE 103 (VNZ/TEZ/D-IVA (n=285), ELX/TEZ/IVA (n=289)) were phase 3, randomised, double-blind, parallel-group studies and in CF patients who are:

- heterozygous for F508del and a minimal function (MF) mutation (F/MF) (SKYLINE 102)

- homozygous for F508del (F/F), heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least one other triple combination responsive (TCR, defined as responsive to ELX/TEZ/IVA) CFTR mutation and no F508del mutation (TCR/non-F) (SKYLINE 103).

They both also had a run-in period of 28 days where patients received ELX/TEZ/IVA also at the licensed dose.

RIDGELINE 105 was a phase 3, single-arm study in children with CF who had at least one TCR mutation (defined as responsive to ELX/TEZ/IVA). It also included a run-in period of 28 days where dose depended on body weight, according to the licence:

- <30 kg at Day -28: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- ≥30 kg at Day -28: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h.

EAG comment: The EAG notes that there is some variation in genotype within and between the various trials, and between the trials and the NICE scope, which raises some concern about applicability to England and Wales clinical practice. The EAG also noted that the company did not perform the subgroup analyses specified in the NICE scope i.e., by number of copies of the CFTR gene with F508del mutations. The EAG therefore requested that the company:[6]

- provide a comparison between the trial populations (SKYLINE 102 and 103, and RIDGELINE 105), and patients in England and Wales in terms of mix of genotypes
- perform these subgroup analyses in order to test for equivalence or at least similarity in all efficacy and safety outcomes
- discuss the implications of any differences in mix of genotypes between the trials and the population in clinical practice in England and Wales in terms of equivalence or similarity in efficacy and safety.

In response the company provided a table comparing the UK CF Registry, an observational study, LONGITUDE, and the three trials (see Table 3.1).[4]

Table 3.1: Distribution of F/any genotypes in the UK CF Registry, the LONGITUDE observational study, and the VNZ/TEZ/D-IVA clinical trials

	Total F508del on ≥1 allele	N (%)				
		F/F	F/MF	F/G + F/R117H	F/RF	F/other
UK CF Registry data (2023)						
England 12+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales 12+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
England 6-11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales 6-11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LONGITUDE observational study (August 2019 – December 2023)						
Aged 12+ years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total F508del on ≥1 allele	N (%)				
		F/F	F/MF	F/G + F/R117H	F/RF	F/other
Aged 6 to 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SKYLINE 102 and 103 & RIDGELINE trials*						
Aged 12+ years	929	446 (48.0)	398 (42.8)	39 (4.2)	46 (5.0)	0 (0.0)
Aged 6 to 11 years	67	37 (55.2)	24 (35.8)	3 (4.5)	1 (1.5)	2 (3.0)

Based on company response to clarification[4]
*The SKYLINE and RIDGELINE trials included participants with non-F508del mutations; these are not included in this table as they fall outside of the scope of the appraisal.
CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator protein; D-IVA = deutivacaftor; F/F = homozygous for the F508del-CFTR mutation; F/G = heterozygous for the F508del mutation and a gating mutation; F/MF = heterozygous for F508del and a minimal function (MF) mutation; F/RF = heterozygous for F508del and a residual function (RF) mutation; TEZ = tezacaftor; UK = United Kingdom; VNZ = vanzacaftor

The EAG agrees with the company that the combined SKYLINE 102 and SKYLINE 103 population included a similar proportion of F/F patients (48%) relative to the age-matched UKCFR population and LONGITUDE ([redacted] and [redacted] respectively). However, there are clearly differences and so the key issue is whether there might be any threat to equivalence or risk that ELX/TEZ/IVA might be superior to VNZ/TEZ/D-IVA in any subgroup. However, the EAG concluded that there is no subgroup where ELX/TEZ/IVA is superior for either the primary outcome of ppFEV1 or the secondary outcome of SwCl (see Section 3.2.2.2). Therefore, the EAG considers that any differences in genotype will probably pose little risk to equivalence in clinical practice based on the RCTs.

3.2.2 Results

The clinical efficacy of VNZ/TEZ/D-IVA in the treatment of CF was assessed through the SKYLINE 102, SKYLINE 103, and RIDGELINE 105 trials.[2]

3.2.2.1 Efficacy versus ELX/TEZ/IVA (patients aged ≥12 years)

In the SKYLINE 102/103 trials, VNZ/TEZ/D-IVA achieved non-inferior improvements in ppFEV1 (1-sided P value for non-inferiority <0.0001) through Week 24 compared with ELX/TEZ/IVA (Table 3.2). There continued to be little difference between the treatments at Week 52 (Figure 4, CS[2]).

Both studies showed a statistically significant improvement in CFTR function, as measured by absolute change in SwCl levels through Week 24 (Table 3.2) and week 52 (Figure 5, CS[2]). Furthermore, pooled analysis demonstrated a statistically significant advantage for VNZ/TEZ/D-IVA in the odds of achieving SwCl <60 mmol/l (odds ratio (OR): 2.21; 95% CI: 1.55 to 3.15; P<0.0001) and SwCl <30 mmol/l (OR: 2.87; 95% CI: 2.00 to 4.12; P<0.0001) at Week 24 compared to ELX/TEZ/IVA (Table 3.3).

Rates of PEx were comparable between treatments, with no statistically significant difference observed at Week 52 in either trial. Similarly, no significant differences were observed in changes from baseline in body mass index (BMI) or weight between VNZ/TEZ/D-IVA and ELX/TEZ/IVA across both studies (Table 3.2.

Additionally, pooled analysis from SKYLINE 102 and 103 showed that VNZ/TEZ/D-IVA led to a statistically significant improvement in CFQ-R-8D utility values compared with ELX/TEZ/IVA [redacted]), suggesting enhanced patient-reported quality of life (Table 3.3).

Table 3.2: Efficacy outcomes (ppFEV1, SwCl, PEx, BMI, Weight) across SKYLINE 102 and 103

Characteristics	SKYLINE 102		SKYLINE 103	
	ELX/TEZ/IVA	VNZ/TEZ/D-IVA	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
ppFEV1: absolute change through Week 24				
n	193	187	276	268
LS mean (SE)	0.3 (0.3)	0.5 (0.3)	0.0 (0.2)	0.2 (0.3)
LS mean difference, 95% CI	N/A	0.2 (-0.7, 1.1)	N/A	0.2 (-0.5, 0.9)
1-sided P value for non-inferiority	N/A	<0.0001	N/A	<0.0001
SwCl: absolute change through Week 24				
n	194	185	276	270
LS mean (SE)	0.9 (0.8)	-7.5 (0.8)	-2.3 (0.7)	-5.1 (0.7)
LS mean difference, 95% CI	N/A	-8.4 (-10.5, -6.3)	N/A	-2.8 (-4.7, -0.9)
P value	N/A	<0.0001	N/A	0.0034
PEx: through Week 52				
Number of participants with events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of events	90	67	79	86
Event rate per year	0.42	0.32	0.26	0.29
Rate difference (95% CI)	N/A	-0.1 (-0.24, 0.04)	N/A	0.03 (-0.07, 0.13)
BMI (kg/m^2): absolute change from baseline at Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference, 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg): absolute change from baseline at Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference, 95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables 12, 13, 15, and 17 of the CS[2]

Notes: PEx were defined as any new or change in antibiotic therapy (intravenous (IV), inhaled, or oral) for ≥4 sinopulmonary signs/symptoms. Total number of days = sum of the individual duration (actual number of days)

Characteristics	SKYLINE 102		SKYLINE 103	
	ELX/TEZ/IVA	VNZ/TEZ/D-IVA	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
of the PEx analysis period across all subjects. Total number of years = total number of days/336; for analysis purposes, one year is defined as 48 weeks or 336 days. BMI = body mass index; CI = confidence interval; CS = company submission; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; LS = least squares; N/A = not applicable; PEx = pulmonary exacerbation; ppFEV1 = percent predicted forced expiratory volume in 1 second; SE = standard error; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor				

Table 3.3: Efficacy outcomes (SwCl, CFQ-R-8D) with SKYLINE 102 and 103 pooled data

Characteristics	SKYLINE 102 and 103 pooled data	
	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
Number (%) of response for SwCl <60 mmol/l		
Baseline	358/483 (74)	361/476 (76)
Average through Week 24	367/479 (77)	399/465 (86)
Estimated OR (95% CI)	N/A	2.21 (1.55 to 3.15)
P value	N/A	<0.0001
Number (%) of response for SwCl <30 mmol/l		
Baseline	99/483 (21)	89/476 (19)
Average through Week 24	108/479 (23)	142/465 (31)
Estimated OR (95% CI)	N/A	2.87 (2.00 to 4.12)
P value	N/A	<0.0001
CFQ-R-8D		
Treatment coefficient (SE)	[redacted]	[redacted]
P value	[redacted]	[redacted]
Based on Table 14 of the CS and Table 1.2.3.1a of REF-25859[2, 7] CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; CS = company submission; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; N/A = not applicable; OR = odds ratio; SE = standard error; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor		

3.2.2.2 Efficacy in patients aged 6 to 11 years (RIDGELINE 105; Cohort B1)

In patients aged 6 to 11 years, efficacy data were derived solely from the single-arm RIDGELINE 105 study. Details can be found in Table 3.4.

Table 3.4: Efficacy outcomes (ppFEV1, SwCl, PEx, CFQ-R-8D, BMI, Weight) from RIDGELINE 105, Cohort B1

Characteristics	RIDGELINE 105
	VNZ/TEZ/D-IVA
SwCl: absolute change through Week 24	
n	77
LS mean (SE)	-8.6 (1.2)
95% CI of LS mean	(-11.0 to -6.3)
Number (%) of response for SwCl <60 mmol/l	
Baseline	65/77 (84.4%)

Characteristics	RIDGELINE 105
	VNZ/TEZ/D-IVA
Average through Week 24	74/78 (94.9%)
Number (%) of response for SwCl <30 mmol/l	
Baseline	30/77 (39.0%)
Average through Week 24	41/78 (52.6%)
ppFEV1: absolute change through Week 24	
n	74
LS mean (SE)	0.0 (1.0)
95% CI of LS mean	(-2.0 to 1.9)
PEx overall: through Week 24	
Number of subjects with events, n (%)	6 (7.7)
Number of events	6
Observed event rate per year	0.15
CFQ-R RD: absolute change through Week 24	
n	75
LS mean (SE)	3.9 (1.2)
95% CI of LS mean	(1.5 to 6.3)
BMI (kg/m^2): absolute change from baseline at Week 24	
n	78
LS mean (SE)	0.22 (0.08)
95% CI of LS mean	(0.05 to 0.38)
Weight (kg): absolute change from baseline at Week 24	
n	78
LS mean (SE)	1.67 (0.17)
95% CI of LS mean	(1.34 to 2.00)

Based on Tables 18, 19, 20, 21, 22, and 23 of the CS[2]
BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; CS = company submission; D-IVA = deutivacaftor; IVA = ivacaftor; LS = least squares; PEx = pulmonary exacerbation; ppFEV1 = percent predicted forced expiratory volume in 1 second; SE = standard error; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor

EAG comment: Generally, the results from the two RCTs show that the efficacy of VNZ/TEZ/D-IVA is equivalent to or better than ELX/TEZ/IVA. However, the EAG note considerable uncertainty in the subgroup of those aged between 6 and 11 due to the absence of direct comparator data. The absolute change in SwCl levels through Week 24 (least squares (LS) mean reduction of 8.6 mmol/l; 95% CI: 6.3 to 11.0) was numerically greater than the reductions observed in SKYLINE 102 (−7.5 mmol/l) and SKYLINE 103 (−5.1 mmol/l). However, for ppFEV1, no improvement was observed in RIDGELINE 105 (LS mean change 0.0; 95% CI: −2.0, 1.9), which contrasts with the small gains seen in SKYLINE 102 and 103. Similarly, the increase in BMI (+0.22 kg/m²) was modest and aligned with or slightly lower than changes seen in the adult/adolescent population. By contrast, the absolute weight gain in RIDGELINE 105 (+1.67 kg) was greater than the gains reported in SKYLINE 102 [redacted]) and SKYLINE 103 [redacted]), potentially reflecting age-related growth differences. However, this is no substitute for comparative evidence, which would imply the need for an ITC (see Section 3.3).

3.2.2.3 Subgroup analyses

EAG comment: As stated above, the EAG requested subgroup analyses by genotype, to which the company responded with subgroup analyses.[4] One was for the primary outcome ppFEV1 presented in response to clarification, which was only feasible for SKYLINE 103, given the genotypical homogeneity of SKYLINE 102 i.e., 100% F/MF. It can be seen that for the F/F subgroup, which is the large majority of patients, there is equivalence (point estimate very slightly favours ELX/TEZ/IVA), and only for F/G and TCR/non-F are the point estimates clearly different to zero (the point of no difference), but the 95% CIs overlap zero and VNZ/TEZ/D-IVA is favoured. The other subgroup analysis was for the secondary outcome SwCl, which showed a statistically significant advantage to VNZ/TEZ/D-IVA for the F/F subgroup. The point estimates for all other subgroups also indicated an advantage to VNZ/TEZ/D-IVA except for F/G, but even for F/G the 95% CI crossed zero.

3.3 Indirect or mixed treatment comparisons

The company did not perform indirect and mixed treatment comparisons for patients aged ≥12 years, because SKYLINE 102 and 103 provided head-to-head comparison data against the comparator of ELX/TEZ/IVA.

For patients aged 6 to 11 years, there were no head-to-head data as RIDGELINE 105 was a single-arm study. For this group of patients. the company made the following statement in the CS:[2] *"an indirect treatment comparison was not carried out for the following reasons:*

- *In RIDGELINE 105, participants received a stable ELX/TEZ/IVA regimen for at least 4 weeks before starting treatment with VNZ/TEZ/D-IVA, meaning that any change from baseline was effectively comparing VNZ/TEZ/D-IVA with ELX/TEZ/IVA.*

- *The underlying aetiology of CF is consistent between younger and older patients. Pharmacokinetic data from RIDGELINE 105 show that the exposures of VNZ, TEZ, D-IVA and their metabolites in 6 to 11-year-olds were within the range of exposure seen in patients aged ≥12 years and were consistent with those seen in previous clinical trials of IVA, TEZ/IVA and ELX/TEZ/IVA. Trials of other CFTRms in 6 to 11-year olds have shown consistent efficacy and safety with patients aged ≥12 years.*

- *Per the principles of efficacy extrapolation to the paediatric population established by the International Council for Harmonization (ICH), VNZ/TEZ/D-IVA is expected to have comparable efficacy in the population enrolled in RIDGELINE 105 to the observed in SKYLINE 102 and 103, with the non-inferiority assumption deemed appropriate for the CF population aged 6 to 11 years. Based on the results from RIDGELINE 105, an ITC was deemed unnecessary to provide a clinical efficacy estimation for VNZ/TEZ/D-IVA vs. ELX/TEZ/IVA."*

EAG comments: The EAG considers that the reasons why the company did not perform indirect and mixed treatment comparisons for patients aged ≥12 years appear to be appropriate. However, there was some doubt in patients aged 6 to 11 years because these patients were excluded from the RCTs and data were only available from the single-arm RIDGELINE 105 study, although outcomes from the RIDGELINE 105 study were similar to those in the VNZ/TEZ/D-IVA arm of the RCTs. In the clarification letter, the EAG requested evidence for the comparator i.e., ELX/TEZ/IVA in this age group in order to demonstrate equivalence or at least similarity in efficacy and safety.[6]

In responding to the EAG's request, the company confirmed that there was no comparative evidence for VNZ/TEZ/D-IVA in children with CF aged 6 to 11 years.[2, 4, 5] The company stated that direct side-by-side comparison of the efficacy and safety between VNZ/TEZ/D-IVA and ELX/TEZ/IVA in the 6-11 age group was not possible.[2, 4, 5] The company provided a summary of the safety and efficacy of ELX/TEZ/IVA in patients aged 6 to 11 years from other relevant studies in the clarification letter.[2, 4, 5] However, the company did not perform an ITC for patients with CF aged 6 to 11 years. Nor did they provide a side-by-side comparison of outcomes, arguing that change from baseline cannot be compared because in RIDGELINE 105, participants were stable on ELX/TEZ/IVA for at least four weeks before receiving VNZ/TEZ/D-IVA, whereas ELX/TEZ/IVA studies (AURORA 6-11 and GALILEO) did not include an active run-in period. They did not explain why LONGITUDE, a non-interventional, observational, retrospective, registry-based cohort using data from the UK Cystic Fibrosis Registry could not have been used for an ITC.[8, 9] The EAG have therefore compiled a table to provide this side-by side-by-side comparison (see Table 3.5).

Table 3.5: Key efficacy endpoints: AURORA 6-11 and AURORA 6-11 OLE

	Absolute change from baseline, LS mean (95% CI)				
	AURORA 6-11 (n=66)	AURORA 6-11 OLE (n=64)		GALILEO (n=61)	RIDGELINE 105, Cohort B1 6-11
	Through Week 24	At OLE Week 96	At OLE Week 192	Through Week 24	Through Week 24
ppFEV1, percentage points	10.2 (7.9 to 12.6)	11.2 (8.3 to 14.2)	9.6 (5.4 to 13.7)	9.5 (6.6 to 12.4)	0.0 (-2.0, 1.9)*
SwCl, mmol/l	-60.9 (-63.7 to -58.2)	-62.3 (-65.8 to -58.8)	-57.9 (-63.3 to -52.5)	-52.1 (-55.0 to -49.2)	-8.6 (-11.0, -6.3)*
CFQ-R respiratory domain score, points	7.0 (4.7to 9.2)	13.3 (11.4 to 15.1)	10.0 (6.9 to 13.0)	5.9 (2.8 to 9.1)	3.9 (1.5, 6.3)*
$LCI_{2.5}$, units	-1.71 (-2.11 to -1.30)	-2.00 (-2.45 to -1.55)	-2.33 (-2.87 to -1.79)	-2.29 (-2.60 to -1.97)	-0.08 (-0.18, 0.02)*
BMI z-score*	0.37 (0.26 to 0.48)	0.24 (0.11 to 0.37)	0.39 (0.19 to 0.59)	NR	-0.05 (-0.12, 0.02)*

Based on Tables 7 and 10 from clarification response,[4] Table 3.4 above, and *company factual accuracy check.[3]
BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire – Revised; CI = confidence interval; LCI = lung clearance index; LS = least squares; NR = not reported; OLE = open-label extension; ppFEV1 = percent predicted forced expiratory volume in 1 second; SwCl = sweat chloride

It is clear that the values for ppFEV1, SwCl and CFQ-R for VNZ/TEZ/D-IVA, from RIDGELINE 105, despite being similar to those for both VNZ/TEZ/D-IVA and ELX/TEZ/IVA from the SKYLINE RCTs (see Section 3.2.2.1) in the older age group, are very different to those in the same age group for ELX/TEZ/IVA in the AURORA and GALILEO trials. The EAG considers that this is probably explained by the lack of run-in period in the AURORA and GALILEO trials. Therefore, the EAG considers that there is insufficient evidence to demonstrate equivalence in the efficacy and safety of ELX/TEZ/IVA in patients aged 6 to 11 years.

3.4 Adverse events

Table 3.6 shows an overall summary of AEs from the SKYLINE trials.

EAG comment: The EAG considers that there is similarity between the rates of AEs between VNZ/TEZ/D-IVA and ELX/TEZ/IVA.

Table 3.6: Summary of AEs during the treatment period (SKYLINE studies; treatment period safety set)

	SKYLINE 102		SKYLINE 103		Pooled SKYLINE 102 & 103	
	ELX/TEZ/IVA N=202 n (%)	VNZ/TEZ/D-IVA N=196 n (%)	ELX/TEZ/IVA N=289 n (%)	VNZ/TEZ/D-IVA N=284 n (%)	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
Number of AEs (total)	[redacted]	[redacted]	[redacted]	[redacted]	3,795	3,551
Subjects with any AEs	[redacted]	[redacted]	[redacted]	[redacted]	469 (95.5)	459 (95.6)
AEs by strongest relationship						
Not related	[redacted]	[redacted]	[redacted]	[redacted]	182 (37.1)	151 (31.5)
Unlikely related	[redacted]	[redacted]	[redacted]	[redacted]	112 (22.8)	140 (29.2)
Possibly related	[redacted]	[redacted]	[redacted]	[redacted]	162 (33.0)	159 (33.1)
Related	[redacted]	[redacted]	[redacted]	[redacted]	13 (2.6)	9 (1.9)
AEs by maximum severity						
Mild	[redacted]	[redacted]	[redacted]	[redacted]	145 (29.5)	166 (34.6)
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	269 (54.8)	239 (49.8)
Severe	[redacted]	[redacted]	[redacted]	[redacted]	54 (11.0)	54 (11.3)
Life-threatening	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	0
Death	[redacted]	[redacted]	[redacted]	[redacted]	0	0
Other AE types						
AEs leading to study drug discon-tinuation	[redacted]	[redacted]	[redacted]	[redacted]	18 (3.7)	18 (3.8)
AEs leading to study drug inter-ruption	[redacted]	[redacted]	[redacted]	[redacted]	12 (2.4)	20 (4.2)
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	81 (16.5)	68 (14.2)

	SKYLINE 102		SKYLINE 103		Pooled SKYLINE 102 & 103	
	ELX/TEZ/IVA N=202 n (%)	VNZ/TEZ/D-IVA N=196 n (%)	ELX/TEZ/IVA N=289 n (%)	VNZ/TEZ/D-IVA N=284 n (%)	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
Related SAEs[a]	[redacted]	[redacted]	[redacted]	[redacted]	12 (2.6)	7 (1.5)
AEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	0	0

Based on Table 25 of the CS[2]

Notes: When summarising number of events, a subject with multiple events within a category was counted multiple times in that category. When summarising number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

[a]When summarising number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

AE = adverse event; CS = company submission; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; n: size of subsample; N = total sample size; SAE = serious adverse event; TEZ = tezacaftor; VNZ = vanzacaftor

4. EAG critique of cost comparison evidence submitted

4.1 Company cost comparison model

The company provided a cost comparison model to assess the costs associated with using VNZ/TEZ/D-IVA versus ELX/TEZ/IVA to treat patients aged 6 years and over with CF who have at least one F508del mutation in the CFTR gene.

The model compares the total costs per patient between the two treatments over a time horizon of 5 years, without discounting. The general features of the Cost Comparison Analysis model are summarised in CS report Table 31.[2] The time horizon was deemed sufficient given that all costs included in the model are assumed to be time-invariant.

4.2 Model parameters

4.2.1 Acquisition costs

Both treatments had comparable annual costs of [redacted]. However, this total was composed of different components for the two treatments:

- VNZ/TEZ/D-IVA: comprised of VNZ/TEZ/D-IVA tablets, priced at [redacted] per 28-day pack (Patient Access Scheme (PAS) price). Note that this price relates to both VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg and VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg.

- ELX/TEZ/IVA: comprised of ELX/TEZ/IVA tablets, with a PAS price of [redacted] per 28-day pack, plus IVA tablets with a PAS price of [redacted] per 28-day pack. Note that here as well the price is independent of the dosage of the tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg versus ELX 100 mg/TEZ 50 mg/IVA 75 mg and IVA 75 mg versus IVA 150 mg).

The full details of the intervention and comparator acquisition costs are presented in CS Table 32.[2]

The model did not incorporate costs related to treatment discontinuation due to AEs, suggesting an assumption of full adherence throughout the time horizon for all patients.

4.2.2 Treatment administration costs

In the model, oral administration was assumed for both treatments, with initiation by a healthcare provider followed by home use. As administration requirements and prescribing frequencies were identical, administration costs were set to £0 for both treatments.

4.2.3 Monitoring costs

Monitoring costs related to CFTRm administration or CF disease management were not included in the model, as these are assumed to be equivalent across both treatments in the model, and will thus not impact the incremental costs between the treatments.

4.2.4 Costs due to pulmonary exacerbations

As the rates of pulmonary exacerbations were similar between the two treatments (see CS Table 15) no costs related to treatment of these exacerbations were included in the base-case analysis. A scenario analysis was included incorporating the costs of pulmonary exacerbations requiring intravenous antibiotics or hospitalisation.

4.2.5 Adverse event costs

Treatment-related serious adverse events (TRSAEs) were included for both treatment arms, based on events occurring in at least one subject in either treatment arm in the SKYLINE 102 and 103 trials (see CS Table 33 and Table 34).[2] Events were mapped to National Health Service (NHS) cost codes (ICD-10 to HRG4+) and priced accordingly. VNZ/TEZ/D-IVA had a fewer and less costly AEs, resulting in an annual TRSAE cost of [redacted], compared to [redacted] for ELX/TEZ/IVA. The model also explored a broader AE definition (any SAE occurring in ≥2 patients) and exclusion of AEs in scenario analyses.

The EAG are comfortable with the assumptions made by the company.

4.3 EAG model check

The EAG conducted a range of checks on the company's cost comparison model and found no issues or errors.

4.4 Company's model results

4.4.1 Company base-case results

In the base-case analysis, the total 5-year costs of VNZ/TEZ/D-IVA and ELX/TEZ/IVA were found to be nearly identical, with a slight cost advantage for VNZ/TEZ/D-IVA. [redacted] This difference is relatively modest, with an annual cost saving of [redacted], on a yearly treatment cost of over [redacted]. Thus, the base-case results suggest that the two treatments are essentially cost-neutral[redacted].

4.4.2 Sensitivity and scenario analyses

Both a deterministic sensitivity analysis and scenario analyses were conducted. The former analysis showed that the model outcomes are only somewhat sensitive to assumptions about TRSAE incidence rates and associated unit costs. The estimated cost savings are most sensitive to changes in the rate of distal intestinal obstruction syndrome, which is explained by the fact that this AE is associated with the highest treatment costs. In the model, drug acquisition and administration costs were held constant, as they were assumed to be fixed in clinical practice.

Scenario analyses were also conducted. The scenario analyses assessed the impact of structural changes in the model. Table 41 in the CS shows the results of the scenario analyses. Most informative is the scenario in which pulmonary exacerbation costs are included, based on pooled trial data. Including these increases the cost saving of VNZ/TEZ/D-IVA to [redacted] over five years. Using a broader definition of AEs, i.e., any serious adverse event occurring in at least two patients, resulted in an incremental cost difference of [redacted]. These analyses confirm that it is likely that treatment with VNZ/TEZ/D-IVA will lead to a modest cost saving compared to ELX/TEZ/IVA.

The EAG is content with the analyses undertaken by the company, and did not undertake any additional exploratory analyses.

5. EAG commentary on the robustness of evidence submitted by the company

The company's evidence appears to be robust enough to confirm comparability of efficacy and safety between the intervention, VNZ/TEZ/D-IVA and the comparator, ELX/TEZ/IVA, in those aged at least 12 years. However, no comparative evidence was presented for those aged between 6 and 11. The EAG can confirm the lack of comparability between the VNZ/TEZ/D-IVA trial (RIDGELINE 105, Cohort B1) and the ELX/TEZ/IVA trials (AURORA 6-11, AURORA 6-11 OLE and GALILEO) in this population, as indicated by the large variation in outcomes, which is probably due to lack of run-in in the comparator trials.

In considering the robustness of the cost comparison analysis, the EAG note the following:

- The time horizon was deemed sufficient given that all costs included in the model are assumed to be time-invariant.
- The model did not incorporate costs related to treatment discontinuation due to AE, suggesting an assumption of full adherence throughout the time horizon for all patients.
- The EAG are comfortable with the assumptions made by the company.
- The EAG conducted a range of checks on the company's cost comparison model and found no issues or errors.
- The base-case results suggest that the two treatments are essentially cost-neutral, with only minor variation due to adverse event rates and costs.
- The sensitivity and scenario analyses confirm that it is likely that treatment with VNZ/TEZ/D-IVA will lead to a modest cost saving compared to ELX/TEZ/IVA.

The EAG therefore considers that the cost comparison was sufficiently robust to demonstrate that VNZ/TEZ/D-IVA costs no more than ELX/TEZ/IVA.

6. References

[1] National Institute for Health and Care Excellence. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over [ID6372]: final scope [Internet]*. London: NICE, 2025. 4p. Available from: https://www.nice.org.uk/guidance/gid-ta11430/documents/final-scope

[2] Vertex. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutation in the CFTR gene in people aged 6 years and over [ID6372]: submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Vertex, 2025. 128p.

[3] National Institute for Health and Care Excellence. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over [ID6372]: EAG report - factual accuracy check and confidential information check*. London: NICE, 2025. 5p.

[4] National Institute for Health and Care Excellence. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people aged 6 years and over [ID6372]: Response to request for clarification from the EAG*. London: NICE, 2025. 19p.

[5] Vertex. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutation in the CFTR gene in people aged 6 years and over [ID6372]: submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendices*: Vertex, 2025. 159p.

[6] National Institute for Health and Care Excellence. *Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people aged 6 years and over [ID6372]: Clarification questions*. London: NICE, 2025. 3p.

[7] Vertex. *REF-25859. HEOR - CFQ-R-8D treatment-specific utility increment for VNZ/TEZ/D-IVA (pooled 121-102/103) [Data on file]*, 2024

[8] Vertex. *LONGITUDE: an observational study of the long-term effectiveness of ELX/TEZ/IVA in people with CF aged >=6 years using data from the UK CF registry (2024 analysis) [Data on file]*, 2025

[9] Vertex. *Study report: an observational study of users of Kaftrio, Orkambi and Symkevi in the UK Cystic Fibrosis Registry to satisfy data collection agreement in the UK (LONGITUDE). Final analysis (FA) for Kaftrio [Data on file]*, 2023

Cost Comparison Appraisal

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

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 27 May 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as ‘depersonalised data’ in pink.

Issue 1 6-11 age group side-by-side comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Section 3.3, Table 3.5: '*The EAG have therefore compiled a table to provide this side-by side-by-side comparison (see Table 3.5)*.'	'*The EAG have therefore compiled a table to provide this side-by side-by-side comparison (see Table 3.5). However, it is acknowledged that the lack of run-in period in the AURORA and GALILEO trials means that drawing conclusions is not appropriate*.'	The EAG note in the paragraph under Table 3.5 when characterising differences in efficacy that '*..this is probably explained by the lack of run-in period in the AURORA and GALILEO trial*s.' Given the prominence of Table 3.5, this statement should form part of the description prior to presentation of Table 3.5. We agree with the EAG's conclusion, that comparing efficacy between a population that is stable on ELX/TEZ/IVA with populations that were predominantly treatment naïve is likely the explanation for any observed differences.	Not a factual inaccuracy.

Issue 2 Cost savings narrative

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Section 4.4.1: '*In the base-case analysis, the total 5-year costs of VNZ/TEZ/D-IVA and ELX/TEZ/IVA were found to be nearly identical, with a slight cost advantage for* ***ELX/TEZ/IVA***.'	'*In the base-case analysis, the total 5-year costs of VNZ/TEZ/D-IVA and ELX/TEZ/IVA were found to be nearly identical, with a slight cost advantage for* ***VNZ/TEZ/D-IVA***.'	Typographical error. As the EAG explain later in the paragraph, it is VNZ/TEZ/D-IVA that is cost saving, not ELX/TEZ/IVA.	Amended.

Issue 3 Updated SmPC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8, Section 2: The EAG presents the recommended dose for VNZ/TEZ/D-IVA based on the draft SmPC	Updating of the dosing schedule per Table 1 of the Alfytrek SmPC (https://www.medicines.org.uk/emc/product/100699/smpc#gref). Age 6-11 is weight-based dosing, with one recommended dose for patients 12+	The EAG's write-up is consistent with what was submitted. However, this was based on a draft SmPC. Since submission, the final SmPC is now available, with an updated dosing schedule.	Amended. Also amended Section 4.2.1 in line with this change.

Issue 4 Reporting of data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, Table 3.2, PEx through Week 52 The 95% CIs for the rate differences are missing Page 16, Table 3.5 a) The ppFEV$_1$, SwCl, and CFQ-R respiratory domain data RIDGELINE 105 are presented as LS mean (SE), rather than LS mean (95% CI) b) The BMI z-score and LCI$_{2.5}$ data for RIDGELINE 105 are given as 'not reported'. However, these data are available in Tables 23 and 24 of the CS, respectively	Page 12, Table 3.2: Please amend the rate difference (95% CI) values for PEx through Week 52 as follows: SKYLINE 102: **-0.1 (-0.24, 0.04)** SKYLINE 103: **0.03 (-0.07, 0.13)** Page 16, Table 3.5: Please amend the RIDGELINE 105 data as follows: ppFEV$_1$: **0.0 (-2.0, 1.9)** SwCl: **-8.6 (-11.0, -6.3)** CFQ-R respiratory domain: **3.9 (1.5, 6.3)** LCI$_{2.5}$: **-0.08 (-0.18, 0.02)** BMI z-score: **-0.05 (-0.12, 0.02)**	For accuracy in reporting and consistency, both within the EAG report and between the EAG report and the CS	Amended.

Issue 5 RIDGELINE 105 run-in period

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10, Section 3.2.1: '*It also included a run-in period of 28 days where dose depended on body weight, according to the licence*'	Suggest replace with: '*all children were either on a stable regimen of ELX/TEZ/IVA (defined as receiving ELX/TEZ/IVA for at least 28 days before the screening visit) or received ELX/TEZ/IVA for 4 weeks as part of the study run-in period to establish a stable on-treatment baseline*'	The additional detail helps to provide greater clarity on the RIDGELINE 105 run-in period per protocol.	Not a factual inaccuracy.

Issue 6 Comparator arm dosing SKYLINE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9, Section 3.2.1: '*with ELX/TEZ/IVA at the licensed dose of elexacaftor (ELX) 200 mg qd/TEZ 100 mg qd and IVA 150 mg* ***every 12 hours (q12h) in patients aged at least 12.***'	'*with ELX/TEZ/IVA at the licensed dose of elexacaftor (ELX) 200 mg/TEZ 100 mg/IVA 150 mg in the morning and IVA (150 mg)* ***in the evening in patients aged at least 12***.'	The proposed wording aligns with the licensed dose of ELX/TEZ/IVA as well as the dosing schedule followed for the ELX/TEZ/IVA arm in the SKYLINE 102 and SKYLINE 103 trials	Amended.