Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Contents:

The following documents are made available to stakeholders:

The final scope and final stakeholder list are available on the NICE website.

1. **Correspondence from NICE to Vertex regarding the interim access agreement and considerations for future appraisals**

2. **Company submission** from Vertex

3. **Clarification letter and response** from Vertex

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Cystic Fibrosis Trust
   b. Cystic Fibrosis Voices submission and appendix
   c. Association of Chartered Physiotherapists in Cystic Fibrosis
   d. British Dietetic Association
   e. British Paediatric Respiratory Society
   f. British Thoracic Society
   g. Cystic Fibrosis Digicare
   h. UK CF Medical Association
   i. UK Psychosocial Professionals Cystic Fibrosis

5. **Expert personal perspectives** from:
   a. Christina Walker, CF Voices organiser – patient expert nominated by CF Voices
   b. Professor Andrew Jones, Consultant Physician in Adult Cystic Fibrosis – clinical expert nominated by NHSE and Cystic Fibrosis Trust
   c. Andrew Lilley, Pharmacy Clinical Services Lead – clinical expert nominated by Neonatal and Paediatric Pharmacists Group (NPPG)
   d. Dr Don Urquhart, Consultant in Paediatric Respiratory Medicine – clinical expert nominated by Scottish Medicines Consortium / Healthcare Improvement Scotland
   e. Yasmin Stammers, Senior Programme of Care manager, Internal Medicine – NHS commissioning expert nominated by NHS England

6. **Company responses to the EAG report consultation** from Vertex

7. **Consultee and commentator responses to the EAG report consultation:**
    a. CF Trust
    b. CF Voices
    c. Quest for a CF Cure
    d. Association of Chartered Physiotherapists in Cystic Fibrosis
    e. British Dietetic Asscociation
    f. Cystic Fibrosis Nursing Association
    g. UK CF Medical Association
    h. UK Cystic Fibrosis Pharmacy Group
    i. UK Psychosocial Professionals in CF

8. **External Assessment Group response to stakeholder consultation comments** prepared by BMJ Technology Assessment Group

9. **External Assessment Group (EAG) report** prepared by BMJ Technology Assessment Group, updated following consultation

10. **External Assessment Group (EAG) report addendum** prepared by BMJ Technology Assessment Group

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

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29/06/2020

Dear [redacted],

I am aware that Vertex and NHS England have been discussing commercial and other terms associated with extending the existing interim access agreement for lumacaftor-ivacaftor and tezacaftor-ivacaftor, to provide access for patients to the triple combination therapy, elexacaftor-tezacaftor-ivacaftor over a 4 year period.

Like before, the interim access agreement would allow real world data to be collected and fed into the NICE technology appraisal(s) with final recommendations to be available by the end of the interim access period to inform future commissioning arrangements. I believe we are all committed to making this happen.

As the interim access agreement is contingent on Vertex submitting these products for NICE technology appraisal, I am writing to provide clarification and, wherever possible, certainty around some key principles that will underpin those future appraisals. When we get to those appraisals, new methods will be in place, which we expect to be applied. I don't expect the new methods to influence the principles behind the clarification provided below, except to provide more technical detail to support measurement and calculation, where appropriate.

I recognise that this letter provides clarification on matters of particular interest at this stage of the proceedings, but I would like to also use this opportunity to reiterate our support for companies in putting forward an evidence submission to NICE. We have put in place various steps in the process in which we provide companies the opportunity to work with our team to get a better understanding of what is likely to be required when we get to review by the independent committee. It is in our interest to get this right from an early stage, to prevent delays and to support early or continued patient access.

I provide the clarification in this letter to the best of my ability, and without prejudice of what the independent appraisal committee will make of the case for value of your products when they get to review them, or how they will approach their work, which will be guided by our published processes and their independent judgement. NICE will share a copy of this letter with the appraisal committee at the time of the review to ensure that the appraisal of the products considers the following:

- **Rate of decline**. NICE will consider the long-term rate of decline from evidence generated for the 'triple therapy', where that is available. I can also confirm that where that evidence cannot reasonably be generated for the 'triple therapy' itself, we will explore using the rate of decline for tezacaftor-ivacaftor or lumacaftor–ivacaftor where this is appropriate, including taking into account data from longer follow-up of patients.
- **CFQR-8D**. For the appraisal of all of the Products, NICE shall use the EuroQoL-5D descriptive system and the Cystic Fibrosis Questionnaire - Revised 8D ("**CFQR-8D**") with appropriate mapping to generate utility as inputs for the cost-effectiveness model, as well as available quality of life (QoL) data on the caregiver at the time of submission; these data may be available from existing clinical studies in people with cystic fibrosis or collected in the Interim Access Period and included in Vertex's submissions to NICE.
- **Compliance rates**. NICE acknowledges that clinical trial compliance can be an overestimate of real-world compliance. NICE confirm that if Vertex includes the impact of compliance/adherence to treatment in their submission, the appraisal committee will take this into account. Evidence from use of the products in real life, outside of clinical trials, is important in this respect, including data collected during the interim access period from patients in the UK.
- **Weighted-average ICER**. NICE wants to understand the value of each of the products in patient populations specified in the marketing authorisation, as well as supporting equity of access where that is clinically reasonable. The deliberative process used by our independent committee is usually sufficient to ensure we develop guidance that allows access to as many patients as is possible. A recent example of a pragmatic approach in this context is the appraisal of histology-independent cancer drugs. NICE will use a 'weighted-average' ICER if the evidence, licensing status, clinical input and value proposition make this reasonable.
- **Active comparator for the Triple Product**. NICE accepts that because the objective is to establish whether use of triple therapy in patients otherwise eligible for existing products (ie CFTR modulators) leads to an acceptable use of NHS resources, these products will be the main

comparator. In clinical scenarios where patients are not eligible for those products the focus will be a comparison with best supportive care without CFTR modulator therapies.

I trust this clarification is helpful and remain at your disposal if you have further questions or would like to discuss the contents of this letter.

Kind regards,

Meindert Boysen

Deputy CEO & Director of CHTE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Ivacaftor/tezacaftor/elexacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor fixed dose combination therapies for treating cystic fibrosis

[ID3834]

Document B

Company evidence submission

17 March 2023

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AR	Annual review
AST	Aspartate transferase
BIC	Bayesian information criterion
BL	Baseline
BMI	Body mass index
BSC	Best supportive care
CDC	Centre for Disease Control and Prevention
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CF	Cystic fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFLD	Cystic fibrosis-associated liver disease
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	CFTR modulator
CGRO	Caregiver-reported outcomes
CI	Confidence interval
CPH	Cox proportional hazards
CPK	Creatine phosphokinase
CrI	Credible interval
CSR	Clinical study report
DCA	Data Collection Agreement
DIOS	Distal intestinal obstruction syndrome
DSA	Deterministic sensitivity analysis
ECFS	European Cystic Fibrosis Society
ECG	Electrocardiogram
ECM	Established clinical management
EMA	European Medicines Agency
EMR	Electronic medical record
EPAR	European public assessment report
EQ-5D	EuroQol-Five Dimension

EQ-5D-3L	EuroQol 5-dimension 3-level questionnaire
ETT	Early termination of treatment
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
FEV_1	Forced expiratory volume in 1 second
GGT	Gamma-glutamyl transferase
GLI	Global Lungs Initiative
H-CFTRm naïve	Historical cystic fibrosis transmembrane regulator modulator naïve
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost effectiveness ratio
ICF	Informed consent form
IQR	Interquartile range
IRT	Immunoreactive trypsinogen
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVA	Ivacaftor
IVA/TEZ/ELX	Ivacaftor-tezacaftor-elexacaftor in combination with ivacaftor
LCI	Lung clearance index
LFT	Liver function test
LoE	Loss of exclusivity
LOS	Length of stay
LS	Least squares
LTSS	Long-term safety study
LUM/IVA	Lumacaftor-ivacaftor
LY	Life year
LYG	Life years gained
MAA	Managed access agreement
MCID	Minimal clinically important difference

MF	Minimal function
MMRM	Mixed effects model for repeated measures
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NR	Not reported
OE	Ophthalmological examination
OL	Open-label
OLE	Open-label extension
PBO	Placebo
PDPE	Protocol defined pulmonary exacerbation
PEx	Pulmonary exacerbation
PK	Pharmacokinetics
PO	Per os (orally administered)
$ppFEV_1$	Percentage of predicted FEV_1
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
pwCF	People with cystic fibrosis
Q12h	Every 12 hours
QALY	Quality adjusted life year
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval on electrocardiogram
RCT	Randomised controlled trial
RD	Respiratory domain
RF	Residual function
RTI	Respiratory tract infection
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-12	12-Item Short Form Health Survey
SF-6D	Short Form-Six Dimension
SLR	Systematic literature review

SLR	Systematic literature review
SoC	Standard of care
STA	Single technology appraisal
SwCl	Sweat chloride
TEAE	Treatment emergent adverse event
TEZ/IVA	Tezacaftor-ivacaftor in combination with ivacaftor
TSQM	Treatment satisfaction questionnaire for medication
UK	United Kingdom
UKCFR	UK cystic fibrosis registry
US	United States
VAS	Visual analogue scale
vs	Versus
WFAZ	Weight-for-age z-score
WPAI + CIQ: SHP	Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Specific Health Problem.

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

B.1.1 Decision problem

The objective of this technology appraisal is to assess the clinical and cost-effectiveness of ivacaftor-tezacaftor-elexacaftor (IVA/TEZ/ELX) + ivacaftor (IVA), lumacaftor-ivacaftor (LUM/IVA), and tezacaftor-ivacaftor (TEZ/IVA) + IVA according to their licensed indications:

- IVA/TEZ/ELX in a combination regimen with IVA is being appraised for the treatment of people with cystic fibrosis (pwCF) aged six years or older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (1)
- LUM/IVA is being appraised for the treatment of cystic fibrosis (CF) in patients aged two years or older, who are homozygous for the *F508del* mutation in the *CFTR* gene (2, 3)
- TEZ/IVA in a combination regimen with IVA is being appraised for the treatment of pwCF aged six years or older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G*, and *3849+10kbC→T* (4).

The submission covers the full marketing authorisation of each technology appraised, at the point of submission. All three products are currently available to patients in the United Kingdom (UK) under an access agreement with the National Health Service (NHS) (5). The NHS England (NHSE) commissioning statement 210508P v2.0 outlines the reimbursement status of these treatments (6). The decision problems addressed within this submission are presented in Table 1. Hereafter, IVA/TEZ/ELX in combination with IVA will be referred to as IVA/TEZ/ELX, and TEZ/IVA in combination with IVA will be referred to as TEZ/IVA.

Table 1. Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	• Ivacaftor, tezacaftor and elexacaftor combination therapy (Kaftrio) • Tezacaftor and ivacaftor combination therapy (Symkevi) • Lumacaftor and ivacaftor combination therapy (Orkambi)	Same	
Population	PwCF with at least one *F508del* mutation	Same	
Subgroups	People who are • homozygous for the *F508del* mutation, or • heterozygous for the *F508de*l mutation and a residual function mutation	PwCF with at least one *F508del* mutation in the *CFTR* gene are in scope.	It is not relevant or appropriate to consider subgroups within CF since all CF patients within the licensed indications will benefit clinically from the indicated CFTR modulator (as demonstrated for example for IVA/TEZ/ELX in Middleton et al., 2019) (7).
Comparator(s)	• Established clinical management (ECM) including o best supportive care o mannitol dry powder for inhalation o inhaled mucolytics o nebulised hypertonic saline o anti-inflammatory agents o bronchodilators o vitamin supplements o pancreatic enzymes • The interventions will be compared to each other	**<u>Relevant comparators for IVA/TEZ/ELX:</u>** **In pwCF aged 6 years or older who are homozygous for the *F508del* mutation:** • ECM without IVA/TEZ/ELX **In pwCF aged 6 years or older who are heterozygous for the *F508del* mutation:** • ECM without IVA/TEZ/ELX for those heterozygous for the *F508del* mutation with one of the specified licensed minimal function mutations (F/MF) or one of the specified licensed residual function mutations (F/RF) (*P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*) • IVA monotherapy in combination with ECM for those heterozygous for the *F508del* mutation with one of the specified licensed gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H*) • ECM without IVA/TEZ/ELX for all remaining indicated mutations **<u>Relevant comparators for LUM/IVA</u>** • ECM without LUM/IVA	• IVA monotherapy is a relevant comparator in PwCF who are heterozygous for the F508del mutation and a gating mutation, and should therefore be added to the list of comparators • It is not necessary or appropriate to compare the interventions to one another: o The current uptake figures for pwCF aged 6+ years with at least one *F508del* mutation show that [redacted] in England. Data collected through the Data collection agreement [redacted] of the UK CF Registry Study in July 2022. [redacted] due to LUM/IVA's licence in 2-5 year old population which is not at present

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Relevant comparators for TEZ/IVA **PwCF aged 6 years or older who are homozygous for the *F508del* mutation:** • ECM without TEZ/IVA **PwCF aged 6 years or older who are heterozygous for the *F508del* mutation with one of the specified licensed residual function mutations (F/RF)** *(P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T)*: • ECM without TEZ/IVA	covered by the IVA/TEZ/ELX licence. In the same period, [redacted] (8). ○ The ECFS consensus statement on standards of care for CFTR variant-specific therapy stipulates that pwCF "aged six years or older, with one or two F508del variants, should have daily treatment with triple modulator therapy (IVA/TEZ/ELX)" (9). The market share data in conjunction with ECFS statement suggest that IVA/TEZ/ELX is standard of care for the vast majority of eligible pwCF in the UK while alternatives are only suitable if IVA/TEZ/ELX is not indicated or tolerated. ○ It is inappropriate to compare the interventions to one another given that the NICE methods clearly state technologies recommended in managed access agreements are not considered suitable comparators, and LUM/IVA and TEZ/IVA fall into this category (10).
Outcomes	The outcome measures to be considered include: • Mortality • Forced expiratory volume • Lung function • Body mass index • Respiratory symptoms • Pulmonary exacerbations • Pulmonary bacterial colonisation • Frequency and severity of acute infections • Need for hospitalisation and other treatments • Exercise tolerance/capacity • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Mortality • Lung function ○ Forced expiratory volume (FEV) ○ Lung clearance index 2.5 ($LCI_{2.5}$) • Body mass index • Respiratory symptoms • Pulmonary exacerbations • Lung transplants • Need for hospitalisation & other treatments • Adverse effects of treatments • Health-related quality of life	The following important outcomes in CF should be included in the scope of the appraisal: • Lung transplants • Lung clearance index 2.5 ($LCI_{2.5}$) On the other hand, given that pulmonary exacerbations are acute infections, including acute infections as a separate outcome is duplicative; acute infections were therefore not included in this submission. Furthermore, exercise tolerance is not a relevant outcome for CF.
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.	• Cost-effectiveness results are expressed in terms of ICER • A lifetime horizon is used in the model	Uniform discounting of costs and benefits, although recommended by majority of national HTA guidelines, leads to prioritisation of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 and cost of biosimilar and generic products should be taken into account.	• Costs are considered from a National Health Service and Personal Social Services perspective • A differential annual discount rate of 1.5% for health outcomes and 3.5% for costs is applied in the base case • QALY shortfall analyses has been conducted to reflect the high degree of the severity of CF • The impact of loss of exclusivity on cost-effectiveness is considered in a scenario analysis	treatments with immediate health benefits and works against preventative health programmes and other interventions characterised by early investment and late accrual of health benefits. The national HTA guidelines of Belgium, Poland and the Netherlands, recommend using a lower discount rate for outcomes (1.5%, 1.5% and 3.5%, respectively) compared with costs (3%, 4% and 5%, respectively), arguing that this is a normative decision taken to "avoid too strong penalisation of interventions such as screening or vaccination programmes" where uniform discounting could lead to perpetual deferral of investment (11-14). It has been shown that equal discount rate for costs and outcomes is appropriate for decision making in a society maximising the present value of health under the conditions of a fixed NHS budget and a constant willingness-to-pay threshold (15). However, it is likely that the value of health over time will increase due to rising social expectations regarding maintaining good health and income growth (16). The increase in the threshold would mean that future additional costs will displace less health; a lower discount rate for health outcomes vs costs would account for such future increase in the value of health benefits (15, 17).
Equality and other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.	An appraisal approach of subgrouping the indicated populations according to *CFTR* genotype or baseline lung function may raise equality concerns.	

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator gene protein; *CFTR*, cystic fibrosis transmembrane conductance regulator gene; ECFS, European Cystic Fibrosis Society; ECM, established care management; ELX, elexacaftor; FEV, forced expiratory volume; F/F, homozygous for the *F508del-CFTR* 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 activity ('residual function'); HRQoL, health related quality of life; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; LUM, lumacaftor; $LCI_{2.5}$, lung clearance index 2.5; NHS, National Health Service; pwCF, people with CF; TEZ, tezacaftor.

B.1.2 Description of the technology being appraised

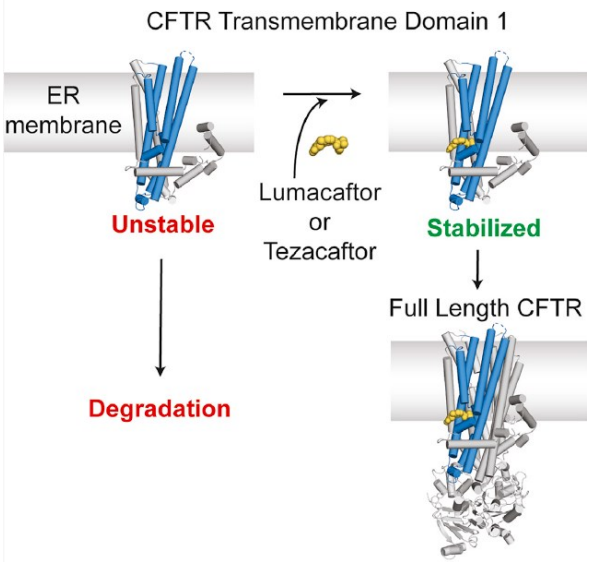
B.1.2.1 Mechanism of action

The CFTR protein acts as a chloride channel on the apical membrane of epithelia lining multiple organs, most notably the airways, intestines, pancreatic ducts, and reproductive tracts (18). Within the epithelial cells, CFTR protein controls the chloride ion secretion and, indirectly, sodium and water movement, thereby affecting the viscoelastic properties of mucus (18, 19). PwCF have two mutant *CFTR* alleles resulting in little-to-no CFTR protein quantity, impaired CFTR protein function, or both (19-21).

CFTR modulators (CFTRms) consist of potentiators and correctors that directly target the CFTR protein (22). CFTR potentiators (i.e., IVA[1]) increase the probability of open channel conformation of CFTR through direct binding to the channel and thus require its presence at the cell surface to function (19). CFTR correctors (e.g., LUM, TEZ, and ELX) increase the quantity of CFTR protein delivered to the cell surface via improved processing and trafficking (19, 23). A recent study of the CFTR binding sites of LUM and TEZ found that these correctors insert into a hydrophobic pocket in the first transmembrane domain (TMD1) of CFTR. This stabilises the four helices of TMD1, making CFTR protein less vulnerable to intracellular degradation, thereby increasing the probability of forming a fully assembled CFTR (Figure 1) (24). Although the mechanism of action of ELX has not been conclusively defined, it has been suggested that ELX stabilises the nucleotide binding domain-2 of CFTR (25, 26).

[1] IVA increases the function of CFTR proteins associated with several common CF alleles, including *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R, R117H.*

Figure 1. LUM or TEZ binding with CFTR protein



Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ER, endoplasmic reticulum.
Reference: Fiedorczuk et al (24)

The three treatments appraised in this submission each contain a combination of a potentiator (IVA) with at least one corrector. The main characteristics of IVA/TEZ/ELX, LUM/IVA and TEZ/IVA are summarised in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Lumacaftor, ivacaftor (Orkambi®)	Tezacaftor, ivacaftor (Symkevi®)	Ivacaftor, tezacaftor, elexacaftor (Kaftrio®)
Mechanism of action	LUM/IVA is a combination therapy that includes a CFTR corrector (LUM) and a CFTR potentiator (IVA) (2, 3). The combination increases both the quantity and function of *F508del*-CFTR at the cell surface, resulting in increased chloride ion transport (2, 3).	TEZ/IVA is a combination therapy that includes a CFTR corrector (TEZ) and a potentiator (IVA) (4). The combination increases both the quantity and function of *F508del*-CFTR at the cell surface, resulting in increased chloride ion transport (4).	IVA/TEZ/ELX is a combination therapy that includes CFTR correctors (ELX and TEZ) and a potentiator (IVA) (4). The combination increases both the quantity and function of *F508del*-CFTR at the cell surface, resulting in increased chloride ion transport (1, 27). The CFTR correctors ELX and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone (1, 27, 28).
Marketing authorisation/CE mark status	LUM/IVA was first issued a marketing authorisation which was valid throughout the European Union in 2015 for the treatment of CF in patients aged 12 years or older who are homozygous for the *F508del* mutation in the *CFTR* gene (29). Since then the licence has been expanded to include patients aged 2 years or older who are homozygous for the *F508del* mutation (30).	TEZ/IVA was first issued a marketing authorisation which was valid throughout the European Union in 2018 (31, 32) for patients 12 years or older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G,* and *3849+10kbC→T*. Since then the licence was expanded to include patients aged 6 years or older with the same mutations as originally licenced (33).	IVA/TEZ/ELX was first issued a marketing authorisation which was valid throughout the European Union in 2020 for patients aged 12 or older with one *F508del* mutation and one minimal function mutation, or two *F508del* mutations in the *CFTR* gene (34). Since then the licence was expanded to include patients aged 6 years or older who have at least one *F508del* mutation in the *CFTR* gene (35).
Indications and any restriction(s) as described in the summary of product characteristics	LUM/IVA granules are indicated in patients aged 2 years or older whilst the film coated tablets are indicated in patients aged 6 years or older (2, 3). Lumacaftor/ivacaftor should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks (2, 3). Refer to Document B2 Appendix C for further details of special warnings and precautions. Contraindications: Hypersensitivity to the active substance(s) or to any of the excipients (2, 3).	TEZ/IVA in combination with IVA should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks (4). Refer to Document B2 Appendix C for further details of special warnings and precautions. Contraindications: Hypersensitivity to the active substance(s) or to any of the excipients (4).	IVA/TEZ/ELX in combination with IVA should be used with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks (1). Refer to Document B2 Appendix C for further details of special warnings and precautions. Contraindications: hypersensitivity to the active substance(s) or to any of the excipients (1)
Method of administration and dosage	• PO • One sachet of LUM 100 mg/IVA 125 mg every 12 hours (for patients aged 2 to 5 years and weighing less than 14 kg) (2) • One sachet of LUM 150 mg/IVA 188 mg every 12 hours (for patients aged 2 to 5 years and weighing 14 kg or more) (2) • 2 tablets of LUM 100 mg/IVA 125 mg every 12 hours	• PO • One tablet containing TEZ 50 mg/IVA 75 mg in the morning and one tablet containing IVA 75 mg in the evening (for patients aged 6 to < 12 years weighing < 30 kg). • One tablet containing TEZ 100 mg/IVA 150 mg in the morning and one tablet containing IVA 150 mg in the evening (for patients aged 6 to < 12 years weighing ≥	• PO • Two tablets, each containing IVA 37.5 mg/TEZ 25 mg/ELX 50 mg in the morning and one tablet containing IVA 75 mg in the evening (for patients aged 6 to <12 years weighing <30 kg) • Two tablets, each containing IVA 75 mg/TEZ 50 mg/ELX 100 mg in the morning and one tablet containing IVA 150 mg in the evening (6 to <12 years

UK approved name and brand name	Lumacaftor, ivacaftor (Orkambi®)	Tezacaftor, ivacaftor (Symkevi®)	Ivacaftor, tezacaftor, elexacaftor (Kaftrio®)
	(for patients aged 6 to 11 years) • 2 tablets of LUM 200 mg/IVA 125 mg every 12 hours (for patients aged 12 years or older) (3). Dose adjustments are recommended in patients with moderate to severe hepatic impairment. Refer to Appendix C for further details (2, 3).	30 kg and ≥ 12 years) (4). Dose adjustments are recommended in patients with moderate to severe hepatic impairment and when co-administered with moderate and strong CYP3A inhibitors (4). Refer to Appendix C for further details.	weighing ≥30 kg, and ≥ 12 years) (1) Refer to Appendix C for further details on dose adjustments (1).
Additional tests or investigations	If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the *F508del* mutation on both alleles of the *CFTR* gene (2, 3). Assessments of liver function tests are recommended before initiating LUM/IVA, every 3 months during the first year of treatment, and annually thereafter (2, 3). For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered (2, 3). Refer to Appendix C for further details.	If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of an indicated mutation using a genotyping assay (4). Liver functions tests are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter (4). For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered (4). Refer to Appendix C for further details.	If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of at least one *F508del* mutation using a genotyping assay (1). Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter (1). For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered (1). Refer to Appendix C for further details.
List price and average cost of a course of treatment	• Cost per 112-day pack of LUM/IVA (film-coated tablets): £8,000 (36) • Cost per 28-day pack of LUM/IVA (granules sachets): £8,000 (37) • Annual acquisition cost (at List Price): £104,357.	• Cost per 28-day pack of TEZ/IVA: £6,294 (38) • Cost per 28-day pack of IVA: £7,000 (39) • Annual acquisition cost (at List Price): £173,414.	• Cost per 28 day pack of IVA/TEZ/ELX : £8,346 (40) • Cost per 28-day pack of IVA: £7,000 (39) • Annual acquisition cost (at List Price): £200,187 .
Patient access scheme (if applicable)	Confidential commercial access agreement between Vertex and NHSE is currently in place.		

Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; CE, European conformity; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELX, elexacaftor; IVA, ivacaftor; NHSE, National Health Service England; PO, per os (orally administered); TEZ, tezacaftor.

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

B.1.3.1 Disease background

Aetiology and pathophysiology

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 (41, 42). In pwCF, mutations in both copies of the *CFTR* gene (one gene from each parent) lead to disordered expression and/or function of CFTR protein compared to people with at least one wild type copy of the *CFTR* gene, 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 (21, 43). 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. Dysfunctional CFTR protein also leads to progressive damage of the pancreas, intestinal tract and liver so that patients experience severe symptom burden associated not only with lung damage, but also malabsorption, constipation, CF-related diabetes (CFRD) and CF-related liver disease (44).

Classification of CFTR mutations

To date, over 2,000 different *CFTR* mutations have been identified (45). These have commonly been categorised into five classes (46, 47). Class I mutations are nonsense, frameshift or splice mutations which interfere with *CFTR* gene transcription and result in the complete absence of CFTR protein. Class II mutations lead to CFTR proteins that are abnormally folded such that they are marked for subsequent degradation by the cell, resulting in little-to-no CFTR protein. Class III mutations yield protein with impaired gating mechanism, precluding regulation of the chloride transport through the apical membrane. Similarly, Class IV mutations result in sufficient protein trafficked to the apical membrane, however, the mutation affects the conductive properties of CFTR channels, limiting the transport of chloride out of the cell. Finally, Class V

mutations lead to reduced amounts of functional CFTR protein (46, 47). This classification system is summarised in Table 3.

Table 3. Classification of CFTR mutations

Mutation class	Result of mutation
I	Defective protein production
II	Defective processing
III	Defective regulation
IV	Defective conductance
V	Reduced amounts of functional CFTR
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator protein Reference: Koch et al (46)	

The majority of CFTR mutations are rare and the pathogenic mechanisms for some of them have yet to be determined, making classification according to the mechanism by which mutation affects CFTR protein function impractical (48). Consequently, there has been a recent shift towards an alternative approach, classifying mutations as those that reduce the quantity of CFTR reaching the cell surface, those that impair CFTR function, and those that reduce both the quantity and function of CFTR at the cell surface (49). This classification approach aligns with the mechanism of action of CFTRms, which were designed to improve CFTR quantity and/or function of CFTR at the cell surface (49).

For example, the *F508del* mutation results in CFTR protein misfolding and retention in the endoplasmic reticulum, and thus leads to a net loss in both the quantity and function of CFTR protein (48, 50). The *F508del* is a deletion of three base-pairs resulting in the omission of phenylalanine at position 508 of the CFTR protein and is the most common *CFTR* mutation in pwCF: around 90% of the UK CF population carries this mutation on at least one *CFTR* allele (51, 52).

As with *F508del*, other types of CFTR mutations are increasingly classified according to their effect(s) on CFTR protein quantity and/or function with an emphasis on responsiveness to CFTRms in certain instances. Mutations that produce no CFTR protein or are unresponsive to CFTRms in vitro are classified as “minimal function” (MF) mutations (53). Residual function (RF) mutations result in a moderate loss of CFTR-mediated chloride transport and, finally, gating mutations result in CFTR proteins that reach the cell surface but have defective anion channel activity as they fail to open and close properly, leading to reduced chloride transport (54). A list of CFTR genotypes abbreviations that are used throughout the document, is presented in Table 4.

Table 4. CFTR genotype abbreviations

Abbreviations	Definition	Examples of mutations on the second *CFTR* allele
F508del/F508del (F/F)	Homozygous for the *F508del-CFTR* mutation	N/A
F508del/MF (F/MF)	Heterozygous for the *F508del-CFTR* mutation and another mutation that produces no CFTR protein or is unresponsive to CFTRms ('minimal function')	*G542X, N1303K*
F508del/RF (F/RF)	Heterozygous for the *F508del* mutation and a mutation associated with residual CFTR protein activity ('residual function')	*R117H*, *R334W*, *R347P*
F508del/Gating (F/Gating)	Heterozygous for the *F508del* mutation and a gating mutation	*G511D, G178R, S1255P*
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, CFTR modulator; *F508del*, mutation leading to the deletion of phenylalanine 508 from the CFTR protein.		

Clinical Burden

CF is a congenital, multisystem disease characterised by progressive damage to numerous organs, with symptom burden starting at birth in the severest cases (55, 56). Severity of disease can be impacted by genotype, age and the stage of disease progression (57, 58). In 2021 there were 10,908 CF patients in the UK (59). The UK has the second highest incidence of CF in Europe of 1:2800, second only to Ireland (60) and similar to that seen in the United States (US) (61). While there have been improvements in CF care over the past years, there was little incremental effect on predicted survival prior to the introduction of CFTRms (62). CFTRms were first adopted in the UK in 2013 (63) and in 2011 the median age at death was only 26 years (62). In 2021, however, the median age at death for CF patients was 38 years (59), indicating a significant improvement since the introduction of CFTRms in the UK.

Key drivers for morbidity and mortality in CF include:

- Inevitable decline in lung function (percent predicted forced expiratory volume in one second [ppFEV1]) with each 1% reduction in ppFEV1 increasing the risk of death over 5 years by 4% (64).
- Number of pulmonary exacerbations (PEx) per year. Compared to having no exacerbations in a year, 1–2 exacerbations per year increases the risk of death 3-fold ($p<0.0001$) and 3 or more exacerbations per-year increases the risk of death 4.5-fold ($p<0.001$) (65)
- Poor nutritional status (low body mass index [BMI] and weight) (64, 65).

Survival models based on registry data have also consistently reported that clinical characteristics such CFRD and pancreatic sufficiency are reliable predictors of survival

in pwCF (64-66). The pulmonary and extra-pulmonary manifestations of CF are described below.

Progressive damage to lung function and structure

Common lung and airway abnormalities in pwCF include:

- A build-up of mucus in the airways known as mucus plugging that restricts airflow and causes air to become trapped within distal lung airspaces after expiration, resulting in pulmonary hyperinflation and breathing difficulties (67, 68)
- Airway wall thickening in early stages of chronic infection and inflammation (69)
- Bronchiectasis, a later stage in lung disease caused by long-term excessive inflammation of the airways resulting in irreversible tissue breakdown, permanent abnormal widening of the airways and mucus deposition (70). Symptoms include chronic productive cough and shortness of breath that worsens over time (70)
- Nasal polyps (soft growths within the nose), likely caused by the chronic congestion or infection common in CF, with symptoms including nasal congestion and a loss of smell (71)
- Lung collapse, caused by air leaks into the space between the lung and the chest wall. Symptoms include chest pain and shortness of breath. The severity depends on how much of the lung has collapsed, but it can be life threatening. Damaged lung tissue due to CF-related lung disease increases the likelihood of lung collapse (72, 73).

Structural lung damage often occurs at a very early age, with many infants presenting with structural deformities at diagnosis some of which can be irreversible (55, 74). It worsens with age (75-77) and as the disease progresses, further irreversible changes develop, such as bronchiectasis (78). In a longitudinal study of pwCF aged 9 to 24 years, most bronchiectasis developed within the 2-year time frame between successive scans, frequently without any indication on earlier scans (75).

The presence and extent of structural lung abnormalities in early childhood appear to predict the rate of subsequent lung disease progression, with more severe

abnormalities being associated with significantly worse lung function in later life compared to patients with milder abnormalities or normal lung structure (79). Turkovic and colleagues showed that mucus plugging and air trapping at 5 to 6 years of age are strongly associated with lower FEV_1 z-scores between the ages of 5 and 15 years (80). Given the presence of structural damage and disease progression in younger pwCF, sustained early intervention is critical to improve long-term outcomes (81).

PwCF commonly experience daily coughing, wheezing, and shortness of breath significantly limiting their routine daily physical activities (82, 83).

Pulmonary Exacerbations

PEx are intermittent episodes of acute worsening of lung disease symptoms, which are usually triggered by bacterial infection (84-87). Data from the US CF patient registry has shown that, in both children and adults, lower lung function measured in $ppFEV_1$, is associated with more frequent PEx (Table 5) (87). Furthermore, a Canadian retrospective study (N=851) found that, in the course of a mean follow-up of 8 years, people with ≥1 PEx during the study period had an annual rate of decline in lung function of 2.5%, over twice the rate in people without a PEx (88). This decline in lung function after a PEx is not fully reversible, setting a new baseline value which is lower than the baseline value prior to the PEx (89).

Table 5. Relationship between lung function ($ppFEV_1$) and number of PEx/year in pwCF derived from US CF Patient Registry data for 2004

Annual rates of PEx by $ppFEV_1$ decile in the US CF Patient Registry				
Mean $ppFEV_1$ of each decile	≥80	60-79	40-59	20-39
Mean annual PEx rate per decile	0.3	0.7	1.1	1.8

Abbreviations: CF, cystic fibrosis; PEx, pulmonary exacerbations; $ppFEV_1$, percent of predicted forced expiration volume in one second; pwCF, people with cystic fibrosis; US, United States.
Reference: Adapted from Goss and Burns (87).

Those aged 6 years or older with at least one *F508del-CFTR* mutation typically experience at least one PEx annually, usually requiring intensified antibiotic therapy and prolonged hospitalisation, which have a significant impact on patients' quality of life (QoL) (90-92). PEx have an acute negative effect on patient health and QoL, as well as several long-term consequences, including a faster rate of lung function decline (88), an increased risk of future exacerbations and hospitalisation (90), a higher likelihood of lung transplantation (93) and an increased mortality risk (64, 65, 88).

Lung transplant

CF is the third most common cause of lung transplantation globally (94). Out of 10,655 registered pwCF in the UK in 2019, 96 were accepted for transplant, and 51 of these patients received a bilateral lung transplant (95). Bilateral lung transplantation is complex, high risk, and expensive, but may be appropriate in CF patients with advanced or severe lung disease that has failed to respond to standard therapy (96). The median survival of pwCF post-lung transplant is approximately 7.5 years (97).

Extra-pulmonary manifestations

CFRD: CFRD is the most common CF-related co-morbidity, occurring in approximately 40%-50% of adults with CF (98). The prevalence of CFRD rises quickly in adolescence and adulthood, initially presenting as endocrine pancreatic dysfunction, which over time can lead to CFRD (99, 100). The incidence is also higher in certain genotypes, with Class I or II *CFTR* mutations[2] associated with a CFRD incidence of 92.3% (101).

Gastrointestinal disease: Loss of CFTR function makes the luminal environment of the small intestine dehydrated and more acidic, leading to mucus accumulation, frequent bacterial colonisation, malabsorption and poor growth (102). Increased levels of proinflammatory cytokines increase the risk of inflammatory bowel disease, such as Crohn's disease and coeliac disease (102) by 17 times and 3 times that of the general population, respectively (103, 104). Failure to thrive and low BMI are associated with increased susceptibility to lung infections (105, 106) and a higher rate of lung function decline (107, 108). The most serious acute intestinal complication of CF is intestinal obstruction, which can lead to chronic constipation and abdominal discomfort, as well as intestinal perforation and sepsis if left untreated (102).

CF associated liver disease (CFLD): CFLD is caused by the accumulation of thickened bile in the biliary ducts (109). The bile accumulation damages and inflames liver epithelial cells, causing localised fibrosis. Over time, prolonged epithelial damage can lead to inflammation throughout the liver, causing fibrosis, cirrhosis, and portal hypertension (109). In general, CFLD risk appears highest in those with CF mutations that result in little-to-no CFTR activity, such as *F508del* (110). A retrospective analysis

[2] This refers to the CF mutation classification system described in section

Disease background.

of the French CF Modifier Gene Study database found that the incidence of CFLD increased with age, reaching 32.2% by 25 years of age (111).

Factors affecting prognosis in CF

The clinical burden is impacted by the stage of the disease as measured by $ppFEV_1$ (112). A retrospective cohort study found that the steepness of the rate of decline in $ppFEV_1$ is inversely related to patient age at death and patients with $ppFEV_1$<30% have a 50% chance of dying within two years. After adjustment for age and sex, the relative risk of death within two years was 2.0 (95% confidence interval [CI]: 1.9 to 2.2) for each decrement in the FEV_1 of 10 percent below the predicted value (112). Thus, slowing down the decline in $ppFEV_1$ as early as possible is critical in CF treatment.

The number of PEx per year also impacts the clinical burden experienced by patients. Compared to having no exacerbations in a year, 1–2 exacerbations per year increases the risk of death 3-fold (P<0.0001) and 3 or more exacerbations per-year increases the risk of death 4.5-fold (P<0.001) (65). Poor nutritional status (low BMI and weight) is also a key driver for morbidity and mortality (64, 65).

Overall, CF is described by the patient community as a “deadly, progressive disease” and for pwCF and their caregivers there is a “daily battle” to slow the disease’s progression (113).

B.1.3.2 Impact of CF and current treatment on the healthcare budget, patients and their carers

Economic burden

A 2012 retrospective, cross-sectional study of CF patients in the UK conducted prior to the introduction of CFTRms found that the average annual direct healthcare cost of non-institutionalised patients diagnosed with CF was £15,146 (42.9 % of total costs) (114, 115). The number of PEx a patient experiences per year and the severity of lung function impairment have been identified as strong predictors of economic burden in the UK (116). The average annual healthcare cost for a patient with severe lung function impairment could be as much as seven times higher than for a person with mild disease (117). 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 (116).

Hospitalisation costs represent a large component of total direct medical costs in CF (118). According to the British Lung Foundation emergency admissions data from 2008-2012 pwCF in the UK are admitted to hospital on average once per year with an average length of stay (LOS) of 10 days (119). Overall, CF accounts for 9,500 hospital admissions and over 100,000 hospital bed days per year in the UK, with a third of these used by children under 15 years of age (119, 120). Pooled results from two randomised controlled trials (RCTs) conducted across several countries including the UK found the annual hospital admission rates of 0.91 and 0.90 in those receiving standard care in the real life setting and those receiving standard care in the real life setting + mannitol respectively (121-123), with a mean LOS during the 26-week period of 9.91 days (standard deviation [SD] 6.39) and 9.46 days (SD 6.22), respectively (123).

A 2021 UK based longitudinal study reported the mean annual time CF patients spent in hospital per year and the time spent on IV antibiotics before and during IVA treatment (124). It found that patients spent a mean of 23 ± standard error (SE) 6.8 days per year as inpatients pre-IVA, 9.2±SE 4.2 days during the first year of IVA treatment and 4.6±SE 1.7 days in the fifth year of treatment. In the year prior to starting IVA, patients spent a mean of 27.3±SE 6.1 days on IV antibiotics (home and inpatient IV antibiotics). This fell to 11.9±SE 4.8 days in the first year of IVA and remained low through to year 5, where the mean number of days on IV antibiotics was 12.4±SE 5.6.

People with CFRD are reported as having a significantly prolonged LOS (10.6 days) relative to non-diabetic pwCF (8.86 days, $P<0.001$) (125). Hospitalisation rates are also higher in individuals with poorer lung function. In a medical chart review study of 523 individuals with CF aged ≥12 years across France, Germany, Italy, Spain, Australia, and Canada, 67% had ≥1 hospitalisation over a mean of 27 months follow-up, with the rate of hospitalisation higher in those with poorer lung function (severe $ppFEV_1$ group) than those with moderate or mild lung function (Table 6) (126).

Table 6. Hospitalisations in individuals with CF based on lung function

Healthcare Resource Utilisation	Mild	Moderate	Severe
≥1 hospitalisation, %	55%	73%	86%
Hospitalisation rate (per patient-year), n ± SD	0.7 ± 1.1	1.4 ± 1.6	2.1 ± 2.0
Abbreviations: SD, standard deviation. Reference: Hodgkins et al (126)			

Pooled data from two RCT studies conducted across Europe (including the UK), the US, Canada, Argentina and Australia found that the mean costs of medications, hospital visits and community visits were £2,972 (SD, £3,157), £3,125 (SD, £5,745) and £53 (SD, £116) respectively in the control group treated with standard care in the real life setting (Table 7) (123). These costs were all far higher in patients that experienced a PEx during the trial period as compared with those that did not (123).

Table 7. Costs associated with CF treatment over a 26-week trial period

	Cost (£)	Control (N=134)	
		Mean	SD
No PDPE in trial period	Medication	2,617	2,713
	Community visits	53	122
	Hospitalisations	1,994	4,474
	TOTAL	4,664	5,492
PDPE in trial period	Medication	3,976	4,047
	Community visits	53	99
	Hospitalisations	6,325	7,561
	TOTAL	10,354	10,445
All patients	Medication	2,972	3,157
	Community visits	53	116
	Hospitalisations	3,125	5,745
	TOTAL	6,150	7,510
Pooled data; adult population, ITT Abbreviations: PDPE, protocol defined pulmonary exacerbation; SD, standard deviation Reference: NICE (123)			

Nearly 10% of CF patients require lung transplant, which also impacts costs (127) as lung transplant procedures have been estimated at £42,018 per transplantation with significant post-operative treatment costs estimated at £21,634 in year 1, £13,063 in year 2, £13,733 in year 3, £8,249 for years 4-10, and £4,590 for subsequent years (128).

Direct non-healthcare costs also impose a significant cost burden. In a cross-sectional study of adults with CF across eight European countries, Chevreul and colleagues (2016) found that direct non-healthcare costs (including formal and informal care) amounted to £17,638 per patient per year in the UK, with informal care being the highest cost item. Informal caregivers provide a valuable contribution as the cost of replacing their care with paid help was estimated at £13,373 (129, 130).

Indirect costs are also an important contributor to the economic burden of CF, however, there is a paucity of published data for either CF patients or their caregivers

(131). In a study of 254 CF patients in the UK, 40% of patients reported that they had resigned from a job due to CF (132). Chevreul and colleagues (2016) found that the mean annual labour productivity loss was £10,186 per patient per year in the UK (129, 130). Indirect medical costs are also imposed on families of CF patients, as a result of caregiving responsibilities that lead to lower availability to work, productivity loss, greater absenteeism and obstacles to career progression (133). A small study in the UK found that 80% of caregivers had sacrificed paid employment to care for their child (134). Increased out-of-pocket expenditure was found to be associated with caring for an individual with a chronic illness and resulted in financial burden for families of these individuals (134).

Wyatt et al. conducted a retrospective chart review in the UK to look at the resource implications of specific CF genotypes (135). The chart review included 200 CF patients aged 6 years or older. Patients were required to have either the G551D/other or *F508/F508* mutation, representing nearly 60% of UK patients. For each patient included in the study, 2 years of uninterrupted resource use between June 2007 and March 2012 was reviewed. The results show comparable resource implications of the two genotypes, apart from the number of days of home IV; the mean over 2 years was 45 days for the G551D/other mutation and 33 days for the *F508/F508* mutation (Table 8) (135).

Table 8. Two-year healthcare utilisation by pwCF with different genotypes

	Routine Visits Mean (SD)	No. of Hospns Mean (SD)	Total No. of Hosp days Mean (SD)	Hosp IV days Mean (SD)	Home IV days Mean (SD)	Neb AB n (%)	Dornase n (%)
G551D/other (pts, N=63)	14.0 (8.4)	3.4 (3.4)	49 (82)	35 (40)	45 (80)	55 (87)	42 (67)
DF508/DF508 (pts, N=137)	15.7 (9.3)	3.5 (3.3)	48 (84)	39 (46)	33 (49)	119 (87)	98 (72)

Abbreviations: SD, standard deviation; Hospns, hospitalisations; pts, patients.
Reference: Wyatt et al (135).

Humanistic burden

The clinical manifestations of CF also lead to impaired mental and physical health related quality of life (HRQoL) for both pwCF and their families and caregivers (115, 136-138). The prevalence of depression in CF patients ranges from 8% to 29% among children and adolescents and 13 to 33% among adults (139). Patients and parents of children with CF are two to three times more likely to experience anxiety and depression than the general population (139). Day-to-day care (not including CFTRm

therapy) imposes a substantial burden, as the intensive regimen patients follow (including nebulised and inhaled therapies and airway clearance techniques) can take approximately 2-3 hours per day (140, 141). Adolescents with CF report lifestyle restrictions due to their poor health and time-consuming treatments which they feel restrict their freedom (142).

Several disease-related factors are associated with reduced HRQoL in pwCF, including reduced lung function, PEx, low BMI and depression (143). Caregivers of CF patients with greater disease severity reported greater burden, and lower utility and visual analogue scale scores than caregivers of patients with lesser disease severity (129, 144).

Clinical pathway of care and context of the proposed positioning of IVA/TEZ/ELX, LUM/IVA and TEZ/IVA.

Currently there is no cure for CF (145, 146), but early intervention is crucial to attenuate disease progression and prevent further damage (20, 72, 147-149). Existing treatments are broadly classified into two groups based on their expected clinical benefit, including: 1) symptom-based therapies, which comprise the established clinical management (ECM), a term used throughout this document to indicate collectively treatments which do not treat the cause of CF (150) and 2) CFTRms, currently the only disease-modifying treatment options which target the underlying cause of disease (43).

Established clinical management

In the UK National Institute for Health and Care Excellence (NICE) recommends the following symptom-based therapies as ECM of CF (150):

- Airway clearance techniques (breathing techniques, autogenic drainage and airway clearance devices) (151)
- Mucoactive agents (dornase alpha, hypertonic sodium chloride, or mannitol dry powder) to reduce the viscosity and/or adherence of the mucus within the airway, thereby promoting better mucus clearance (152)
- Antibiotics for treating acute and chronic bacterial infections
- Immunomodulatory agents (e.g., azithromycin, corticosteroids)
- Nutritional support to achieve normal growth and development (150, 151)

- Exercise to help clear mucus from the lungs and improve overall lung function (150, 151).

The NHS guidance on CF treatments also indicates that bronchodilators may be used to widen the airways (151). Further treatments are also recommended depending on any complications which may arise such as distal intestinal obstruction syndrome, malabsorption, liver disease, low bone mineral density, CFRD and psychological illness.

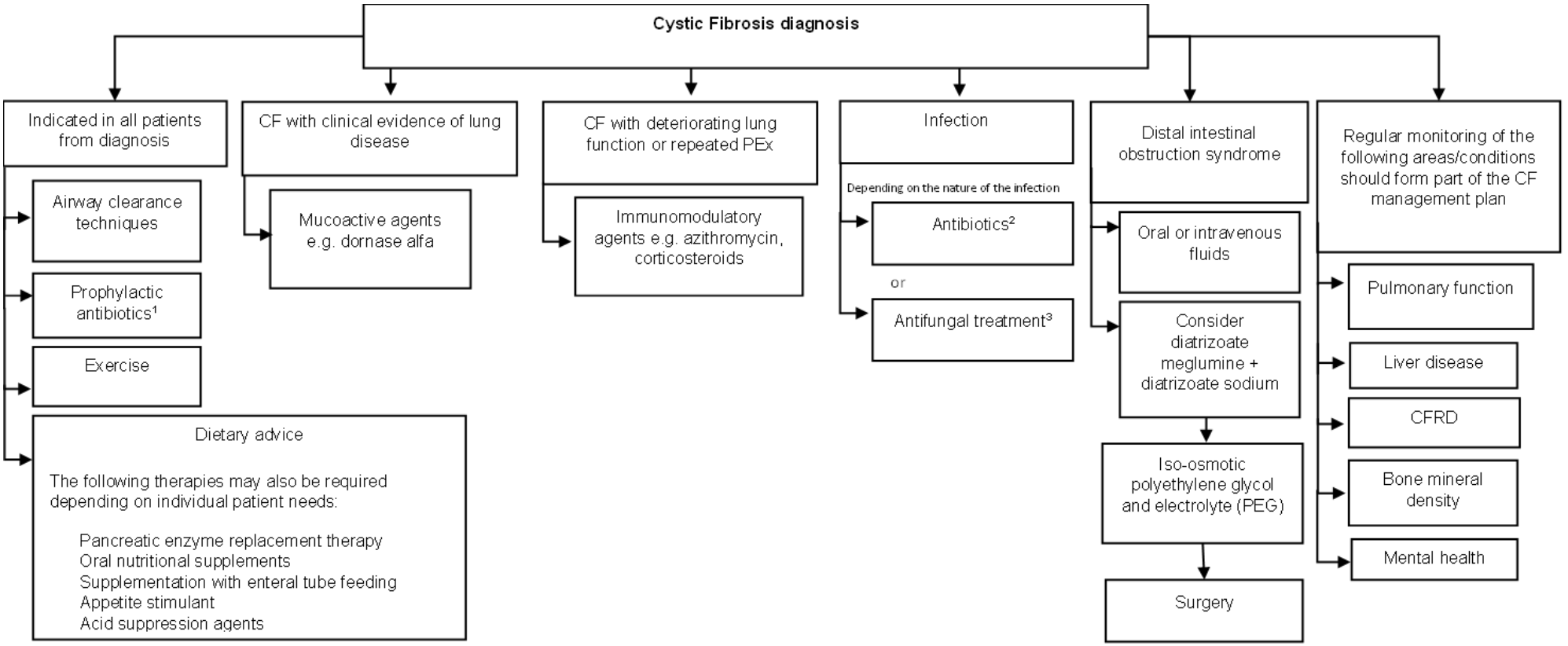
The European CF Society consensus statements on standards of care in CF (9) recommend that:

- Children with CF with eligible CFTR gene variants should be offered treatment with IVA from 4 months of age
- Children with CF who are homozygous for the F508del variant, aged 2–5 years, should be offered treatment with LUM/IVA
- PwCF aged six years or older, with one or two F508del variants, should have daily treatment with IVA/TEZ/ELX
- PwCF and at least one responsive non-F508del variant should be considered for mono (IVA), dual (TEZ/IVA) or triple CFTRm therapy (IVA/TEZ/ELX) (9)

However, such modulators are not included in the NICE guideline (150).

Existing ECM represents a considerable burden on pwCF, as they typically spend 2-3 hours per day on treatment regimens (140, 141). Furthermore, ECM fails to address the underlying cause of CF. The ECM for CF recommended by NICE is described in the diagram in Figure 2.

Figure 2. Established clinical management of CF



[1]At certain ages prophylactic antibiotics are recommended to prevent staphylococcus aureus infection
[2]The antibiotic therapy is dependent on the bacterial strain causing the infection. Refer to NG78 for further details on the choice of antibiotic therapy. Microbiological advice may be required.
[3]Sustained treatment may be required. Microbiological advice is recommended when selecting an antifungal medicine.
Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; PEx, pulmonary exacerbations.
Reference: Adapted from NICE guidance (NG78) (150)

CFTR Modulators

By targeting the underlying cause of CF, CFTRms have shifted the paradigm for the treatment of CF, offering benefits beyond symptom-based therapy (153). Table 9 describes the CFTRm treatments currently indicated in each CF genotype and the respective prevalence of each genotype. These treatments are not currently recommended by NICE (150). However, an NHS commissioning policy exists in England for all three licensed CFTRm combination therapies as well as IVA monotherapy. Only the combination therapies are within the scope of this appraisal (6).

Results from clinical studies of LUM/IVA and TEZ/IVA demonstrate significant improvements in lung function, respiratory symptoms, nutritional status, and mucus clearance, as well as reduced rates of PEx (154-157).

LUM/IVA is the only approved medicine that targets the underlying protein defect in CF patients with the F/F genotype as young as 2 years of age (2, 3). Three RCTs demonstrated a manageable safety profile and consistent improvements in important goals of CF treatment such as lung function and nutritional status in patients 6 years or older homozygous for *F508del* (158, 159). These benefits are maintained long-term with continued LUM/IVA administration (156, 160). Statistically significant improvements in key outcomes such as BMI and weight were also observed in the 2-5 years age group in a phase 3 single-arm trial and its corresponding 96-week extension study (161, 162).

TEZ/IVA represents a disease-modifying treatment option for patients with F/F and F/RF genotypes aged 6 years or older. TEZ/IVA offers an alternative therapeutic option for patients, particularly to those who are not able to tolerate LUM/IVA due to adverse events (AEs) or drug-drug interactions. The efficacy and safety of TEZ/IVA in patients aged 6 years or older has been established in pivotal phase 3 studies, demonstrating TEZ/IVA's ability to address the key primary goals of CF treatment for patients with F/F and F/RF genotypes by improving lung function, reducing PEx, enhancing nutritional status, and improving HRQoL (157, 163-165).

Table 9. CFTR modulator therapies indicated in common CF genotypes

Genotype	Genotype prevalence (166)	Indicated treatments	Guidance
Homozygous for the *F508del-CFTR* mutation (F/F)	54.3%	TEZ/IVA	Commissioning Policy (6)
		LUM/IVA	Commissioning Policy (6)
		IVA/TEZ/ELX	Commissioning Policy (6)
		ECM alone	NG78 (150)
Heterozygous for the *F508del-CFTR* mutation and another 'minimal function' mutation with no/minimal CFTR protein activity (F/MF)	29%	IVA/TEZ/ELX	Commissioning Policy (6)
		ECM alone	NG78 (150)
Heterozygous for the *F508del-CFTR* mutation and a 'residual function' mutation associated with residual CFTR protein activity (F/RF)	6.2%	TEZ/IVA	Commissioning Policy
		IVA/TEZ/ELX	Commissioning Policy (6)
		ECM alone	NG78 (150)
Heterozygous for the *F508del-CFTR* mutation and a gating mutation (F/Gating)	10.6%	IVA	Commissioning Policy (6)
		IVA/TEZ/ELX	Commissioning Policy (6)
		ECM alone	NG78 (150)
Heterozygous for the *F508del* CFTR mutation with other or unknown mutation (F/Other)	NR	ECM alone	NG78 (150)
		IVA/TEZ/ELX	Commissioning Policy (6)

Abbreviations: ECM, best supportive care; 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.

These benefits were generally maintained over an additional 96 weeks of treatment in (163, 167).

More recently, treatment with IVA/TEZ/ELX demonstrated unprecedented improvements in lung function ($ppFEV_1$), improvements in CFTR function, a dramatically reduced risk of PEx and transformative improvements in QoL in RCTs of patients aged ≥12 years with at least one *F508del* mutation (7, 168-172). IVA/TEZ/ELX has also demonstrated robust and durable improvements in measures of lung function (as measured by $ppFEV_1$) and respiratory symptoms in patients with F/F and F/MF genotypes aged 6 through 11 years (173-175). Given the substantial clinical benefit to CF patients from the age of 6 years, IVA/TEZ/ELX could have a significant societal impact by alleviating the physical and psychological caregiver burden and reducing the need for early retirement (115, 176, 177).

Further clinical evidence of the efficacy of these modulators will be discussed in detail in **Section B.2**. As the first class of disease-modifying treatments, CFTRms represent a major advancement in CF management (178). The trial data and real-world evidence as described in **Section B.2**. suggest that these treatments could alleviate key drivers of morbidity and mortality in CF. A simulation study applied to the Canadian pwCF indicates that delayed access to IVA/TEZ/ELX could have a negative impact on patients' lung health, resulting in a higher number of individuals with severe disease who ultimately may require a lung transplant or die (179). If all eligible patients in

Canada started triple therapy in 2021, defined in the study as 'early', the estimated median age at death could increase an additional 9.2 years (95% CI: 7.5 to 10.8) over a 10-year period compared to the baseline scenario, resulting in 74 (95% CI:62, 86) fewer deaths. In contrast, 'delayed' introduction of the triple therapy, i.e., introduction in 2025, would improve the median age at death by only 3.3 years (95% CI: 1.7 to 5.0), resulting in only 31 (95%CI: 19 to 44) fewer deaths between 2021 and 2030. The study also predicted that 'early' availability of the triple therapy could lead to 146 fewer transplants by 2030 due to fewer individuals in the severe lung function category, compared with 98 fewer transplants if the drug's introduction is 'delayed' (179).

Unmet need

While there have been improvements in CF care over the past years, prior to the introduction of CFTRms there has been little incremental effect on predicted age at death (180). CFTRms were first adopted in the UK in 2012, and the previous year (i.e., 2011) the median age of death was only 26 years (62). In 2021, however, the median age at death for pwCF patients was 38 years (59), indicating a significant improvement since the introduction of CFTRms in the UK. However, this is still approximately 46 years below the national median which was 82.3 years for males and 85.8 years for females in the years 2018 to 2020 (181). Furthermore, less than five pwCF received a bilateral lung transplant in 2021, compared to 51 in 2019 (59).Prior to the introduction of IVA/TEZ/ELX, pwCF with the F/MF genotype and those with at least one *F508del-CFTR* allele had no disease modifying treatment option available and faced substantial disease burden (7, 178).

Until recently, clinical management in England focused on controlling symptoms of CF and did not address the underlying cause of this multi-organ disease. Despite ECM, patients experience a high clinical burden including a progressive loss of lung function at an annual ppFEV$_1$ decline of one to three percentage points per year (93, 182). Those with at least one *F508del-CFTR* mutation typically experience at least one PEx annually (90-92). PEx have a significant impact on patient morbidity and mortality and each episode of PEx is associated with long term lung function decline and a higher risk of a future PEx. Subsequent to a PEx episode, patient HRQoL scores have been found to be reduced for several weeks (91). Structural lung damage in CF patients often occurs at a very early age, with many infants presenting with structural

deformities at diagnosis that may be irreversible (55, 74, 149). CF also has significant deleterious effects on the health-related quality of life (HRQoL) of patients, families and caregivers (129, 136, 138) and several studies have shown a high prevalence of depression among pwCF (176, 183).

Sustained early intervention to preserve lung function is critical to improving long-term outcomes. The clinical community has highlighted the need for new therapies that could improve survival and QoL in CF (184) by targeting the underlying protein defect that causes CF, preventing early lung disease in children and altering the course of disease progression. CFTRms are the first treatment option to address the key underlying cause of the disease and restore CFTR protein quantity and function, producing multi-systemic benefits and lower risk of mortality, which have been validated in clinical practice (185).

B.1.3.3 Proposed positioning of IVA/TEZ/ELX, LUM/IVA and TEZ/IVA in the CF treatment pathway in England

IVA/TEZ/ELX, LUM/IVA and TEZ/IVA are indicated as add-on therapy to ECM in the treatment of CF with the choice of CFTRm regimen depending on patient *CFTR* genotype and age as described in Table 2 (1-4). They are recommended for long-term uninterrupted use starting from the age indicated in their respective licences and are currently reimbursed in 24 countries globally (Vertex, internal communication).

The NHSE commissioning statement for IVA, TEZ/IVA, LUM/IVA and IVA/TEZ/ELX sets out the eligibility criteria for pwCF (6). However, none of the three products described in this appraisal are currently recommended in the NICE guidelines (150).

B.1.4 Equality considerations

We do not anticipate that this appraisal raises any equality issues according to the current proposed scope of the appraisal, although an appraisal approach of subgrouping the indicated populations according to *CFTR* genotype or baseline lung function would raise equality concerns.

B.2 Clinical effectiveness

This section describes the available evidence of clinical efficacy and safety for each of the three CFTRms considered in this appraisal. To present the comprehensive

evidence collected for each CFTRm in several subpopulations of pwCF defined by age and *CFTR* genotype, each of the B2 sections is subdivided into three main subsections outlining evidence for each of the interventions (IVA/TEZ/ELX, LUM/IVA or TEZ/IVA). Each subsection is further divided to demarcate the trials according to the age of their enrolled populations, following the chronological sequence of evidence collection and marketing authorisations of CFTRms. Trials in adolescents and adults (≥12 years of age) are presented first, followed by studies in younger children aged 6 to 11 years, and finally, paediatric studies in patients aged 2 to 5 years [where applicable]. In each subsection, pivotal trials were described first, followed by the corresponding open-label extension (OLE) studies and other studies used to support marketing authorisation and/or to inform the cost-effectiveness model.

All clinical studies with CFTRms are abbreviated to the last 6 digits with the first 3 digits denoting the investigational drug (ELX=VX-445; TEZ=VX-661; LUM=VX-809) and the last 3 digits denoting the study number (e.g., study VX14-661-106 is study 661-106).

In all trials, both the intervention and comparator were administered as add-ons to components of ECM and will be described as IVA/TEZ/ELX, LUM/IVA, TEZ/IVA, IVA and placebo (PBO) hereafter, as applicable.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify the available clinical evidence for CFTRms included in the decision problem in indicated populations of pwCF.

The literature search for evidence of clinical efficacy and safety was undertaken in May 2022 in electronic databases (EMBASE, MEDLINE and The Cochrane Library), and was supplemented with hand searches of grey literature sources including conference proceedings, clinical trial registries, health technology assessment (HTA) bodies and medical association websites. Studies were assessed for methodological quality and their data extracted.

The complete reference list of the 184 studies (describing 46 unique trials of CFTRms including IVA and 138 unique trials of components of ECM) identified in the SLR can be found in **Appendix D**. The included trials of CFTRms encompassed seven trials of IVA, 11 of TEZ/IVA, 13 of LUM/IVA and 15 trials of IVA/TEZ/ELX. The identified

IVA/TEZ/ELX, LUM/IVA and TEZ/IVA studies were then assessed for their relevance to the given decision problem (Table 10, Table 11and Table 12).

B.2.1.1 IVA/TEZ/ELX

Of the 15 IVA/TEZ/ELX trials identified in the SLR, six were not considered relevant for the decision problem and are therefore not described further in this appraisal (Table 10). Of the nine studies considered relevant, eight were either pivotal trials or OLE studies included in the European Medicines Agency (EMA) marketing authorisation application or expansion of the marketing authorisation and were also used to inform the CEM (studies 445-102, 445-103, 445-105, 445-104, 445-110, 445-106 Part B, 445-107, and 445-116). These studies are described in detail in Section B.2.1.1. KEPLER study 445-109, which was included in the indirect treatment comparison (ITC) for CF patients aged 12 years or older who are homozygous for *F508del*, is described in more detail in Appendix D.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to IVA/TEZ/ELX for the treatment of CF.

B.2.1.2 LUM/IVA

Of the 13 LUM/IVA trials identified in the SLR, five were not considered relevant for the decision problem and are therefore not described further in this appraisal (Table 11). Of the eight studies considered relevant for the decision problem, seven were either pivotal trials or OLE studies included in the EMA marketing authorisation application, expansion of the marketing authorisation or/and to inform the cost-effectiveness model (TRAFFIC study 809-103, TRANSPORT study 809-104, PROGRESS study 809-105, studies 809-109, 809-110, 809-115B and 809-116) and are described in detail in Section B.2.2.2.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to LUM/IVA for the treatment of CF.

B.2.1.3 TEZ/IVA

Of the 11 TEZ/IVA trials identified in the SLR, six were not considered relevant for the decision problem and are therefore not described further in this appraisal (Table 12). Of the five remaining studies, four were either pivotal trials or OLE studies used to

obtain a marketing authorisation, or to support expansion of the marketing authorisation and/or to inform the cost-effectiveness model (CEM) (studies 661-106, 661-108, 661-110, and 661-115), and are described in detail in Section B.2.2.3. Study 661-113, which was included in the ITC for pwCF aged 6 to 11 years or older with F/F or F/RF genotypes, is described in more detail in Appendix D.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to TEZ/IVA for the treatment of CF.

Table 10. Overview of the studies comprising the clinical trial programme for IVA/TEZ/ELX

CFTRm	Study name	Study identifier	Genotype	Age (yrs)	Interventions	Status	Relevant for this appraisal & reason	Study described in
IVA/TEZ/ELX	Study 445-001 (Part F)*	VX16-445-001 (NCT03227471)	F/MF	18+		Completed	No; does not inform the CEM due to short (4-week) duration	N/A
	AURORA F/F (study 445-103)	VX17-445-103 (NCT03525548)	F/F	12+	IVA/TEZ/ELX vs TEZ/IVA	Completed	Yes; pivotal trial	B2
	KEPLER (study 445-109)	VX18-445-109 (NCT04105972)	F/F	12+	IVA/TEZ/ELX vs TEZ/IVA	Completed	Yes; informs the CEM	Appendix D
	KEPLER OLE (study 445-115)	VX19-445-115 (NCT04362761; EudraCT2019-003455-11)	F/F	12+	IVA/TEZ/ELX	Ongoing	No; does not inform the CEM due to results not being available at the time of submission	N/A
	AURORA OLE (study 445-105)	VX17-445-105 (NCT03525574)	F/F or F/MF	12+	IVA/TEZ/ELX	Ongoing	Yes; supports marketing authorisation and informs the CEM	B2
	SHUTTLE (study 445-113)	VX18-445-113 (NCT04043806)	F/F or F/MF	12+	IVA/TEZ/ELX	Ongoing	No; does not inform the CEM due to results not being available at the time of submission	N/A
	AURORA F/MF (study 445-102)	VX17-445-102 (NCT03525444)	F/MF	12+	IVA/TEZ/ELX vs PBO	Completed	Yes; pivotal trial which also informs the CEM	B2
	VOYAGER (study 445-117)	VX19-445-117 (NCT04599465)	F/MF	12+	IVA/TEZ/ELX	Completed	No; does not inform the CEM due to results not being available at the time of submission	N/A
	Study 445-126	VX20-445-126 (NCT04969224)	F/MF	12+	IVA/TEZ/ELX	Completed	No; does not inform the CEM due to results not being available at the time of submission	N/A
	AURORA F/RF F/Gating (study 445-104)	VX18-445-104 (NCT04058353)	F/RF or F/Gating	12+	IVA/TEZ/ELX vs TEZ/IVA (F/RF) or IVA (F/Gating)	Completed	Yes; supports marketing authorisation and informs the CEM	B2 Appendix D
	AURORA F/RF F/Gating OLE (study 445-110)	VX18-445-110 (NCT04058366)	F/RF or F/Gating	12+	IVA/TEZ/ELX	Completed	Yes; supports marketing authorisation and informs the CEM	B2
	AURORA 6-11 (study 445-106 Part B)	VX18-445-106 (NCT03691779)	F/F or F/MF	6-11	IVA/TEZ/ELX	Completed	Yes; supports marketing authorisation and informs the CEM	B2 Appendix D
	AURORA 6-11 OLE (study 445-107)	VX19-445-107 (NCT04183790; EudraCT 2019-001827-11)	F/F or F/MF	6+	IVA/TEZ/ELX	Ongoing	Yes; informs the CEM	B2
	GALILEO (study 445-116)	VX19-445-116 (NCT04353817; EudraCT2019-003554-86)	F/MF	6-11	IVA/TEZ/ELX vs PBO	Completed	Yes; informs the CEM	B2
	GALILEO OLE (study 445-119)	VX20-445-119 (NCT04545515)	F/MF	6+	IVA/TEZ/ELX	Ongoing	No; does not inform the CEM due to results not being available at the time of submission	N/A

Abbreviations: CEM, cost effectiveness model; ELX, elexacaftor; F/F, homozygous for the *F508del*-CFTR mutation; F/Gating, 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 ('residual function'); IVA, ivacaftor; N/A, not applicable; OLE, open-label extension; PBO, placebo; TEZ, tezacaftor; yrs, years. Colours indicate the age group of enrolled pwCF (green, 18+, blue, 12+, and pink, 6-11 or 6+ years of age)

Table 11. Overview of the studies comprising the clinical trial programme for LUM/IVA

CFTRm	Study name	Study identifier	Genotype	Age (yrs)	Interventions	Status	Relevant for this appraisal & reason	Study described in
LUM/IVA	TRAFFIC (study 809-103)	VX12-809-103 (NCT01807923)	F/F	12+	LUM/IVA vs PBO	Completed	Yes; pivotal trial which also informs the CEM	B2 Appendix D
	TRANSPORT (study 809-104)	VX12-809-104 (NCT01807949)	F/F	12+	LUM/IVA vs PBO	Completed	Yes; pivotal trial which also informs the CEM	B2 Appendix D
	PROGRESS (study 809-104)	VX12-809-105 (NCT01931839)	F/F	12+	LUM/IVA	Completed	Yes; informs the CEM	B2
	Study 809-106	VX14-809-106 (VX14-809-106)	F/F	12+	LUM/IVA	Completed	No; does not inform the CEM	N/A
	Study 809-112	VX15-809-112 (NCT02875366)	F/F	12+	LUM/IVA vs PBO	Completed	No; the primary and key secondary outcomes are related to exercise tolerance, hence the study does not inform the CEM	N/A
	Wark, Cookson, et al. 2017	N/A	F/F	12+	LUM/IVA	Completed	No; does not inform the CEM due to small sample size of only 9 patients	N/A
	Lee, Morton, et al. 2020	N/A	F/F	12+	LUM/IVA	On-going	No; ongoing study that does not inform the CEM	N/A
	Study 809-011 (Part B)	VX13-809-011 (NCT01897233)	F/F	6-11	LUM/IVA	Completed	Yes; this trial does not inform the CEM but is included in the ITC	Appendix D
	Study 809-109	VX14-809-109 (NCT02514473)	F/F	6-11	LUM/IVA vs PBO	Completed	Yes; supports the marketing authorisation and informs the CEM	B2 Appendix D
	Study 809-110 OLE	VX15-809-110 (NCT02544451)	F/F	6+	LUM/IVA vs PBO	Completed	Yes; this study informs the CEM	B2
	Study 809-115 (Part B)	VX15-809-115 (NCT02797132)	F/F	2-5	LUM/IVA	Completed	Yes; supports the marketing authorisation	B2
	Study 809-116 OLE	VX16-809-116 (NCT03125395)	F/F	2+	LUM/IVA	Completed	Yes; supports the marketing authorisation	B2
	Study 809-121 (MRI)	VX16-809-121 (NCT03625466)	F/F	2-5	LUM/IVA vs PBO	Completed	No; this is a phase 2 exploratory study which does not inform the CEM	N/A

Abbreviations: CEM, cost effectiveness model; ELX, elexacaftor; F/F, homozygous for the *F508del*-CFTR mutation; F/Gating, 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 function; ITC, indirect treatment comparison; IVA, ivacaftor; LUM, lumacaftor; MRI, magnetic resonance imaging; N/A, not applicable; OLE, open-label extension; PBO, PBO; TEZ, tezacaftor; yrs, years. Colours indicate the age group of enrolled pwCF (blue, 12+, pink, 6-11 or 6+ years of age and yellow, 2-5 or 2+ years of age)

Table 12. Overview of the studies comprising the clinical trial programme for TEZ/IVA

CFTRm	Study name	Study identifier	Genotype	Age (yrs)	Interventions	Status	Relevant for this appraisal & reason	Study described in
TEZ/IVA	Study 661-103	VX13-661-103 (NCT02070744)	F/F	18+	TEZ/IVA, PBO	Completed	No; does not inform the CEM due to short follow-up period compared to other RCTs in this age/genotype population	N/A
	BEST (study 661-111)	VX14-661-111 (NCT02508207)	F/F	18+	TEZ/IVA, PBO	Completed	No; does not inform the CEM due to short (4-week) duration	N/A
	EVOLVE (study 661-106)	VX14-661-106 (NCT02347657)	F/F	12+	TEZ/IVA, PBO	Completed	Yes; pivotal trial which also informs the CEM	B2 Appendix D
	C-FACT (Study 661-112)	VX15-661-112 (NCT02730208)	F/F	12+	TEZ/IVA, PBO	Completed	No; does not inform the CEM due to its exploratory nature and data availability at 72-week timepoint only	N/A
	ENCOURAGE (study 661-114)	VX16-661-114 (NCT03150719)	F/F	12+	TEZ/IVA, PBO	Completed	No; does not inform the CEM due to short (8-week) duration	N/A
	EXTEND OLE (study 661-110)	VX14-661-110 (NCT02565914)	F/F or F/RF	12+	TEZ/IVA	Ongoing	Yes; supports marketing authorisation	B2
	EXPAND (study 661-108)	VX14-661-108 (NCT02392234)	F/RF	12+	TEZ/IVA, IVA, PBO	Completed	Yes; pivotal trial which also informs the CEM	B2 Appendix D
	ENHANCE (study 661-109)	VX14-661-109 (NCT02412111)	F/Gating	12+	TEZ/IVA, IVA, PBO	Completed	No; F/Gating population not covered by the marketing authorisation	N/A
	ENTRUST (study 661-113)	VX15-661-113 (NCT02953314)	F/F or F/RF	6-11	TEZ/IVA	Completed	Yes; informs the CEM	Appendix D
	EMBRACE (study 115)	VX16-661-115 (NCT03559062)	F/F or F/RF	6-11	TEZ/IVA, PBO	Completed	Yes; supports marketing authorisation and informs the CEM	B2 Appendix D
	Study 661-116 OLE	VX17-661-116 (NCT03537651)	F/F or F/RF	6+	TEZ/IVA	Ongoing	No; does not inform the CEM due to results not being available at the time of model development	N/A

Abbreviations: CEM, cost effectiveness model; F/F, homozygous for the *F508del*-CFTR mutation; F/Gating, heterozygous for the *F508del* mutation and a gating mutation; F/RF, heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein; IVA, ivacaftor; N/A, not applicable; OLE, open-label extension; PBO, placebo; RCT, randomised controlled trials; TEZ, tezacaftor; yrs, years. Colours indicate the age group of enrolled pwCF (green, 18+, blue, 12+, and pink, 6-11 or 6+ years of age)

B.2.2 Summary of methodology of the relevant clinical effectiveness evidence

B.2.2.1 IVA/TEZ/ELX

Evidence for the clinical efficacy and safety of IVA/TEZ/ELX deemed relevant for the decision problem encompasses eight trials outlined in Table 10. Six are completed phase 3 trials with published results while the remaining two, study 445-105 and study 445-107, are the ongoing OLE studies. Detailed methods and results of the six completed phase 3 trials, and interim results from two ongoing phase 3 OLE studies are presented below are presented in Sections B.2.2 to B.2.9.

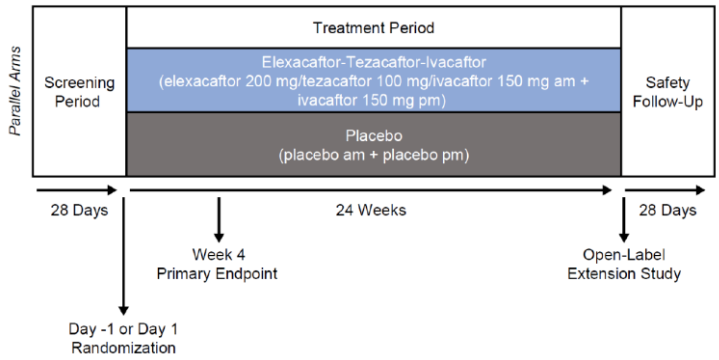
B.2.2.1.1 CF patients ≥12 years of age

Table 13 summarises the trial methodology of relevant IVA/TEZ/ELX studies identified in the pwCF aged ≥12 years, while

Table 14 outlines the baseline characteristics of subjects enrolled in those trials.

Study 445-102 was a randomised, double-blind, PBO-controlled trial that evaluated the efficacy and safety of IVA/TEZ/ELX in CF patients with F/MF genotype who are 12 years of age or older. In this study, patients completed a 28-day screening process prior to a 24-week treatment period. During the double-blind treatment period, patients were randomly assigned in a 1:1 ratio to receive either IVA/TEZ/ELX or PBO. PBO was chosen as the most appropriate comparator, as other CFTRms (IVA, LUM/IVA and TEZ/IVA) are not indicated for F/MF patients. Randomisation was stratified according to percent predicted forced expiratory volume over one second ($ppFEV_1$) at screening (<70% versus [vs] ≥70%), age at screening (<18 years vs ≥18 years), and sex (Figure 3) (7).

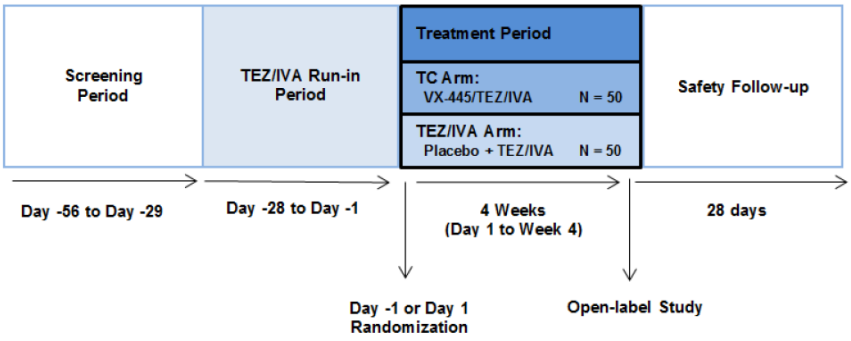
Figure 3. Study 445-102 trial design



Reference: Middleton et al. (7)

Study 445-103 was a randomised, double-blind, active-controlled trial that evaluated the efficacy and safety of IVA/TEZ/ELX compared to TEZ/IVA in CF patients with F/F genotype ≥12 years of age. After a 4-week run-in period, patients were randomly assigned by an interactive web response system in a 1:1 ratio to receive either IVA/TEZ/ELX or TEZ/IVA for 4 weeks (Figure 4) (170). [redacted] PBO tablets were used to maintain double blinding. Randomisation was stratified by $ppFEV_1$ (<70% vs =70%, as determined during the run-in period) and age (<18 vs ≥18 years at the screening visit) (170). Although study 445-103 does not inform clinical inputs in the economic model due to its short, 4-week duration, it is a pivotal trial which supported the EMA marketing authorisation application. It is also one of the parent studies of study 445-105, which is the key source of long-term clinical efficacy inputs for the economic model.

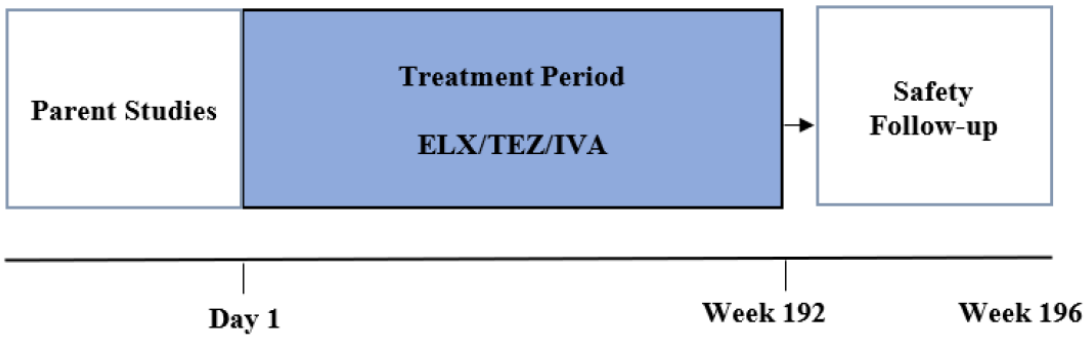
Figure 4. Study 445-103 trial design



Reference: Heijerman et al. (170)

Following participation in study 445-102 and study 445-103 trials, study subjects had the option to enrol in an ongoing 192-week OLE study, **study 445-105,** to evaluate the long-term safety and efficacy of IVA/TEZ/ELX in CF patients with F/F and F/MF genotypes aged 12 years or older. Each subject who completed the treatment period visits in one of these studies was deemed eligible for inclusion in study 445-105. All enrolled patients received treatment with open-label IVA/TEZ/ELX (IVA 150 mg, TEZ 100 mg, ELX 200 mg) as fixed dose combination tablets in the morning and IVA 150 mg as mono tablet in the evening (187). Results from a week 144 interim analysis (IA) of efficacy and pooled safety data, as of March 2022, are described in this dossier. The study design is shown in Figure 5 (188).

Figure 5. Study 445-105 trial design



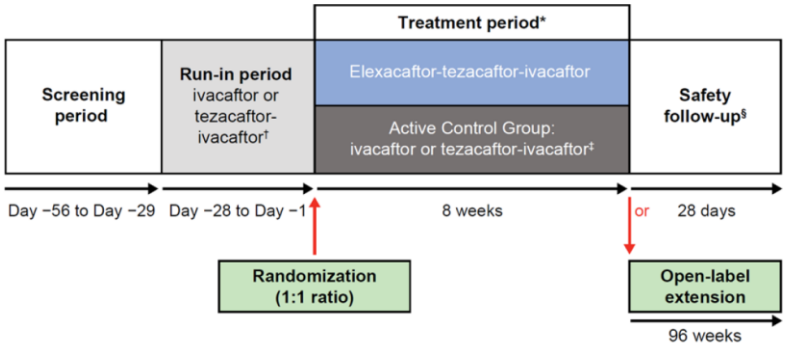
Reference: Vertex, Data on File (188)

Study 445-104 was a randomised, double-blind, active-controlled trial which evaluated the efficacy and safety of IVA/TEZ/ELX compared to IVA or TEZ/IVA in CF patients with F/Gating and F/RF genotypes aged ≥12 years. After a 4-week active run-in period, patients were randomly assigned in a 1:1 ratio to receive IVA/TEZ/ELX (IVA 150 mg Q12h, TEZ 100 mg QD, ELX, 200 mg QD) or active control (IVA or TEZ/IVA) for 8 weeks (Figure 6) (168).

During the 4-week open-label run-in period, patients were assigned to treatment according to their genotype based on the approved indication for CFTRms in each country where the trial was conducted. Thus, F/Gating patients received IVA (150 mg Q12h) and F/RF patients received TEZ/IVA (TEZ 100 mg QD; IVA 150 mg Q12h). The run-in period was included to establish a reliable on-treatment (IVA or TEZ/IVA) baseline for comparisons during the treatment period (168).

In the treatment period, patients who received IVA in the run-in period received IVA in the active control group, while patients in the active control group who received TEZ/IVA in the run-in period received TEZ/IVA (168).

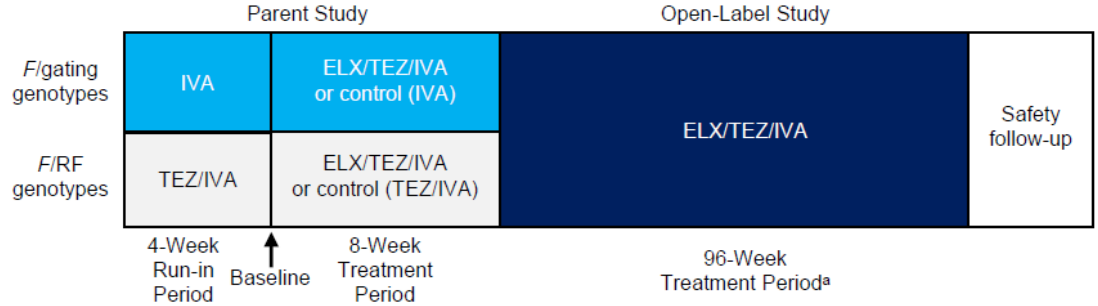
Figure 6. Study 445-104 trial design



*Patients were randomised 1:1 to the IVA/TEZ/ELX group or the active control group (IVA or TEZ/IVA). Randomisation was stratified based on comparator cohort, ppFEV$_1$ as determined during the run-in period and SwCl concentration as determined during the run-in period. The treatment-emergent period included time from the first dose of study drug in the treatment period to 28 days after the last dose of study drug or completion of study participation, whichever occurred first; † In the run-in period, patients were assigned to the IVA or TEZ/IVA comparator cohort based on genotype; ‡ In the treatment period, patients in the active control group who received IVA in the run-in period received IVA; patients in the active control group who received TEZ/IVA in the run-in period received TEZ/IVA; § A safety follow-up visit occurred approximately 28 days after the last dose of study drug for patients who completed study drug dosing and for patients who prematurely discontinued study drug dosing. The safety follow-up visit was not required for patients who complete the Week 8 visit and enrolled in an open-label study (VX18-445-110) within 28 days after the last dose of study drug.
Reference: Barry et al. (168)

Patients who completed the last treatment period visit in study 445-104 and who met the eligibility criteria could enrol in an OLE **study 445-110** to evaluate long-term safety, efficacy, and durability of IVA/TEZ/ELX in CF patients with F/Gating and F/RF genotypes over 96 weeks (Figure 7) (189). All patients received treatment with IVA/TEZ/ELX in the same dosage as that evaluated in the parent study (IVA 150 mg Q12h, TEZ 100 mg QD, ELX, 200 mg QD) (190, 191).

Figure 7. Study 445-110 trial design



Notes: Participants in certain countries who complete the 96-week Treatment Period have the opportunity to continue receiving ELX/TEZ/IVA in a follow-up 48-week Treatment Period.
Reference: Chmiel et al. (190)

Table 13. Comparative summary of trial methodology for IVA/TEZ/ELX, ≥12 years

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 192-194)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 195)	AURORA OLE (study 445-105 IA4) (187, 188)	AURORA F/RF F/G (study 445-104) (168, 196)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (189-191, 197)
Genotype	F/MF	F/F	F/MF, F/F	F/Gating, F/RF	F/Gating, F/RF
Trial design	Phase 3, multicentre, randomised, double-blind, PBO-controlled trial evaluating the efficacy and safety of IVA/TEZ/ELX in CF patients with F/MF genotype ≥12 years of age	Phase 3, multicentre, randomised, double-blind, active-controlled, parallel-group trial evaluating the efficacy and safety of IVA/TEZ/ELX in CF patients with F/F genotype ≥12 years of age	Phase 3, multicentre, open-label extension study evaluating the long-term safety and durability of efficacy of IVA/TEZ/ELX in CF patients with F/F or F/MF genotypes ≥12 years of age	Phase 3, multicentre, randomised, double-blind, active-controlled parallel-group study evaluating the safety and efficacy of IVA/TEZ/ELX treatment in pwCF ≥12 years of age with F/RF or F/Gating genotypes	Phase 3, multicentre, open-label extension study evaluating the long-term safety and efficacy of IVA/TEZ/ELX in CF patients with F/RF or F/Gating genotypes ≥12 years of age
Duration	• Treatment period: 24 weeks • Safety follow-up: 4 weeks	• Run-in period (TEZ/IVA): 4 weeks • Treatment period: 4 weeks • Safety follow-up: 4 weeks	• Treatment period: 192 weeks* • Safety follow-up: 4 weeks	• Run-in period (IVA or TEZ/IVA): 4 weeks • Treatment period: 8 weeks • Safety follow-up: 4 weeks	• Treatment period: 96 weeks • Safety follow-up: 4 weeks
Population	pwCF aged ≥12 years and heterozygous for the *F508del-CFTR* mutation and a minimal-function mutation (F/MF)	pwCF aged ≥12 years homozygous for the *F508del-CFTR* mutation (F/F)	pwCF aged ≥12 years homozygous for the *F508del-CFTR* mutation or heterozygous for the *F508del-CFTR* mutation and a minimal function mutation (F/F or F/FM)	pwCF aged ≥12 years heterozygous for the *F508del* mutation and a gating or residual function mutation (F/Gating, F/RF)	pwCF aged ≥12 years heterozygous for the *F508del* mutation and a gating or residual function mutation (F/Gating, F/RF)
Eligibility criteria for participants	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • 12 years of age or older • CF diagnosis • F/MF genotype • ppFEV$_1$ ≥40% and ≤90% at screening • Stable CF disease • Willing to remain on a stable CF treatment regimen as defined in the study protocol **Exclusion criteria** • History of any illness or any clinical condition that might confound the results or pose additional risks • Abnormal laboratory values at screening (haemoglobin, total	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • 12 years of age or older • CF diagnosis • F/F genotype • ppFEV$_1$ ≥40% and ≤90% at screening • Stable CF disease • Willing to remain on a stable CF treatment regimen as defined in the study protocol **Exclusion criteria** • History of any illness or any clinical condition that might confound the results or pose additional risks • Abnormal laboratory values at screening (haemoglobin, total	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • Did not withdraw consent from a parent study • Completed study drug treatment in a parent study; or had study drug interruption(s) in a parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study • Willing to remain on a stable CF treatment regimen as defined in the study protocol **Exclusion criteria** • History of any comorbidity that might confound the results or pose additional risks	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • 12 years of age or older • CF diagnosis • F/RF or F/G genotype • ppFEV$_1$ ≥40% and ≤90% at screening • Valid sweat sample at screening • Stable CF disease • Willing to remain on a stable CF treatment regimen as defined in the study protocol **Exclusion criteria** • History of any illness or clinical condition that might confound the results or pose additional risks	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures Did not withdraw consent from parent study • Completed study drug treatment in parent study (study 445-104); or had study drug interruption(s) in parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study • Willing to remain on a stable CF treatment regimen as defined in the study protocol **Exclusion criteria** • History of any illness or clinical condition that might

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 192-194)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 195)	AURORA OLE (study 445-105 IA4) (187, 188)	AURORA F/RF F/G (study 445-104) (168, 196)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (189-191, 197)
	bilirubin, AST, ALT, GGT, alkaline phosphatase, renal function) • Acute upper or lower respiratory infection within 28 days • Lung infection with organisms associated with more rapid decline in pulmonary status within the last 12 months • Acute illness not associated with CF within 14 days of run-in period • Ongoing or prior participation in a study of an investigational treatment within 28 days before screening • Use of prohibited medications within specified window before run-in period • Pregnant or nursing females • Participant or close relative of participant is the investigator or involved in the investigating team	bilirubin, AST, ALT, GGT, renal function) • Acute upper or lower respiratory infection within 28 days • Lung infection with organisms associated with more rapid decline in pulmonary status within the last 12 months • Acute illness not associated with CF within 14 days of run-in period • Ongoing or prior participation in a study of an investigational treatment other than a Vertex CFTRm within 28 days before screening • Use of prohibited medications within specified window before run-in period • Pregnant or nursing females • Participant or close relative of participant is the investigator or involved in the investigating team	• Pregnant or nursing females • History of drug intolerance in a parent study that would pose an additional risk to the subject in the opinion of the investigator • Current participation in an investigational drug trial (other than a parent study)	• Abnormal laboratory values at screening (haemoglobin, total bilirubin, AST, ALT, GGT, renal function) • Acute upper or lower respiratory infection within 28 days • Lung infection with pathogens associated with more rapid decline in pulmonary status within the last 12 months • Acute illness not related to CF within 14 days of run-in period • Ongoing or prior participation in a study of an investigational treatment other than a Vertex CFTRm within 28 days before screening • Use of prohibited medications within the specified window before run-in period • Pregnant or nursing females • Patient or a close relative of the patient is the investigator or involved in the investigation team	confound the results or pose additional risks • Pregnant or nursing females • History of drug intolerance in parent study • Current participation in an investigational drug trial (other than the parent study)
Settings and locations where the data were collected	This trial was conducted at 115 sites in 13 countries across the US, Canada, Europe, and Australia. Of those sites, 9 were in the UK	This trial was conducted at 44 sites in four countries (Belgium, Netherlands, UK and USA)	This international multicentre trial took place in: Australia, Austria, Belgium, Canada, Czechia, France, Germany, Greece, Italy, Netherlands, Sweden, UK and USA	This study was conducted in several centres across the US, Canada, UK, EU and Australia	This study was conducted in several centres across the US, Canada, UK, EU and Australia
Trial drugs	**Interventions** • IVA/TEZ/ELX (ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • PBO	**Interventions** • IVA/TEZ/ELX (ELX: 200 mg QD; TEZ 100 mg QD; IVA 150 mg Q12h) **Comparators** • TEZ/IVA (TEZ 100 mg QD; IVA 150 mg Q12h)	**Interventions** • IVA/TEZ/ELX (ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • N/A	**Interventions** • IVA/TEZ/ELX (ELX: 200 mg QD; TEZ 100 mg QD; IVA 150 mg Q12h) **Comparators** • IVA (IVA 150 mg Q12h) • TEZ/IVA (TEZ 100 mg QD; IVA 150 mg Q12h)	**Interventions** • IVA/TEZ/ELX (ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • N/A
Permitted and disallowed concomitant medications	Subjects should remain on a stable treatment regimen for CF from 28 days before Day 1 through completion of study	Subjects should remain on a stable medication regimen for CF from 28 days before run-in/Day -28 through completion.	Subjects should remain on a stable treatment regimen for CF for at least 28 days before Day 1 through completion of study	Subjects should remain on a stable medication regimen for CF from 28 days before Day -28 visit through completion.	Subjects should remain on a stable medication regimen for CF from 28 days before Day 1 visit through completion.

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 192-194)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 195)	AURORA OLE (study 445-105 IA4) (187, 188)	AURORA F/RF F/G (study 445-104) (168, 196)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (189-191, 197)
	participation. Subjects were permitted to receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. Moderate and strong CYP3A inducers, CYP3A inhibitors (except ciprofloxacin) and sensitive OATP1B1 substrates were not allowed within 14 days before the first dose of study drug on Day 1. Information about bronchodilator use during the study was collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study	Patients may receive doses of prednisone or prednisolone of up to 10 mg/day chronically or 60 mg QD, up to 5 days. Moderate and strong CYP3A inducers, CYP3A inhibitors (except ciprofloxacin) and sensitive OATP1B1 substrates were not allowed within 14 days before the first dose of study drug on Day -28. Information about bronchodilator use during the study will be collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study	participation. Subjects were permitted to receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study was collected and documented. No CFTR modulators (investigational or approved, except for study drug in the parent studies and this study) were allowed, since these could confound the results of this study	Patients may receive doses of prednisone or prednisolone of up to 10 mg/day chronically or 60 mg QD, up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study will be collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study	Patients may receive doses of prednisone or prednisolone of up to 10 mg/day chronically or 60 mg QD, up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study will be collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study
Brief description of reported outcomes specified in the decision problem	**Primary outcome** • $ppFEV_1$ **Secondary outcomes** • PEx • CFQ-R RD score • BMI • Safety and tolerability	**Primary outcome** • $ppFEV_1$ **Secondary outcomes** • CFQ-R RD • Safety and tolerability [redacted] • [redacted]	**Primary Outcome** • Safety and tolerability **Secondary outcomes** • $ppFEV_1$ • PEx • BMI • CFQ-R RD score	**Primary outcome** • $ppFEV_1$ for IVA/TEZ/ELX group **Secondary outcomes** • $ppFEV_1$ for IVA/TEZ/ELX group compared to the control group • CFQ-R RD score for IVA/TEZ/ELX group and compared to the control group [redacted] • Safety and tolerability assessments	**Primary Outcome** • Safety and tolerability **Secondary outcomes** • $ppFEV_1$ • BMI • CFQ-R RD score
Primary	• absolute change in $ppFEV_1$	• absolute change in $ppFEV_1$	• safety and tolerability as	• absolute change in $ppFEV_1$	• safety and tolerability as

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 192-194)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 195)	AURORA OLE (study 445-105 IA4) (187, 188)	AURORA F/RF F/G (study 445-104) (168, 196)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (189-191, 197)
outcomes	from baseline through at Week 4 (Global)/through Week 24 (Europe)**	from baseline at Week 4	assessed by number of subjects with AEs and SAEs, from baseline through safety follow-up up to 196 weeks	from baseline through Week 8 for IVA/TEZ/ELX group	assessed by number of subjects with AEs and SAEs, from baseline up to Week 100
Key secondary outcomes (including scoring methods and timings of assessments)	• absolute change in $ppFEV_1$ from baseline through Week 24 (Global)/at Week 4 (Europe)* • number of PEx through Week 24 • absolute change in SwCl from baseline through Week 24 • absolute change in CFQ–R RD score from baseline through Week 24 • absolute change in BMI from baseline at Week 24 • absolute change in SwCl from baseline at Week 4 • absolute change in the CFQ-R RD score from baseline at Week 4	• absolute change in SwCl from baseline at Week 4 • absolute change in CFQ-R RD score from baseline at Week 4 • safety and tolerability assessments	• absolute change in $ppFEV_1$ from baseline through last dose of study drug up to 192 weeks • absolute change in SwCl from baseline through last dose of study drug up to 192 weeks • number of PEx from baseline through last dose of study drug up to 192 weeks • time to first PEx from baseline through last dose of study drug up to 192 weeks • absolute change in BMI from baseline through last dose of study drug up to 192 weeks • absolute change in BMI z-score from baseline through last dose of study drug up to 192 weeks • absolute change in body weight from baseline through last dose of study drug up to 192 weeks • absolute change in CFQ-R RD score from baseline through last dose of study drug up to 192 weeks	• absolute change in SwCl from baseline through Week 8 for IVA/TEZ/ELX group • absolute change in $ppFEV_1$ from baseline through Week 8 for IVA/TEZ/ELX group compared to control group • absolute change in SwCl from baseline through Week 8 for IVA/TEZ/ELX group compared to control group	• absolute change in $ppFEV_1$ from baseline up to Week 96 • absolute change in SwCl from baseline up to Week 96 • absolute change in BMI from baseline up to Week 96 • absolute change in BMI z-score from baseline up to Week 96 • absolute change in body weight from baseline up to Week 96 • absolute change in CFQ-R RD score from baseline up to Week 96
Other secondary outcomes	• time to first PEx through Week 24 • absolute change in BMI z-score from baseline at Week 24 (for subjects ≤20 years of age at baseline) • absolute change in body weight from baseline at Week 24 • [redacted] • safety and tolerability assessments	[redacted]	N/A	• absolute change in CFQ-R RD score from baseline through Week 8 for IVA/TEZ/ELX group • absolute change in CFQ-R RD score from baseline through Week 8 for IVA/TEZ/ELX group compared to control group • absolute change in BMI from baseline at Week 8 [redacted]	• absolute change in CFQ-R non-RD scores from baseline up to Week 96

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 192-194)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 195)	AURORA OLE (study 445-105 IA4) (187, 188)	AURORA F/RF F/G (study 445-104) (168, 196)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (189-191, 197)
				• safety and tolerability assessments	
Trial supports application for marketing authorisation?	Yes	Yes	Yes	Yes	Yes
Trial used in the economic model?	Yes	No	Yes	Yes	Yes
Rationale for use/non-use in the model	Supported marketing authorisation in relevant patient population	Short, 4-week duration	Provides long-term outcomes of the pivotal trials, study 445-102 and study 445-103, in the relevant patient population	Supported marketing authorisation in relevant patient population	Provides long-term outcomes of study 445-104, in the relevant patient population

*Intended full duration of the trial; ongoing study.
**The primary endpoint in the global protocol was absolute change from baseline in $ppFEV_1$ at Week 4. At the request of European regulators, a Europe-specific protocol amendment was made to consider in the European protocol the absolute change from baseline in $ppFEV_1$ through Week 24 as the primary endpoint and the first key secondary endpoint the absolute change from baseline in $ppFEV_1$ at Week 4 (198).
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire-revised; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CYP2C9, cytochrome P450 family 2 subfamily C member 9; ELX, elexacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; INR, international normalized ratio; N/A, not applicable; OATP1B1, organic anion transporting polypeptides 1B1; OATP1B3, organic anion transporting polypeptides 1B3; P-gp, P-glycoprotein; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume over one second; Q12h, once every 12 hours; QD, once daily; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

Table 14. Baseline characteristics of patients in IVA/TEZ/ELX studies, ≥12 years

Baseline characteristic	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 194)		AURORA F/F (study VX17-445-103, NCT03525548) (170)		AURORA OLE (study VX17-445-105 IA4, NCT03525574)* (188)					AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168)		AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (190, 191)	
	IVA/TEZ/ ELX (N=200)	PBO (N=203)	IVA/TEZ/ ELX (N=55)	TEZ/IVA (N=52)	IVA/TEZ/ ELX in study 445-102 (N=196)	PBO in study 445-102 (N=203)	IVA/TEZ/ ELX in study 445-103 (N=55)	TEZ/IVA in study 445-103 (N=52)	Any IVA/TEZ/ ELX (N=506)	IVA/TEZ/ ELX (N=132)	Control ([IVA] or [TEZ/IVA]) (N=126)	IVA/TEZ/ ELX in study 445-104 (N=130)	Control in study 445-104 (N=121)
Age, mean (SD), years	25.6 (9.7)	26.8 (11.3)	28.8 (11.5)	27.9 (10.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37.7 (14.7)	37.6 (14.3)	37.8 (14.6)	38.0 (14.2)
Sex, n (%)	F=96 (48)	F=98 (48.3)	F=31 (56%)	F=28 (54%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	F= 67 (50.8)	F= 61 (48.4)	F=67 (51.5)	F=57 (47.1)
Geographical region, n (%)	Europe or Australia 82 (41) North America 118 (59)	Europe or Australia 83 (40.9) North America 120 (59.1)	North America 34 (62%) Europe 21 (38%)	North America 33 (63%) Europe 19 (37%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	North America 49 (37.1) Europe 70 (53.0) Australia 13 (9.8)	North America 48 (38.1) Europe 64 (50.8) Australia 14 (11.1)	[redacted]	[redacted]
Genotype, n (%)	F/MF 200 (100.0)	F/MF 203 (100.0)	F/F 55 (100.0)	F/F 52 (100.0)	F/MF 196 (100.0)	F/MF 203 (100.0)	F/F 55 (100.0)	F/F 52 (100.0)	–	F/G 50 (37.9) F/RF 82 (62.1)	F/G 45 (35.7) F/RF 81 (64.3)	F/G 49 (37.7) F/RF 81 (62.3)	F/G 43 (35.5) F/RF 78 (64.5)
BMI kg/m^2, mean (SD)	21.49 (3.07)	21.31 (3.14)	21.75 (3.19)	21.88 (4.12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24.07 (4.72)	24.05 (4.71)	24.10 (4.69)	23.91 (4.39)
ppFEV$_1$, mean (SD)	61.6 (15.0)	61.3 (15.5)	61.6 (15.4)	60.2 (14.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67.1 (15.7)	68.1 (16.4)	67.0 (15.8)	67.7 (16.2)
Distribution, n (%) <40% 40 to <70% 70 to ≤90% >90%	 18 (9.0) 114(57.0) 66 (33.0) 2 (1.0)	 16 (7.9) 120(59.1) 62 (30.5) 5 (2.5)	 6 (11%) 31 (56%) 18 (33%) 0	 4 (8%) 34 (65%) 14 (27%) 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	 2 (1.5) 70 (53.0) 53 (40.2) 7 (5.3)	 2 (1.6) 63 (50.0) 52 (41.3) 9 (7.1)	[redacted]	[redacted]
SwCl concentration, mean (SD), mmol/L	102.3 (11.9)	102.9 (9.8)	91.4 (11.0)	90.0 (12.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59.5 (27.0)	56.4 (25.5)	59.7 (27.0)	57.0 (25.4)
CFQ-R RD score, mean (SD)	68.3 (16.9)	70.0 (17.8)	70.6 (16.2)	72.6 (17.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76.5 (16.6)	77.3 (15.8)	76.7 (16.6)	77.2 (15.9)
Prior use of CFTR modulator, n (%)	–	–	32 (58) [§]	34 (65) [§]	–	–	–	–	–	IVA 37 (28.0) TEZ/IVA 26 (19.7)[†]	IVA 39 (31.0) TEZ/IVA 20 (15.9)[†]	–	–

Baseline characteristic	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 194)		AURORA F/F (study VX17-445-103, NCT03525548) (170)		AURORA OLE (study VX17-445-105 IA4, NCT03525574)* (188)					AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168)		AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (190, 191)	
	IVA/TEZ/ ELX (N=200)	PBO (N=203)	IVA/TEZ/ ELX (N=55)	TEZ/IVA (N=52)	IVA/TEZ/ ELX in study 445-102 (N=196)	PBO in study 445-102 (N=203)	IVA/TEZ/ ELX in study 445-103 (N=55)	TEZ/IVA in study 445-103 (N=52)	Any IVA/TEZ/ ELX (N=506)	IVA/TEZ/ ELX (N=132)	Control ([IVA] or [TEZ/IVA]) (N=126)	IVA/TEZ/ ELX in study 445-104 (N=130)	Control in study 445-104 (N=121)
Prior use of dornase alfa, n (%)[§]	162 (81.0)	164 (80.8)	51 (93)	48 (92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	69 (52.3)	66 (52.4)	[redacted]	[redacted]
Prior use of azithromycin, n (%)[§]	110 (55.0)	114 (56.2)	33 (60)	25 (48)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57 (43.2)	57 (45.2)	[redacted]	[redacted]
Prior use of inhaled antibiotic, n (%)[§]	118 (59.0)	132 (65.0)	35 (64)	28 (54)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49 (37.1)	56 (44.4)	[redacted]	[redacted]
Prior use of any bronchodilator, n (%)[§]	[redacted]	[redacted]	54 (98)	47 (90)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	113 (85.6)	111 (88.1)	[redacted]	[redacted]
Prior use of inhaled hypertonic saline, n (%)[§]	147 (73.5)	127 (62.6)	38 (69)	41 (79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57 (43.2)	54 (42.9)	[redacted]	[redacted]
Prior use of inhaled corticosteroids, n (%)[§]	120 (60.0)	119 (58.6)	36 (65)	28 (54)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–	–	–
Pseudomonas aeruginosa-positive within previous 2 years, n (%)	150 (75.0)	142 (70.0)	39 (71%)	31 (60%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	79 (59.8%)	74 (58.7%)	[redacted]	[redacted]

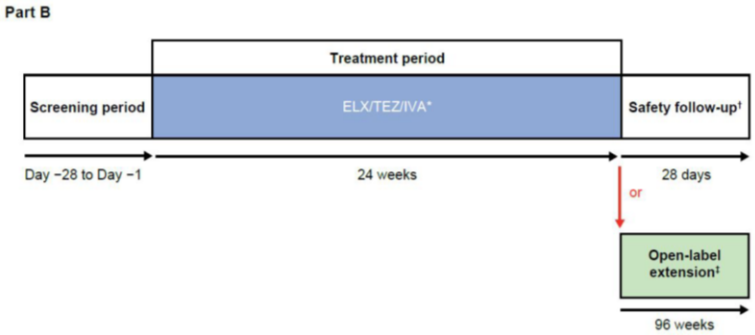
*Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study; [§]Includes medications administered during 56 days before the first dose of study drug; [–] not available; [†] Prior use is defined as anytime within 56 days before the date of first dose in the treatment period, defined as the first dose of IVA/TEZ/ELX, IVA or TEZ/IVA after randomisation. This does not include IVA or TEZ administered during the run-in period.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; ELX, elexacaftor; IVA, ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.2.1.2 CF patients aged 6 to 11 years

Table 15 summarises the methodology of relevant IVA/TEZ/ELX trials in pwCF who aged 6 to 11 years, while Table 16 describes the baseline characteristics of patients enrolled in those trials.

Study 445-106 Part B was a single arm trial that evaluated the safety and tolerability of IVA/TEZ/ELX through Week 24 in subjects with CF and F/F or F/MF genotypes aged 6 to 11 years. Patients weighing <30 kg received IVA 75 mg Q12h, TEZ 50 mg QD and ELX 100 mg QD; whereas patients ≥30 kg received IVA 150 mg Q12h, TEZ 100 mg QD and ELX 200 mg QD (174). [redacted] After completion of the Week 24 study visit, patients who met eligibility criteria could enrol in an OLE study or complete a 28-day safety follow-up (Figure 8) (174).

Figure 8. Study 445-106 Part B trial design

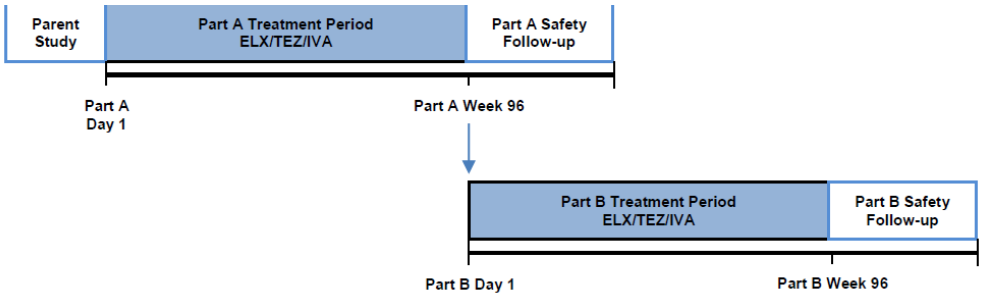


*Study drug was administered from Day 1 through the evening before the Week 24 visit. For patients enrolling in the optional OLE safety study, the first dose of OLE study drug was administered at the Week 24 visit. †Safety follow-up visit was scheduled to occur 4 weeks (±7 d) after the last dose. This visit was not required for patients who enrolled in the OLE study within 28 days of the last dose. ‡Patients who completed the visits in Part B treatment period, regardless of whether they did so while on a treatment interruption, were offered the opportunity to enrol in the OLE study.
Reference: Zemanick et al. (174)

The primary objective of **study 445-107** is to evaluate the long-term safety and tolerability of IVA/TEZ/ELX in CF patients with F/F or F/MF genotypes aged 6 years or older. Following participation in study 445-106 Part B, patients who completed study drug treatment and who were deemed eligible had the option to enrol in this ongoing

OLE study which consisted of 2 parts (Part A and B), each with a 96-week treatment period followed by a 4-week safety follow-up period. Subjects who completed Part A had the opportunity to participate in Part B (Figure 9) (200, 201). Results for Part A (96 weeks) are currently available. Patients weighing <30 kg received IVA 75 mg Q12h, TEZ 50 mg QD and ELX 100 mg QD; whereas patients ≥30 kg received IVA 150 mg Q12h, TEZ 100 mg QD and ELX 200 mg QD (201, 202). The estimated completion date for this ongoing study is April 2024 (203).

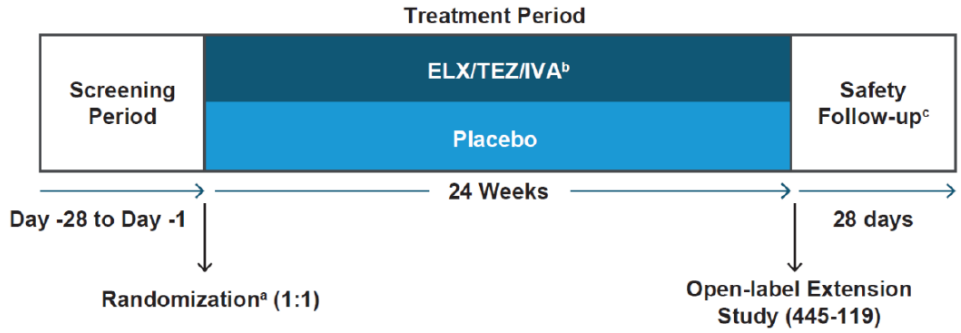
Figure 9. Study 445-107 trial design



Notes: The parent study is VX18-445-106 Part B, a phase 3 study investigating IVA/TEZ/ELX in subjects aged 6 to 11 years. The figure is not drawn to scale.
Reference: Wainwright,et al. (201)

Study 445-116 was a randomised, double-blind, PBO-controlled phase 3b study that evaluated the efficacy and safety of IVA/TEZ/ELX compared to PBO in CF patients aged 6 to 11 years with F/MF genotype. The study consisted of a 4-week screening period, followed by a 24-week treatment period and either a 4-week safety follow-up period or enrolment in an OLE study (study 445-119). Patients were randomised in a 1:1 ratio to receive treatment with either IVA/TEZ/ELX (IVA 150 mg Q12h, TEZ 100 mg QD and ELX 200 mg QD for patients ≥30 kg or IVA 75 mg Q12h, TEZ 50 mg QD and ELX 100 mg QD for patients <30 kg) or PBO, over a 24-week period (Figure 10) (204).

Figure 10. Study 445-116 trial design



[a] Randomisation was stratified by $LCI_{2.5}$ at screening (<10 vs ≥10) and weight at screening (<30 kg vs ≥30 kg); [b] Dosing regimen based on weight at screening visit. [c] For children who did not enrol in an optional OLE (study 445-119), a safety follow-up visit was specified to occur 28 days (±7 days) after the last dose of study drug in the treatment period.
Reference: Mall et al. (204)

Table 15. Comparative summary of trial methodology for IVA/TEZ/ELX, 6-11 years

Study	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174, 200, 205)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (173, 201-203, 206)	GALILEO (study VX19-445-116, NCT04353817) (204, 207, 208)
Genotype	F/MF, F/F	F/MF, F/F	F/MF
Trial design	Phase 3, two-part, multicentre, open-label trial evaluating the PK, safety, tolerability, efficacy, and pharmacodynamic effect of IVA/TEZ/ELX in CF patients aged 6 to 11 years with F/F and F/MF genotypes. Part B evaluated safety and tolerability (primary objective), efficacy and PK over a 24-week treatment period	Phase 3, open-label extension study evaluating the long-term safety and efficacy of IVA/TEZ/ELX in subjects with CF who are ≥ 6 years of age	Phase 3b, randomised, multicentre, double-blind, PBO-controlled, parallel-group study evaluating the efficacy and safety of IVA/TEZ/ELX in CF patients aged 6 to 11 years with F/MF genotype
Duration	• Treatment period: 24 weeks • Safety follow-up: 4 weeks	• Treatment period: 192 weeks* • Safety follow-up: 4 weeks (Part A) + 4 weeks (Part B)	• Treatment period: 24 weeks • Safety follow-up: 4 weeks
Population	pwCF aged 6 to 11 years and either F/MF or F/F genotypes	pwCF aged ≥6 years with F/MF or F/F genotypes	pwCF aged 6 to 11 years with CF and F/MF genotype
Eligibility criteria for participants	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • 6 to 11 years of age • Body weight ≥15 kg • Confirmed CF diagnosis • F/F or F/MF genotype • ppFEV1 ≥40% at screening • Stable CF disease • Willing to remain on a stable CF treatment regimen (other than CFTR modulators) • Able to swallow tablets • Negative serum pregnancy test at screening (female patients) • Meet contraception requirements (sexually active patients of childbearing potential) • Able to understand protocol requirements and restrictions **Exclusion criteria** • History of any illness or any clinical condition that may confound study results or pose additional risks • Abnormal laboratory values at screening (haemoglobin, total bilirubin, AST, ALT, GGT, alkaline phosphatase, renal function) • Respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before the first dose of study drug • Lung infection with organisms associated with a more rapid decline in pulmonary status • Acute illness not related to CF within 14 days before the first dose of study drug • Ongoing or prior participation in a study of an	**Inclusion criteria** • Patient (or authorised representative) signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • Did not withdraw consent from a parent study • Completed study drug treatment in parent study (study 445-106 Part B), or had study drug interruption(s) in parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study • Willing to remain on a stable CF treatment regimen **Exclusion criteria** • History of any comorbidity that might confound the results or pose additional risks • Pregnant or breast-feeding females • History of study drug intolerance in parent study that would pose an additional risk to the subject in the opinion of the investigator • Current participation in an investigational drug trial (other than the parent study)	**Inclusion criteria** • Patient's authorised representative signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • 6 to 11 years of age • Body weight ≥15 kg • Confirmed CF diagnosis • F/MF genotype • $ppFEV_1$ ≥70% at screening • $LCI_{2.5}$ ≥7.5 • Stable CF disease • Willing to remain on a stable CF treatment regimen (other than CFTR modulators) • Able to swallow tablets • Able to understand protocol requirements and restrictions **Exclusion criteria** • History of any illness or any clinical condition that may confound study results or pose additional risks • Abnormal laboratory values at screening (haemoglobin, total bilirubin, AST, ALT, GGT, renal function) • Respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before the first dose of study drug • Lung infection with organisms associated with a more rapid decline in pulmonary status • Acute illness not related to CF within 14 days before the first dose of study drug • Ongoing or prior participation in a study of an

Study	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174, 200, 205)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (173, 201-203, 206)	GALILEO (study VX19-445-116, NCT04353817) (204, 207, 208)
	investigational treatment within 28 days before screening • Use of restricted medications as defined in the study protocol • Patient or close relative is the investigator or involved in the investigating team		investigational treatment within 28 days before screening • Use of restricted medications as defined in the study protocol • Pregnant and breast-feeding females • Participant or close relative of participant is the investigator or involved in the investigating team
Settings and locations where the data were collected	This multicentre trial was conducted at 21 sites across the US, Australia, Canada, Ireland and UK	This multicentre trial was conducted at 21 sites across the US, Australia, Canada, Ireland and UK	This multicentre trial was conducted at 34 sites in Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, and the United Kingdom
Trial drugs	**Interventions** • IVA/TEZ/ELX (ELX: 100 mg QD; TEZ: 50 mg QD; IVA: 75 mg Q12h [patients weighing <30 kg]; ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h [patients weighing ≥30 kg]) **Comparators** • N/A	**Interventions** • IVA/TEZ/ELX (ELX: 100 mg QD; TEZ: 50 mg QD; IVA: 75 mg Q12h [patients weighing <30 kg]; ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h [patients weighing ≥30 kg]) **Comparators** • N/A	**Interventions** • IVA/TEZ/ELX (ELX: 100 mg QD; TEZ: 50 mg QD; IVA: 75 mg Q12h [patients weighing <30 kg]; ELX: 200 mg QD; TEZ: 100 mg QD; IVA: 150 mg Q12h [patients weighing ≥30 kg]) **Comparators** • PBO
Permitted and disallowed concomitant medications	Subjects should remain on a stable treatment regimen for CF from 28 days before Day 1 through completion of study participation. Subjects could receive doses of prednisone/prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study was collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study	Subjects should remain on a stable treatment regimen for CF from for at least 28 days before Part A Day 1 through completion of study participation. Subjects could receive doses of prednisone/prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study was collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study	Subjects should remain on a stable treatment regimen for CF from 28 days before Day 1 through completion of study participation. Subjects could receive doses of prednisone/prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. OATP1B1 and OATP1B3 substrates (statins, glyburide, nateglinide, repaglinide) should be used with caution, as well as digoxin or other substrates of P-gp with narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus. Additional monitoring of the INR is recommended during coadministration with warfarin (CYP2C9 substrate). Other CYP2C9 substrates such as glimepiride and glipizide should be used with caution. Information about bronchodilator use during the study was collected and documented. No CFTR modulators (investigational or approved, except for study drugs) were allowed, since these could confound the results of this study
Brief description of reported outcomes specified in the decision	**Primary outcome** • Safety and tolerability **Secondary outcomes** • $ppFEV_1$ • CFQ-R RD score • BMI and BMI-for-age z-score	**Primary Outcome** • Safety and tolerability **Secondary outcomes** • $ppFEV_1$ • CFQ-R RD score • BMI and BMI-for-age z-score	**Primary outcome** • $LCI_{2.5}$ **Secondary outcomes** • Safety and tolerability • $ppFEV_1$ • CFQ-R RD

Study	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174, 200, 205)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (173, 201-203, 206)	GALILEO (study VX19-445-116, NCT04353817) (204, 207, 208)
problem	• PEx • $LCI_{2.5}$ • [redacted]	• PEx • $LCI_{2.5}$	
Primary outcomes	• safety and tolerability through safety follow-up visit up to Week 28	• safety and tolerability as assessed by AEs and SAEs up to Week 100	• absolute change in $LCI_{2.5}$ from baseline through Week 24
Key secondary outcomes (including scoring methods and timings of assessments)	• absolute change in $ppFEV_1$ from baseline through Week 24 • absolute change in CFQ-R RD score from baseline through Week 24 • absolute change in BMI and BMI-for-age z-score from baseline at Week 24 • absolute change in weight and weight-for-age z-score from baseline at Week 24 • absolute change in height and height-for-age z-score from baseline at Week 24 • drug acceptability using Modified Facial Hedonic Scale at Week 24 • number of PEx and CF-related hospitalisations through Week 24 • PK parameters of IVA/TEZ/ELX and relevant metabolites • absolute change in $LCI_{2.5}$ from baseline through Week 24	• absolute change in $ppFEV_1$ from baseline up to Week 96 • absolute change in SwCl from baseline up to Week 96 • absolute change in CFQ-R RD score from baseline up to Week 96 • absolute change in BMI and BMI-for-age z-score from baseline up to Week 96 • number of PEx and CF-related hospitalisations up to Week 96 • absolute change in $LCI_{2.5}$ from baseline up to Week 96 • absolute change in weight and weight-for-age z-score from baseline up to Week 96 • absolute change in height and height-for-age z-score from baseline up to Week 96	• safety and tolerability assessments
Other secondary outcomes	[redacted]	[redacted]	• absolute change in $ppFEV_1$ from baseline through Week 24 • absolute change in CFQ-R RD score from baseline through Week 24
Trial supports application for marketing authorisation?	Yes	No	No
Trial used in the economic model?	Yes	Yes	Yes
Rationale for use/non-use in the model	Supported marketing authorisation in relevant patient population	Provides long-term outcomes from study 445-106 Part B	Provides PBO-adjusted estimates in relevant patient population

*Intended full duration of the trial – ongoing study; Part A 96 weeks + Part B 96 weeks.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire-revised; CYP2C9, cytochrome P450 family 2 subfamily C member 9; ECG, electrocardiogram; ELX, elexacaftor; FE-1, fecal elastase-1; GGT, gamma-glutamyl transferase; IVA, ivacaftor; INR, international normalized ratio; IRT, immunoreactive trypsinogen; $LCI_{2.5}$, lung clearance index 2.5; N/A, not applicable; non-RD, non-respiratory domain; OATP1B1, organic anion transporting polypeptides 1B1; OATP1B3, organic anion transporting polypeptides 1B3; OLE, open-label extension; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume over one second; P-gp, P-glycoprotein; PK, pharmacokinetics; Q12h, once every 12 hours; QD, once daily; RD, respiratory domain; SAE, serious adverse event; SwCl, sweat chloride; TEZ, tezacaftor.

Table 16. Baseline characteristics of patients in IVA/TEZ/ELX studies, 6-11 years

Baseline characteristic	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (201, 202)	GALILEO (study VX19-445-116, NCT04353817)* (204)	
	IVA/TEZ/ELX (N=66)†	IVA/TEZ/ELX (N=64)	IVA/TEZ/ELX (N=60)	PBO (N=61)
Age, mean (SD), years	9.3 (1.9)	9.3 (1.8)	9.1 (1.8)	9.2 (1.7)
Sex, n (%)	F=39 (59.1)	F=39 (60.9)	35 (58.3)	35 (57.4)
Geographical region, n (%)	North America 47 (71.2) Europe and Australia 19 (28.8)	[redacted]	Europe 43 (71.7) Other countries (Australia, Canada, Israel) 17 (28.3)	Europe 49 (80.3) Other countries (Australia, Canada, Israel) 12 (19.7)
Genotype, n (%)	F/F 29 (43.9) F/MF 37 (56.1)	F/F 28 (43.8) F/MF 36 (56.2)	F/MF 60 (100.0)	F/MF 61 (100.0)
Weight group, n (%) <30 kg ≥30 kg	 36 (54.5) 30 (45.5)	 35 (54.7) 29 (45.3)	 39 (65.0) 21 (35.0)	 38 (62.3) 23 (37.7)
Weight, mean (SD), kg	30.0 (7.7)	29.9 (7.7)	29.1 (7.6)	29.8 (8.6)
Weight-for-age z-score, mean (SD)	-0.22 (0.76)	-0.24 (0.76)	−0.27 (0.99)	−0.29 (0.96)
Height, mean (SD), cm	134.1 (12.3)	134.0 (12.3)	132.3 (11.7)	134.6 (13.3)
Height-for-age z-score, mean (SD)	0.11 (0.98)	-0.11 (0.99)	−0.17 (1.02)	0.01 (1.26)
BMI, mean (SD), kg/m^2	16.39 (1.69)	16.32 (1.66)	16.33 (1.84)	16.11 (2.32)
BMI-for-age z-score, mean (SD)	-0.16 (0.74)	-0.19 (0.73)	−0.17 (0.85)	−0.39 (0.92)
ppFEV$_1$, mean (SD)	88.8 (17.7)	88.3 (17.6)	91.4 (13.8)	87.2 (15.8)
Distribution, n (%) <70% ≥70 to ≤90% >90% Missing	 10 (15.2) 22 (33.3) 30 (45.5) 4 (6.1)	[redacted]	 4 (6.7) 20 (33.3) 36 (60.0) 0	 10 (16.4) 23 (37.7) 28 (45.9) 0
SwCl concentration, mean (SD), mmol/L	102.2 (9.1)	102.2 (9.2)	102.8 (10.0)	102.6 (8.6)
CFQ-R RD score (Child's version), mean (SD)	80.3 (15.2)	79.8 (15.2)	85.7 (11.7)	82.7 (14.1)
LCI$_{2.5}$, mean (SD)	9.77 (2.68)	9.87 (2.68)	10.26 (2.22)	9.75 (1.95)
Prior use of CFTR modulator, n (%)§	14 (21.2)	[redacted]	–	–
Prior use of dornase alfa, n (%)§	54 (81.8)	[redacted]	42 (70.0)	41 (67.2)
Prior use of azithromycin, n (%)§	19 (28.8)	[redacted]	11 (18.3)	9 (14.8)
Prior use of inhaled antibiotic, n (%)§	8 (12.1)	[redacted]	15 (25.0)	8 (13.1)
Prior use of bronchodilator, n (%)§	61 (92.4)	[redacted]	38 (63.3)	46 (75.4)
Prior use of inhaled hypertonic saline, n (%)§	52 (78.8)	[redacted]	46 (76.7)	46 (75.4)
Prior use of inhaled corticosteroids, n (%)§	–	–	15 (25.0)	18 (29.5)
Pseudomonas aeruginosa-positive within previous 2 years, n (%)	26 (39.4)	[redacted]	–	–

†All patients in the full analysis set; §Includes medications administered during 56 days before the first dose of study drug; *Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period; – not available.

Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; ELX, elexacaftor; IVA, ivacaftor; LCI$_{2.5}$, lung clearance index 2.5; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.2.2 LUM/IVA

Evidence for the clinical efficacy and safety of LUM/IVA relevant for the decision problem encompasses eight trials outlined in **Error! Reference source not found.**. Detailed methods and results of seven of these trials are presented in Sections B.2.2 to B.2.9. Study 809-011 (Part B) is described in Appendix D.

B.2.2.2.1 CF patients aged ≥ 12 years

Table 17 summarises the trial methodology of relevant LUM/IVA studies identified in the pwCF aged ≥12 years. Table 18 and Table 19 describe the baseline characteristics of patients enrolled in those trials.

The evidence base in this population comprises **study 809-103** and **study 809-104** which were both phase 3, randomised, double-blind, PBO-controlled trials. Each of the trials investigated the efficacy and safety of LUM/IVA compared to PBO in patients with the F/F genotype ≥12 years of age through 24 weeks of treatment. The two studies had a nearly identical design, their difference limited to the inclusion of ambulatory electrocardiogram parameters as a safety outcome in study 809-103 and adolescent PK assessments in study 809-104 for a subgroup of patients (Table 17). Therefore, a prespecified pooled analysis of results from both studies was conducted and these studies have been grouped together in subsequent tables in the dossier. The pooled analysis of study 809-103 and study 809-104 is the basis of the integrated summary of efficacy intended to evaluate the totality of the data and is reported for the LUM 400 mg-IVA 250 mg treatment group only within this submission as this is the licensed dose (3). In both studies, patients were randomly assigned to receive either LUM (600 mg once daily or 400 mg every 12 hours) in combination with IVA (250 mg every 12 hours) or matched PBO for 24 weeks. However, as the 400mg every 12 hours in combination with IVA 250mg every 12 hours is the licenced dose that is being assessed in this submission, only the results from this group and PBO are described in this section. Patients who completed 809-103 or 809-104 were eligible to rollover into the long-term extension **study 809-105** (Figure 11). Study 809-105 is a phase 3, 96-week rollover study of patients evaluating the long-term safety and efficacy of LUM/IVA in CF patients aged 12 years or older with the F/F genotype. It consisted of two parts (Part A and Part B). Part A enrolled subjects from 809-103 or 809-104. Part

B enrolled subjects from study 809-102 cohort 4. Only Part A will be described in this submission. Those that had received LUM/IVA treatment in the parent studies continued their respective doses, whilst those that received PBO in the parent studies were randomised to receive one of the two doses previously described (LUM [600 mg once daily or 400 mg every 12 hours] in combination with IVA [250 mg every 12 hours]). Again, only the '400mg every 12 hours in combination with IVA 250mg every 12 hours' dose is described in this submission.

Figure 11. Trial design of study 809-103, study 809-104 and study 809-105

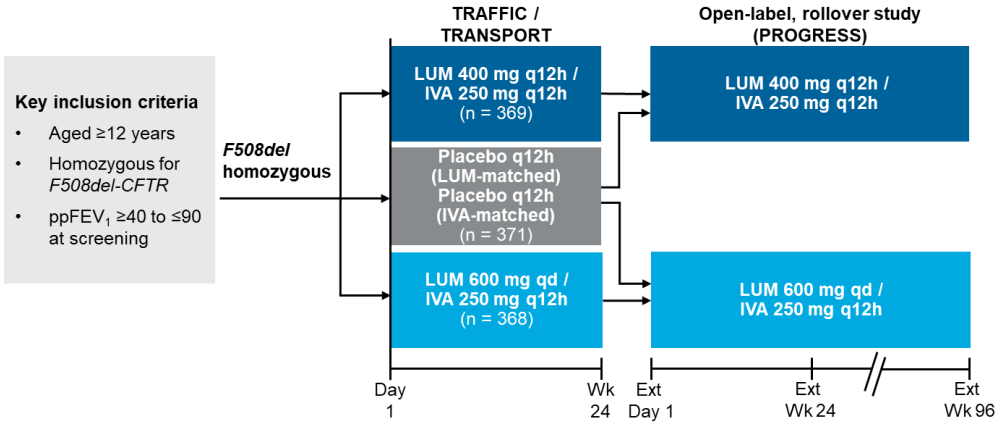


Table 17. Comparative summary of methodology of trials for LUM/IVA in CF patients aged ≥12 years

Study	TRAFFIC (study VX12-809-103, NCT01807923) & TRANSPORT (study VX12-809-104, NCT01807949) (158, 209) (158, 210)	PROGRESS (study VX12-809-105, NCT01931839) (155, 211)
Genotype	F/F	F/F
Trial design	Phase 3, randomised, double-blind, PBO-controlled, parallel-group multicentre trial evaluating the efficacy of LUM/IVA in CF patients with F/F genotype aged 12 years or older	Phase 3, parallel-group, multicentre, 96-week study of patients who completed study 809-103 and study 809-104 in CF patients with F/F genotype aged 12 years or older
Duration	Treatment period: 24 weeks	Treatment period of participants who received PBO in the parent study: 96 weeks Treatment period of participants who received LUM/IVA in the parent study: 120 weeks
Population	Patients aged 12 years or older with CF who are homozygous for the *F508del-CFTR* mutation (209)	Patients aged 12 years or older with CF and homozygous for the *F508del-CFTR* mutation
Eligibility criteria for participants	**Inclusion criteria** • Confirmed diagnosis of CF • Homozygous for the *F508del CFTR* mutation • FEV_1 (≥) 40% and ≤) 90% of predicted normal for age, sex, and height • Willing to remain on a stable CF medication regimen through Week 24 or, if applicable, the safety follow up visit **Exclusion criteria** • An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before first dose of study drug • History of solid organ or haematological transplantation • History of alcohol or drug abuse in the past year • Ongoing or prior participation in an investigational drug study (including studies investigating lumacaftor and/or ivacaftor) within 30 days of screening • Use of strong inhibitors, moderate inducers or strong inducers of CYP3A within 14 days before Day 1 of dosing	**Inclusion criteria** • Signed ICF, and where appropriate, signed assent form. • Subjects entering the part A treatment cohort were required to meet both of the following criteria: • Completed 24 weeks of study drug treatment in study 809-103 and study 809-104. Subjects who had study drug interruptions, but completed study visits up to Week 24 of studies 809-103 and 809-104 were eligible. Subjects who were not taking study drug at the Week 24 visit, including subjects who required study drug interruption to be either continued or initiated at Day 1 in study 809-105, were required to have Vertex approval for enrolment/randomisation in the Part A treatment cohort. • Elected to enrol in the Part A Treatment Cohort **Exclusion criteria** • Any comorbidity or laboratory abnormality that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject (e.g., cirrhosis with portal hypertension). • Pregnant and nursing females. Females of childbearing potential were required to have a negative urine pregnancy test at the Day 1 visit (enrolment/randomisation) and before receiving the first dose of study drug • Sexually active subjects of reproductive potential who were not willing to follow the contraception requirements • History of drug intolerance in the previous study that would have posed an additional risk to the subject in the opinion of investigator or Vertex. Examples of subjects who may not have been eligible for any of the treatment arms include the following: o Subjects with a history of allergy or hypersensitivity to the study drug o LFT abnormality during study drug treatment in the parent study for which a clear cause was not identified. o Other severe or life-threatening reactions to the study drug in the previous study • History of poor compliance with study drug and/or procedures in the previous study as deemed by the investigator.

Study	TRAFFIC (study VX12-809-103, NCT01807923) & TRANSPORT (study VX12-809-104, NCT01807949) (158, 209) (158, 210)	PROGRESS (study VX12-809-105, NCT01931839) (155, 211)
		• Participation in an investigational drug trial (including studies investigating LUM and/or IVA. Participation in a noninterventional study (including observational studies and studies requiring blood collections without administration of study drug) was permitted.
Settings and locations where the data were collected	Study 809-103 took place in 90 locations across the US, Canada, Australia and Europe. Study 809-104 took place in 82 locations across the US, Canada, Australia and Europe	The trial took place at 191 sites in 15 countries across the US, Canada, Australia and Europe
Trial drugs	**Interventions** • LUM 600 mg qd; IVA 250 mg q12h* Or • LUM 400 mg q12h; IVA 250 mg q12h **Comparator** • PBO	**Interventions** • LUM 600 mg qd; IVA 250 mg q12h* Or • LUM 400 mg q12h; IVA 250 mg q12h **Comparator** • N/A
Permitted and disallowed concomitant medications	Permitted concomitant medications: • Patients continued to take their pre-study medications Disallowed concomitant medications: • Ongoing or prior participation in an investigational drug study (including studies investigating lumacaftor and/or ivacaftor) within 30 days of screening • Use of strong inhibitors, moderate inducers or strong inducers of CYP3A within 14 days before Day 1 of dosing	Participation in an investigational drug trial (including studies investigating LUM or IVA, or both), although participation in a non-interventional study (including observational studies and studies requiring blood collections without administration of study drug) was permitted.
Brief description of reported outcomes specified in the decision problem	Primary outcome (209) • $ppFEV_1$ (absolute) Secondary outcomes • $ppFEV_1$ (relative) • BMI • CFQ-R RD score • PEx • EQ-5D-3L VAS • TSQM • Adverse events (209)	Primary outcome (155) • Long-term safety Secondary outcomes • $ppFEV_1$ • BMI • CFQ-R RD score • PEx (155, 211)
Primary outcomes	• Absolute change from baseline in $ppFEV_1$ at Week 24, calculated by averaging the mean absolute change at Week 16 and at Week 24	• Long-term safety based on TEAEs, clinical laboratory values including serum chemistry, haematology, coagulation studies, and urinalysis, standard electrocardiograms, vital signs, and pulse oximetry. Scheduled clinic visits: Day 1, Day 15, Week 4, 8, 16, 24, 36, 48, 60, 72, 84 and 96
Key secondary outcomes (including scoring methods and timings of assessments)	Relative change in $ppFEV_1$ at Week 24 (average at Week 16 and Week 24) • Absolute change from baseline in BMI at Week 24 • Absolute change from baseline in the CFQ-R respiratory domain score at Week 24 • Response, defined as ≥5% increase in average relative change from baseline in ppFEV1 at Week 16 and at Week 24 • Number of PEx from baseline through Week 24	• Absolute change from baseline of the parent study in $ppFEV_1$ up to Week 72 • Relative change from baseline of the parent study in $ppFEV_1$ up to Week 72 • Absolute change from baseline of the parent study in BMI up to Week 72 • Absolute change from baseline of the parent study in BMI z-score for subjects up to Week 72 (Part A only) • Absolute change from baseline of the parent study in body weight up to Week 72 • Number of PEx starting from baseline of the parent study (Part A only) • Absolute change from baseline of the parent study in the CFQ-R respiratory domain score up to Week 72 • Time-to-first PEx including PEx in the previous study (Part A only) up to Week 72

Study	TRAFFIC (study VX12-809-103, NCT01807923) & TRANSPORT (study VX12-809-104, NCT01807949) (158, 209) (158, 210)	PROGRESS (study VX12-809-105, NCT01931839) (155, 211)
		(Part A only) • Risk of having at least one exacerbation including PEx in the previous study up to Week 72 (Part A only)
Other secondary outcomes	• Absolute change in FEV_1 (in litres) at Week 24 • Number of PEx requiring hospitalisation at Week 24 • Number of PEx requiring IV antibiotics at Week 24 • Time-to-PEx through Week 24 • Risk of having at least one exacerbation at Week 24 • Number of days with PEx at Week 24 • Absolute change in weight at Week 24 • Absolute change in BMI z-score at Week 24 (patients 12–20 years old) • Absolute change from baseline in the EQ-5D 3L single utility index and VAS at Week 24 • Absolute change in TSQM domains from baseline at Week 24 • Safety and tolerability assessments based on AEs, clinical laboratory values (haematology, serum chemistry, coagulation studies, and urinalysis), standard digital ECGs, ambulatory ECGs, vital signs, and pulse oximetry • PK parameters	• Number of PEx requiring hospitalisation starting from the previous study (Part A only) up to Week 72 (Part A only) • Number of PEx requiring IV antibiotics starting from the previous study (Part A only) up to Week 72 (Part A only)
Trial supports application for marketing authorisation?	Yes (2, 3, 212)	Yes (2, 3, 212)
Trial used in the economic model?	Yes	Yes
Rationale for use in the model	These pivotal trials inform the safety and clinical efficacy inputs of the CEM	Provides long-term outcomes of the pivotal trials, study 809-103 and study 809-104, in the relevant patient population
*There were two treatment regimens in this trial. However, only results for the LUM 400 mg-IVA 250 mg treatment group are reported within this submission as this is the licensed dose (3). Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CYP3A, cytochrome P450 3A; BMI, body mass index; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; ECG, electrocardiogram; EQ-5D-3L VAS, EuroQol 5-dimension 3-level visual analogue scale; FEV_1, forced expiratory volume in the first second; F/F, homozygous for the *F508del-CFTR* mutation; h, hour; ICF, informed consent form; IVA, ivacaftor; kg, kilogram; LFT, liver function test; LUM, lumacaftor; m^2, metre squared; mg, milligrams; PBO, placebo; PEx, pulmonary exacerbation; PK, pharmacokinetic; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily; TEAE, treatment emergent adverse event; TSQM, treatment satisfaction questionnaire for medication		

Table 18. Baseline characteristics of CF patients enrolled in LUM/IVA trials of subjects aged 12 years or older (study 809-103 and study 809-104)

Baseline characteristic		TRAFFIC (study VX12-809-103, NCT01807923) (158)		TRANSPORT (studyVX12-809-104, NCT01807949) (158)	
		PBO (N=184)	LUM (400 mg q12h)/ IVA (250 mg q12h) (N=182)	PBO (N=187)	LUM (400mg q12h)/ IVA (250 mg q12h) (N=187)
Age, mean (min, max)		[redacted]	[redacted]	[redacted]	[redacted]
Age groups (years), N (%)	12 to <18	[redacted]	[redacted]	[redacted]	[redacted]
	≥18	[redacted]	[redacted]	[redacted]	[redacted]
Sex, N (%)		[redacted]	[redacted]	[redacted]	[redacted]
$ppFEV_1$, mean (min, max)		[redacted]	[redacted]	[redacted]	[redacted]
$ppFEV_1$ at baseline, N (%)	<40	[redacted]	[redacted]	[redacted]	[redacted]
	≥40 to <70	[redacted]	[redacted]	[redacted]	[redacted]
	≥70 to ≤90	[redacted]	[redacted]	[redacted]	[redacted]
	>90	[redacted]	[redacted]	[redacted]	[redacted]
Chronic pulmonary or respiratory CF therapy use at baseline, N (%)	Bronchodilators	[redacted]	[redacted]	[redacted]	[redacted]
	Dornase alfa	[redacted]	[redacted]	[redacted]	[redacted]
	Inhaled antibiotics	[redacted]	[redacted]	[redacted]	[redacted]
	Azithromycin	[redacted]	[redacted]	[redacted]	[redacted]
	Inhaled hypertonic saline	[redacted]	[redacted]	[redacted]	[redacted]
	Inhaled corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
Region	North America	[redacted]	[redacted]	[redacted]	[redacted]
	Europe	[redacted]	[redacted]	[redacted]	[redacted]
	Australia	[redacted]	[redacted]	[redacted]	[redacted]
Race	White	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]
	American Indian or Alaska native	[redacted]	[redacted]	[redacted]	[redacted]
	Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]
	Not collected per local regulations	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]
Positive P. aeruginosa status, N (%)		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; FEV_1, forced expiratory volume in the first second; h, hour; IVA, ivacaftor; kg, kilogram; LUM, lumacaftor; m^2, metre squared; mg, milligrams; max, maximum; min, minimum; PBO, placebo; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily

Table 19. Baseline characteristics of CF patients enrolled in study 809-105 extension study

Baseline characteristic		PROGRESS (study VX12- 809-105, NCT01931839)	
		PBO transitioned to LUM/IVA (N=176)	LUM/IVA (N=176)
Age, mean (SD)		24.9 (10.1)	25.1 (9.3)
Age groups (years), N (%)	12 to <18	47 (27)	94 (28)
	≥18	129 (73)	246 (72)
Sex, N (%)		F=86 (49)	F=164 (48)
BMI (kg/m^2), mean (SD)		20.9 (2.8)	21.4 (2.9)
Pseudomonas positive, N (%)		126 (72)	261 (77)
ppFEV$_1$ at Baseline Mean (SD)		60.2 (13.8)	60.4 (14.2)
Race, N (%)	White	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	American Indian or Alaska native	[redacted]	[redacted]
	Not collected per local regulations	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Region, N (%)	North America	[redacted]	[redacted]
	Europe	[redacted]	[redacted]
	Australia	[redacted]	[redacted]
Prior use of medication at baseline, N (%)	Bronchodilators	156 (88.6)	317 (93.2)
	Dornase alfa	125 (71.0)	254 (74.7)
	Inhaled antibiotics	117 (66.5)	208 (61.2)
	Inhaled hypertonic saline	106 (60.2)	214 (62.9)
	Inhaled corticosteroids	106 (60.2)	193 (56.8)
Positive P. aeruginosa status, N (%)		126 (71.6)	261 (76.8)

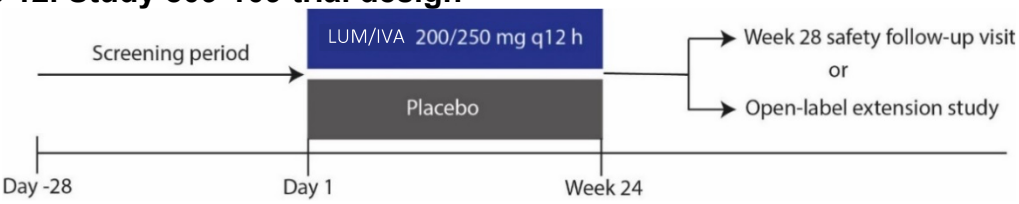
Data reported are baseline from study 809-103 or study 809-104 for patients who rolled over into study 809-105.
Abbreviations: BMI, body mass index; h, hour; IVA, ivacaftor; kg, kilogram; LUM, lumacaftor; m^2, metre squared; mg, milligrams; max, maximum; min, minimum; PBO, placebo; ppFEV$_1$, percent predicted FEV$_1$; q, every; qd, once daily; SD, standard deviations

B.2.2.2.2 CF patients aged 6 to 11 years

Table 20 summarises the trial methodology of relevant LUM/IVA studies identified in the pwCF aged 6 to 11 years. Table 21 and Table 22 describe the baseline characteristics of patients enrolled in those trials.

Study 809-109 was a phase 3, randomised, double blind, PBO-controlled trial that evaluated the efficacy and safety of LUM/IVA in patients aged 6 to 11 years with the F/F genotype (159, 213). Patients were stratified by weight (<25 kg vs ≥25 kg) and ppFEV$_1$ severity (<90 vs ≥90) determined at the screening visit, and randomly assigned 1:1 to treatment using an interactive web response system to receive 200 mg LUM and 250 mg IVA every 12 hours or matched PBO for 24 weeks. Figure 12 illustrates the trial design, while its methodology is summarised in Table 20. Table 21 describes the baseline characteristics of study 809-109.

Figure 12. Study 809-109 trial design



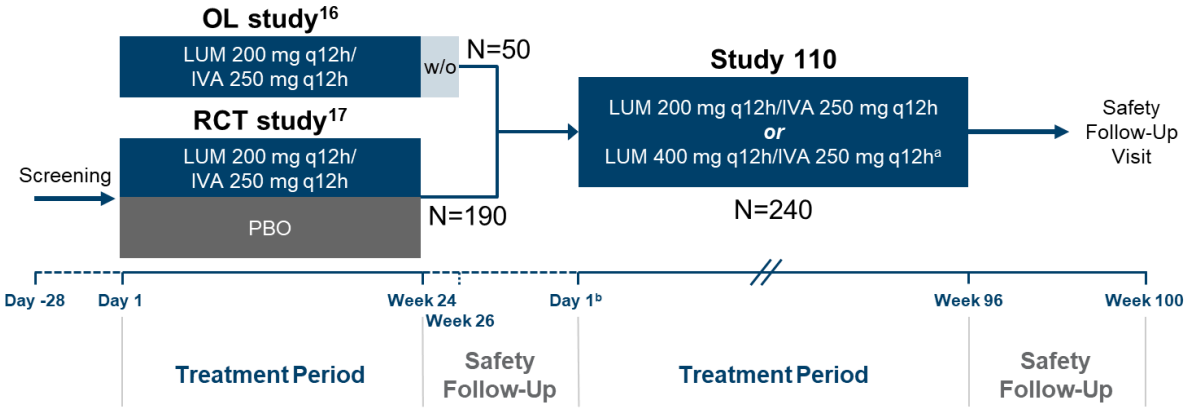
q12h = every 12 hours.
Reference: Adapted from (Ratjen et al., 2017).

Treatment cohort period 1 of **study 809-110** is a 96-week open label phase 3 rollover study designed to evaluate the long-term safety and efficacy of LUM/IVA in pwCF, homozygous for the *F508del-CFTR* mutation and who initiated LUM/IVA treatment during ages 6 to 11 (156). Paediatric patients who completed study 809-011B, an open-label, single arm, safety study of LUM/IVA in children aged 6 to 11 years (214), or study 809-109 were eligible to enrol in study 809-110 (Figure 13). Table 22 describes the baseline characteristics of study 809-110.

After completing a safety follow-up visit at the end of the parent studies patients initiated the study 809-110 treatment period, which consisted of 96 weeks of treatment with LUM/IVA (LUM 200 mg/IVA 250 mg every 12 hours for patients aged 6 to 11 years, LUM 400mg/IVA 250 mg every 12 hours for patients who turned age 12 during follow up) (156). Thus, patients who had received LUM/IVA in the parent study received a total of up to 120 weeks of LUM/IVA treatment by the end of study 809-110; patients who had received PBO in the parent study received a total of up to 96

weeks of LUM/IVA treatment by the end of study 809-110. Patients also completed a safety follow-up visit 4 weeks after completing study 809-110 if they did not transition to commercial LUM/IVA at the completion of study 110 (156). There was also an observational cohort which included subjects who received at least 4 weeks of study drug in study 809-109 or study 809-011B and completed visits up to Week 24 of study 109 or Week 26 of study 011B but were not eligible or did not elect to continue LUM/IVA treatment in study 809-110. This cohort is not described in this section as patients were not receiving LUM/IVA treatment. [redacted] Hereafter, where study 809-110 is mentioned in this submission it refers only to treatment cohort period 1 of the study.

Figure 13. Study 809-110 Design



[a] Once children reached age 12, they began receiving LUM 400 mg q12h/IVA 250 mg q12h at the next scheduled visit.
[b] The Day 1 visit of study 809-110 was the same day as the Week 24 visit (last treatment period visit) of the RCT study or the week 26 visit (safety follow-up visit) of the OL study for participants at study 809-110 sites that had been activated by the time the Week 24 visit (RCT study) or the Week 26 visit (OL study) had been completed. The Day 1 visit of study 809-110 did not coincide with the Week 24 visit (last Treatment Period visit) of the RCT study or the Week 26 visit (safety follow-up visit) of the OL study for participants at study 809-110 sites that had not been activated by the time the Week 24 visit (RCT study) or the Week 26 Visit (OL study) had been completed. Participants at these nonactive sites had to repeat any study 809-110 Day 1 assessments (in addition to completing study 809-110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (RCT study) or the Week 26 Visit (OL study).
Reference: Chilvers et al. (156)
Abbreviations: OL, open-label; PBO, PBO; q12h, every 12 hours; RCT, randomised controlled trial; w/o, washout.

Table 20. Comparative summary of methodology of LUM/IVA trials in CF patients aged 6 to 11 years

Study	Study VX14-809-109, NCT02514473) (159, 213)	Study VX15-809-110 (NCT02544451) (215, 216)
Genotype	F/F	F/F
Trial design	A phase 3, double blind, PBO controlled, parallel group study to evaluate the efficacy and safety of LUM/IVA in subjects aged 6 to 11 years with CF, homozygous for the *F508del-CFTR* mutation	A phase 3, rollover study to evaluate the safety and efficacy of long-term treatment with lumacaftor in combination with ivacaftor in subjects aged 6 years or older with CF, homozygous for the *F508del-CFTR* mutation
Duration	24 weeks	96 weeks
Population	Subjects aged 6 - 11 years with CF homozygous for the *F508del-CFTR* mutation	Subjects aged 6 years or older who are homozygous for the *F508del*-CFTR mutation.
Eligibility criteria for participants	**Inclusion Criteria** • Weight ≥15 kg (without shoes) • CF diagnosis • Homozygous for the F508del-CFTR mutation ppFEV1 of ≥70 percentage points adjusted for age, sex, and height • Subjects with a screening $LCI_{2.5}$ result greater than or equal to 7.5 **Exclusion Criteria** • Comorbidity that might pose additional risk or confound study results (e.g., history of cirrhosis with portal hypertension, history of risk factors for torsades de pointes) • Clinically significant abnormalities (haemoglobin <10 g/dL, abnormal liver or renal function) • Acute upper or lower respiratory infection, PEx or changes in therapy for pulmonary disease within 28 days before day 1 of the study • History of solid organ or haematological transplantation	**Inclusion criteria** • Subject's legally appointed and authorised representative (e.g., parent or legal guardian) signed and dated an ICF and the subject signed and dated an assent form (if applicable). • Subjects entering treatment cohort period 1 were required to meet both of the following criteria: ○ Completed 24 weeks of study drug treatment in study 809-109 or completed 24 weeks of study drug treatment and the Week 26 safety follow-up in study 809-011B. Subjects who had study drug interruptions but completed study visits up to Week 24 of study 809-109 or Week 26 of study 809-011B were eligible (this was Day 1 of study 809-110 for subjects at study 809-110 active sites). Subjects who were not taking study drug at the end of the parent study treatment period (subjects from study 809-011B had a planned washout period from Week 24 to Week 26 and must still have completed the Week 26 safety follow-up), including subjects who required study drug interruption to be either continued or initiated at Day 1 in study 809-110, must have received Vertex approval for enrolment in the treatment cohort. ○ Elected to enrol in treatment cohort period 1 (subjects who prematurely discontinued study drug treatment were not eligible for enrolment in treatment cohort period 1. Subjects who completed treatment cohort period 1 could discontinue from study 809-110 to participate in another qualified Vertex study. **Exclusion Criteria** • History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject (e.g., cirrhosis with portal hypertension). • Pregnant and nursing females. • Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements. • History of drug intolerance in the prior study that would pose an additional risk to the subject in the opinion of investigator

Study	Study VX14-809-109, NCT02514473) (159, 213)	Study VX15-809-110 (NCT02544451) (215, 216)
		• History of poor compliance with study drug and/or procedure in the previous study as deemed by the investigator. • Participation in an investigational drug trial (including studies investigating LUM and/or IVA).
Settings and locations where the data were collected	The trial took place in 54 locations in nine countries (the USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK).	The trial took place in 61 locations across 9 countries (the USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK).
Trial drugs	Intervention: LUM 200 mg q12h/IVA 250 mg q12h Comparator: PBO	Intervention: Subjects aged 6–11 years at the start of the parent study received: LUM 200 mg q12h/IVA 250 mg q12h Subjects who turned 12 years of age in the previous (parent) study or on Day 1 of this rollover study began receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turned 12 years of age after the Day 1 visit of this rollover study began receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit. Comparator: N/A
Permitted and disallowed concomitant medications	Patients were permitted to continue receiving their existing medications during the study period, including dornase alfa and hypertonic saline	CYP3A inducers were not allowed. No other medications were permitted
Brief description of reported outcomes specified in the decision problem	**Primary outcome** • $LCI_{2.5}$ **Secondary outcomes** • BMI • CFQ-R RD score • $LCI_{5.0}$ • $ppFEV_1$ • PEx • Adverse events	**Primary outcome** • Safety **Secondary outcome** • $LCI_{2.5}$ • BMI • CFQ-R RD score • $LCI_{5.0}$ • $ppFEV_1$ • PEx
Primary outcomes	• Mean absolute change in $LCI_{2·5}$ from all study visits up to and including Week 24	The overall safety profile of study drug was assessed in terms of the following safety and tolerability endpoints: • AEs up to Week 96 • Clinical laboratory values (haematology, serum chemistry, coagulation studies, and urinalysis) up to Week 96 • Standard digital ECGs up to Week 96 • Vital signs up to Week 96 • Pulse oximetry up to Week 96 • OEs at Week 48 and Week 96 • Spirometry up to Week 96
Key secondary outcomes (including scoring methods and timings of assessments)	• Average absolute change in SwCI from baseline at Day 15 and at Week 4 • Absolute change in BMI from baseline at Week 24, • Average absolute change in CFQ–RD score from baseline study visit up to and including Week 24	• Absolute change in $LCI_{2.5}$ from parent study baseline at Week 96 • Absolute change in BMI from parent study baseline at Week 96 • Absolute change in CFQ-RD score from parent study baseline at Week 96 • Absolute change in SwCI from parent study baseline at Week 96

Study	Study VX14-809-109, NCT02514473) (159, 213)	Study VX15-809-110 (NCT02544451) (215, 216)
Other secondary outcomes	• Absolute change in $LCI_{5.0}$ (average of all visits up to and including Week 24) • Absolute change in SwCl from baseline at Week 24 • Absolute and relative change in $ppFEV_1$ (average of all visits up to and including Week 24) • Absolute change in BMI-for-age z-score from baseline at Week 24 • Absolute change in weight from baseline at Week 24 • Absolute change in weight-for-age z-score from baseline at Week 24 Absolute change in height from baseline at Week 24 • Absolute change in height-for-age z-score from baseline at Week 24 • Absolute change in TSQM domains from baseline through Week 24 • Time-to-first PEx (up to Week 24) • Event of having at least one PEx (up to Week 24) • Number of PEx (up to Week 24) • Safety and tolerability • PK parameters	• Absolute change in $LCI_{5.0}$ from parent study baseline at Week 96 • Absolute change in $ppFEV_1$ from parent study baseline at Week 96 • Relative change in $ppFEV_1$ from parent study baseline at Week 96 • Absolute change in BMI-for-age z-score from parent study baseline at Week 96 • Time-to-first PEx from parent study baseline through Week 96 • Percentage of participants having at least 1 PEx event from parent study baseline through Week 96 • Number of PEx events per patient-year from parent study baseline through Week 96 • Rate of change in $LCI_{2.5}$ from day 15 after first dose of LUM/IVA through Week 96 • Rate of change in $LCI_{5.0}$ from Day 15 after first dose of LUM/IVA through Week 96 • Rate of change in $ppFEV_1$ from Day 15 after first dose of LUM/IVA through Week 96 • Absolute change from baseline in body weight from parent study baseline at Week 96 • Absolute change from baseline in body weight z-score for subjects aged <20 years from parent study baseline at Week 96 • Absolute change from baseline in height from parent study baseline at Week 96 • Absolute change from baseline in height z-score for subjects aged <20 years from parent study baseline at Week 96 • Absolute change from baseline in TSQM from parent study baseline at Week 96
Trial supports application for marketing authorisation?	Yes (2, 3, 212)	Yes
Trial used in the economic model?	Yes	Yes
Rationale for use in the model	Supportive data for the marketing authorisation; this study is included in the ITC and informs clinical efficacy inputs in the CEM	Provides long-term efficacy outcomes of the studies 809-109 and 809-011B in the relevant patient population
Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CYP3A, cytochrome P450 3A; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; h, hour; ICF, informed consent form; IVA, ivacaftor; kg, kilogram; LCI, lung clearance index; LUM, lumacaftor; m^2, metre squared; mg, milligrams; N/A, not applicable; PBO, placebo; PEx, pulmonary exacerbation; PK, pharmacokinetics; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily; SwCl, sweat chloride; TEAE, treatment emergent adverse event; TSQM, treatment satisfaction questionnaire for medication		

Table 21. Baseline characteristics of CF patients enrolled in LUM/IVA studies of subjects aged 6 to 11 years (study 809-109)

Baseline characteristic		Study VX14- 809-109 (NCT02514473) (159)	
		LUM/IVA (N=103)	PBO (N=101)
Sex, N (%)		F= 63 (61)	F= 58 (57)
Age at baseline, years (SD)		8.7 (1.6)	8.9 (1.6)
Geographical distribution, N (%)	North America	59 (57)	60 (59)
	Europe	28 (27)	29 (29)
	Australia	16 (16)	12 (12)
Height, cm (SD)		133.2 (10.8)	134.4 (10.3)
Height-for-age z-score (SD)		−0.1 (1.0)	−0.2 (0.8)
Weight, kg (SD)		29.4 (6.5)	30.2 (6.8)
<25Kg, N (%)		30 (29)	28 (28)
≥25 kg, N (%)		73 (71)	73 (72)
Weight-for-age z-score (SD)		−0.2 (0.8)	−0.2 (0.8)
BMI, kg/m² (SD)		16.4 (1.7)	16.6 (2.0)
BMI-for-age z-score (SD)		−0.1 (0.8)	−0.1 (0.9)
$LCI_{2.5}$ (SD)		10.3 (2.4)	10.3 (2.2)
SwCl concentration, mmol/L (SD)		102.6 (10.3)	103.4 (9.8)
$ppFEV_1$, percentage points (SD)		88.8 (13.7)	90.7 (10.8)
$ppFEV_1$	<70, N (%)	10 (10)	1 (1)
	≥70 to <90, N (%)	42 (41)	47 (47)
	≥90 to ≤105, N (%)	38 (37)	44 (44)
	>105, N (%)	12 (12)	9 (9)
Patients receiving medications prior to day 1, N (%)	Dornase alfa	88 (85)	88 (87)
	Any inhaled antibiotic	20 (19)	30 (30)
	Any inhaled bronchodilator	85 (83)	82 (81)
	Any inhaled hypertonic saline	67 (65)	54 (53)
	Any inhaled corticosteroids	38 (37)	47 (47)
Pseudomonas positive, N (%)		44 (43)	43 (43)

Abbreviations: BMI, body mass index; cm, centimetre; F, female; h, hour; IVA, ivacaftor; kg, kilogram; $LCI_{2.5,}$ lung clearance index 2.5; LUM, lumacaftor; m^2, metre squared; mg, milligrams; mmol, millimole; PBO, placebo; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviations; SwCl, sweat chloride.

Table 22. Baseline characteristics of CF patients enrolled in extension study 809-110

Baseline characteristic		Study VX15-809-110 (NCT02544451) (156, 215)	
		Treatment-to treatment group (N=143)*	PBO-to treatment group (N=96)*
Sex, N (%)		F = 83 (58)	F = 56 (58)
Age at baseline, years (SD)		8.9 (1.56)	9.0 (1.54)
Geographical distribution, N (%)	North America	[redacted]	[redacted]
	Europe		
	Australia		
Race	White	140 (98%)	92 (96%)
	Asian	0	0 1 (1%)
	Not collected per local regulations	1 (1%)	1 (1%)
	Other	2 (1%)	2 (2%)
Height, cm (SD)		[redacted]	[redacted]
Height-for-age z-score (SD)			
Weight, kg (SD)			
Weight-for-age z-score (SD)			
BMI, kg/m² (SD)		16.56 (1.79)	16.58 (2.00)
BMI-for-age z-score (SD)		-0.09 (0.88)	-0.16 (0.90)
$LCI_{2.5}$ (SD)		10.2 (2.4);	10.2 (2.2) ;
SwCl concentration, mmol/L (SD)		103.6 (10.7), N=142	103.4 (10.0) N=93
$ppFEV_1$, percentage points (SD)		89.3 (13.7) N=142	90.7 (10.7)
<90, N (%)		[redacted]	[redacted]
≥90 N (%)			

Baseline is based on the start of studies 809-109 and 809-011B
Baseline for SwCl was defined as the average of the measurements at screening and on Day 1 predose in study 809-109 and study 809-011B; baseline for other variables was defined as the most recent measurement before the first dose of study drug in study 809-109 or study 809-011B
*N is per the header row unless otherwise specified in a cell
Abbreviations: BMI, body mass index; cm, centimetre; F, female; h, hour; IVA, ivacaftor; kg, kilogram; $LCI_{2.5,}$ lung clearance index 2.5; LUM, lumacaftor; m^2, metre squared; mg, milligrams; mmol, millimole; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; q, every; qd, once daily; SD, standard deviations; SwCl, sweat chloride.

B.2.2.2.3 CF patients aged 2 to 5 years

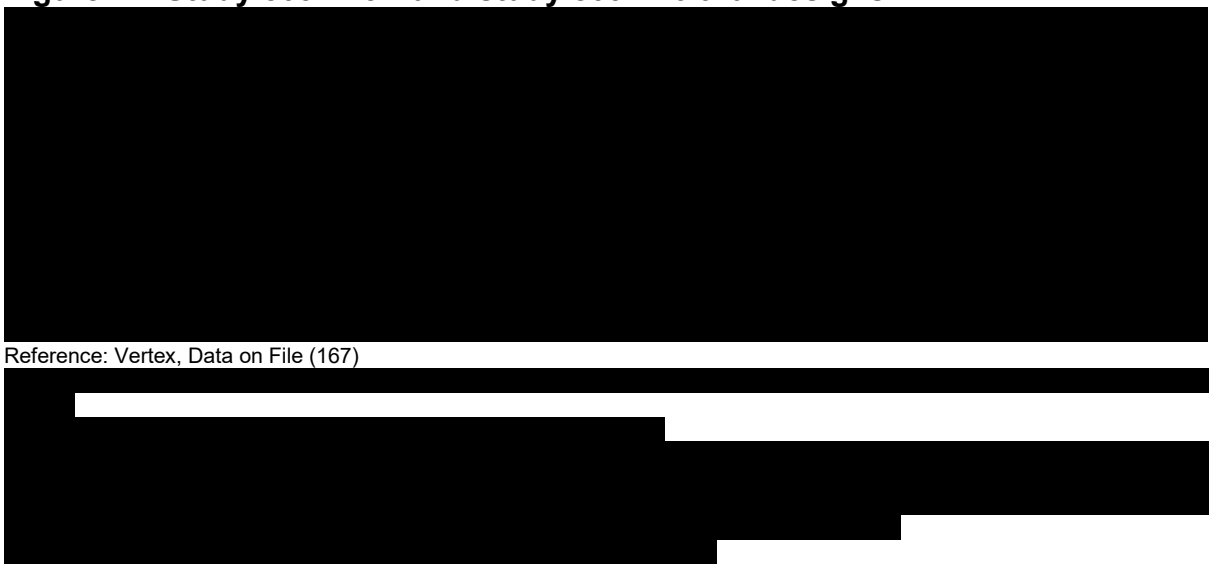
Table 23 summarises the methodology of relevant LUM/IVA clinical trials in the pwCF aged 2 to 5 years, while Table 24 describes the baseline characteristics of patients enrolled in those trials.

Study 809-115B was a phase 3, single arm, open-label study evaluating the efficacy and safety of LUM/IVA in patients aged 2 to 5 years with the F/F genotype (162, 217). Children of bodyweight less than 14 kg received LUM 100 mg and IVA 125 mg whilst children of bodyweight equal or greater than 14 kg received LUM 150 mg and IVA 188 mg (orally every 12 h). This was a two-part study. Part A was a 15-day pharmacokinetics (PK) and safety study, whereas part B was a 24-week study to assess safety, pharmacokinetics, pharmacodynamics and efficacy. Only the methodology and results of part B are presented in this submission.

The 24-week treatment period of study 809-115B was followed by a 2-week washout period. Children who completed the required part B visits were then eligible to enrol in a 96-week extension study (study 809-116) (Figure 14).

Study 809-116 was a phase 3, single arm, 96-week OLE study of patients who completed study 809-115B, designed to evaluate the long-term safety and efficacy of LUM/IVA in patients with the F/F genotype aged 2 years or older (Figure 14) (161, 218).

Figure 14. Study 809-115B and study 809-116 trial designs



Reference: Vertex, Data on File (167)

Table 23. Comparative summary of methodology of trials of LUM/IVA in subjects with CF aged 2 to 5 years

Study	Study VX15-809-115 Part B (NCT02797132)(162, 217, 219)	Study VX16-809-116 (NCT03125395) (161, 218, 220)
Genotype	F/F	F/F
Trial design	Phase 3 open-label, multicentre study evaluating the safety, efficacy, and tolerability of multiple doses of LUM/IVA in subjects with CF aged 2 to 5 years and homozygous for *F508del CFTR* mutation.	A phase 3, rollover study to evaluate the safety of long-term treatment with LUM/IVA combination therapy in subjects with CF aged 2 years and homozygous for *F508del CFTR* mutation
Duration	24 weeks	96 weeks (total treatment duration for participants was 120 weeks as this is an OLE of study 809-115B)
Population	Subjects aged 2 - 5 years with CF homozygous for the *F508del-CFTR* mutation	Subjects aged 2 years or older with CF homozygous for the *F508del-CFTR* mutation
Eligibility criteria for participants	**Inclusion criteria** • Subjects who weigh ≥8 kg without shoes and wearing light clothing at the screening visit • Subjects with confirmed diagnosis of CF at the screening visit • Subjects who are homozygous for the F508del-CFTR mutation **Exclusion criteria** • Any clinically significant laboratory abnormalities at the screening visit that would interfere with the study assessments or pose an undue risk for the subject • An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 • A standard 12-lead ECG demonstrating QTc >450 millisecond at the screening visit • History of solid organ or haematological transplantation • Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the screening visit • History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the ophthalmologic examination at the screening visit	**Inclusion criteria** • Completed 24 weeks of LUM/IVA treatment and the safety follow-up visit in study VX15-809-115 Part B (study 809-115B, NCT02797132) • Willing to remain on a stable CF medication regimen through the safety follow-up visit **Exclusion criteria** • Prematurely discontinued LUM/IVA treatment in study 809-115B. • History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject • History of drug intolerance or other serious reactions to LUM/IVA in study 809-115B that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor. • Subjects with a history of allergy or hypersensitivity to LUM/IVA. • LFT abnormality meeting criteria for LUM/IVA treatment interruption at the completion of study 1809-115B, for which no convincing alternative aetiology is identified. • QTc value at the completion of study 809-115B that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor • History of poor compliance with LUM/IVA and/or procedures in study 809-115B as deemed by the investigator. • Participation in an investigational drug trial (including studies investigating LUM and/or IVA) other than study 809-115B.
Settings and locations where the data were collected	The trial took place in 20 locations across the US and Canada	The trial took place in 20 locations across the US and Canada
Trial drugs	Intervention: • Children weighing <14kg: LUM 100 mg/IVA 125 mg q12h • Children weighing ≥14kg: LUM 150 mg/IVA 188 mg q12h	Intervention • Children weighing <14kg and <6 years: LUM 100 mg/IVA 125 mg q12h • Children weighing ≥14kg and <6 years: LUM 150 mg/IVA 188 mg q12h

Study	Study VX15-809-115 Part B (NCT02797132)(162, 217, 219)	Study VX16-809-116 (NCT03125395) (161, 218, 220)
		• Children ≥ 6 years: LUM 200 mg/IVA 250 mg q12h
Permitted and disallowed concomitant medications	Permitted concomitant medications: • Patients continued to take their pre-study medications Disallowed concomitant medications: • Use of strong inducers of CYP3A • Use of strong inhibitors or strong inducers of CYP3A within 14 days before Day 1 of dosing	Permitted concomitant medications: • It is recommended that subjects remain on a stable medication regimen for their CF from study 809-115B through the safety follow-up visit in study 116 Use with caution: • CYP3A inhibitors Disallowed concomitant medications: • Use of strong inducers of CYP3A
Brief description of reported outcomes specified in the decision problem	Primary outcome: • Adverse events Secondary outcomes: • BMI • PEx • Number of CF-related hospitalisations • $ppFEV_1$ • $LCI_{2.5}$ • $LCI_{5.0}$	Primary outcome: • Adverse events Secondary outcomes: • BMI • PEx • Number of CF-related hospitalisations • $LCI_{2.5}$ • $LCI_{5.0}$
Primary outcomes	• Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, haematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, OEs, and spirometry up to Week 26	• Safety and tolerability assessments based on AEs, changes in clinical laboratory values, ECGs, vital signs, pulse oximetry, OEs, and spirometry up to Week 98
Key secondary outcomes (including scoring methods and timings of assessments)	• Absolute change from baseline in SwCl at Week 24 • Absolute change from baseline in BMI at Week 24 • Absolute change from baseline in BMI for-age z-score at Week 24 • Absolute change from baseline in weight and weight-for-age z-score at Week 24 • Absolute change from baseline in stature and stature-for-age z-score at Week 24 • Time-to-first PEx through Week 24 • Number of PEx (from baseline through Week 24) • Number of CF-related hospitalisations from baseline through Week 24 • Absolute change from baseline in LCI2.5 from baseline at Week 24 • Absolute change from baseline in LCI5.0 from baseline at Week 24 • Absolute change in FE-1 levels from baseline at Week 24 • Absolute change in serum levels of IRT from baseline at Week 24 • Change in microbiology cultures from baseline at Week 24 • Absolute change from baseline in ppFEV1 at Week 24 • Absolute change in SwCl from Week 24 at Week 26 • Acceptability/palatability of LUM/IVA granules at Day 1 • PK parameters	• Absolute change from parent study baseline in SwCl at Week 96 • Absolute change from parent study baseline in BMI at Week 96 • Absolute change from parent study baseline in BMI for-age z-score at Week 96 • Absolute change from parent study baseline in weight and weight-for-age z-score at Week 96 • Absolute change from parent study baseline in stature and stature-for-age z-score at Week 96 • Time to first PEx from parent study baseline through Week 96 • Number of PEx (from parent study baseline through Week 96 • Number of CF-related hospitalisations from parent study baseline through Week 96 • Absolute change from parent study baseline in FE-1 levels at Week 96 • Absolute change from parent study baseline in serum levels of IRT at Week 96 • Change from baseline in microbiology cultures at Week 96 • Absolute change from baseline in LCI2.5 from parent study baseline at Week 96 • Absolute change from parent study baseline in LCI5.0 from baseline at Week 96
Other secondary outcomes	• N/A	N/A

Study	Study VX15-809-115 Part B (NCT02797132)(162, 217, 219)	Study VX16-809-116 (NCT03125395) (161, 218, 220)
Trial supports application for marketing authorisation?	Yes (2, 3, 212)	Yes (2, 3, 212)
Trial used in the economic model?	Yes	No
Rationale for use/non-use in the model	This trial informs the safety and clinical efficacy inputs of the CEM	This trial informs the discontinuation rate in the CEM

Abbreviations :AE, adverse events; BMI, body mass index; CF, cystic fibrosis; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; CFTR, cystic fibrosis transmembrane conductance regulator C_{trough}, pre-dose concentration; CYP3A, cytochrome P450 3A; ECG, electrocardiogram; EQ-5D-3L VAS, euroqol 5-dimension 3-level visual analogue scale;FE-1, faecal elastase-1 FEV_1, forced expiratory volume in the first second; F/F, homozygous for the *F508del-CFTR* mutation; h, hour; IRT, Immunoreactive Trypsinogen; IVA, ivacaftor; kg, kilogram; LCI, lung clearance index; LFT, Liver function test; LUM, lumacaftor; m^2, metre squared; mg, milligrams; OE, ophthalmological examination; PEx, pulmonary exacerbation; PK, pharmacokinetic; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily; QTc, corrected QT interval on electrocardiogram; SAE, serious adverse events; SwCl, sweat chloride; TSQM, treatment satisfaction questionnaire for medication

Table 24. Baseline characteristics of CF patients enrolled in LUM/IVA studies of subjects aged 2 to 5 years

		Study VX15-809-115 Part B (NCT02797132) (162)		Study VX16-809-116 (NCT03125395)
		Weight <14 kg, lumacaftor 100 mg plus ivacaftor 125 mg every 12 h (N=19)	Weight ≥14 kg, lumacaftor 150 mg plus ivacaftor 188 mg every 12 h (N=41)	N=57
Sex (F) N(%)		9 (47)	20 (49)	28 (49)
Age (months) (SD)		31.6 (5.1)	49.9 (10.6)	43.2 (12.2)
Race, N (%)	White	[redacted]	[redacted]	56 (98.2)
	Other	[redacted]	[redacted]	1 (1.8)
Weight, kg (SD)		12.7 (1.0)	17.1 (2.3)	15.6 (2.8)
Stature, cm (SD)		89.1 (3.4)	103.4 (6.1)	98.4 (8.4)
BMI, kg/m² (SD)		16.0 (1.1)	16.0 (1.0)	15.99 (1.05)
BMI-for-age z-score (SD)		–0.10 (0.85)	0.30 (0.76)	0.16 (0.82)
SwCl, mmol/L (SD)		105.5 (8.0); N=19	106.0 (7.2); N=37	105.8 (7.3)*
$LCI_{2.5}$ (SD)		7.6 (0.9); N=5	9.3 (2.0); N=32	8.81 (1.87)**
$ppFEV_1$ (SD)		[redacted]	[redacted]	[redacted]

*Data were available for 53 participants.
**Data were available for 22 participants
Abbreviations: BMI, body-mass index; $LCI_{2.5}$,,lung clearance index 2.5; SD, standard deviation

B.2.2.3 TEZ/IVA

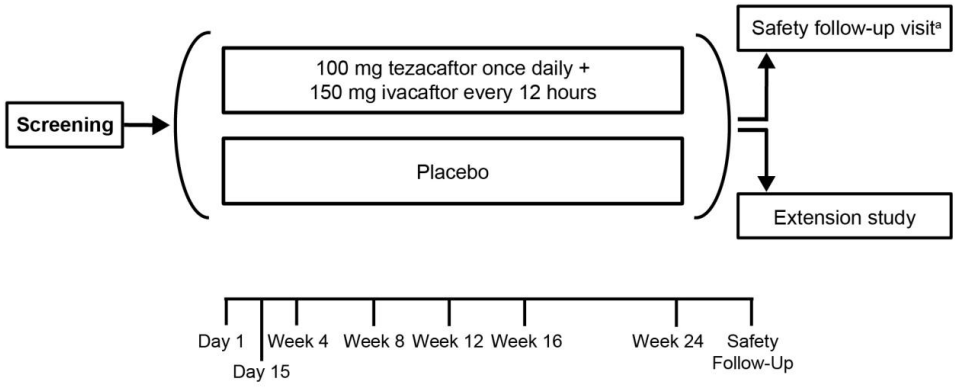
Evidence for the clinical efficacy and safety of TEZ/IVA deemed relevant for the decision problem includes five phase 3 trials as outlined in Table 12. Detailed methods and results of these trials are presented in Sections B.2.2 to B.2.9.

B.2.2.3.1 CF patients ≥12 years of age

Table 25 summarises the methodology of relevant TEZ/IVA clinical studies in tF aged ≥12 years, while Table 26 outlines the baseline characteristics of subjects enrolled in those trials.

Study 661-106 was a randomised, double-blind, PBO-controlled, parallel-group trial that evaluated the efficacy and safety of TEZ/IVA in CF patients with F/F genotype aged 12 years or older. In this study, patients completed a 28-day screening period followed by a 24-week treatment period (Figure 15). Patients were randomised in a 1:1 ratio to receive either TEZ/IVA or matched PBO. Randomisation was stratified according to age (<18 years vs ≥18 years), sex, and ppFEV$_1$ (<70% vs ≥70%) at screening. After completing the trial, patients could enrol in a 96-week OLE study (study 661-110) (157, 221).

Figure 15. Study 661-106 trial design

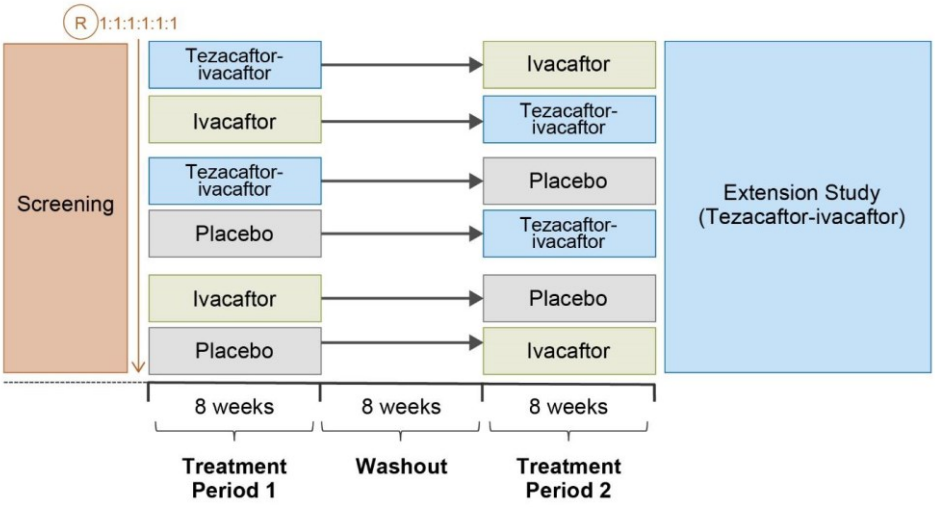


Reference: Taylor-Cousar et al. (157)

Study 661-108 was a randomised, double-blind, PBO-controlled, 2-period, 3-treatment crossover trial that evaluated the efficacy and safety of TEZ/IVA in CF patients with F/RF genotype ≥12 years of age. This trial consisted of a screening period, two treatment periods of 8 weeks separated by a washout period of 8 weeks and a safety follow-up visit. Each patient received two of the following three treatments: TEZ/IVA, IVA or PBO. Study participants were stratified by age at

screening (<18 vs ≥18 years), ppFEV1 at screening (<70% vs ≥70%), and type of residual function mutation (class V noncanonical splice or class II-IV residual function (missense) mutations), and then randomised (1:1:1:1:1:1) to one of six treatment sequences (Figure 16) (164).

Figure 16. Study 661-108 trial design



Reference: Rowe et al. (164)

Study 661-110 was a 96-week, multicentre, OLE study that evaluated the long-term safety, tolerability and efficacy of TEZ/IVA in pwCF aged 12 years or older who were homozygous or heterozygous for the *F508del-CFTR* mutation and had completed one of six previous studies of TEZ/IVA (661-103, 661-106, 661-107, 661-108, 661-109 and 661-111). Participants were eligible if they had completed study treatment during the treatment period in the parent studies. This study consisted of a 96-week Treatment Cohort and an Observational Cohort. Subjects who were not eligible for the Treatment Cohort or who elected not to enrol in the Treatment Cohort and met the eligibility criteria were offered the opportunity to enrol in the Observational Cohort (Figure 17) (222, 223). [redacted]

Figure 17. Study 661-110 trial design

Reference: Vertex, Data on File (225)

Table 25. Comparative summary of trial methodology for TEZ/IVA studies, ≥12 years

Study	EVOLVE (study VX14-661-106, NCT02347657) (157, 221, 226)	EXPAND (study VX14-661-108, NCT02392234) (164, 227)	EXTEND OLE (study VX14-661-110, NCT02565914) (222, 223, 228)
Genotype	F/F	F/RF	F/F, F/RF
Trial design	Phase 3, randomised, double-blind, multicentre, PBO-controlled, parallel-group study evaluating the efficacy and safety of TEZ/IVA in CF patients ≥12 years of age with F/F genotype. Patients were randomly assigned in a 1:1 ratio to receive either TEZ/IVA or PBO for 24 weeks	Phase 3, randomised, double-blind, multicentre, PBO-controlled, two-period, three-intervention crossover study evaluating the efficacy and safety of TEZ/IVA in CF patients ≥12 years of age with F/RF genotype. Patients were randomly assigned in a 1:1:1:1:1:1 ratio to one of six intervention sequences (TEZ/IVAàIVA, IVAàTEZ/IVA, TEZ/IVAàPBO, PBOàTEZ/IVA, IVAàPBO, PBOàIVA). The study included a screening period (up to 6 weeks), two intervention periods (8 weeks) separated by a washout period (8 weeks)	Phase 3, multicentre, open-label, 3-part rollover study evaluating the safety and efficacy of long-term treatment with TEZ/IVA in CF patients ≥12 years of age who were homozygous or heterozygous for the *F508del-CFTR* Mutation. Participants completed one of six parent studies (study 661-103, study 661-106, study 661-107, study 661-108, study 661-109, study 661-111). The study consisted of a Treatment Cohort and an Observational Cohort. Subjects who were not eligible or who elected not to enrol in the Treatment Cohort, could enrol in the Observational Cohort. Treatment Cohort will be addressed in the following sections/tables
Duration	• Treatment period: 24 weeks • Safety follow-up: 4 weeks	• Treatment period 1: 8 weeks • Washout period: 8 weeks • Treatment period 2: 8 weeks • Safety follow-up: 4 weeks	• Treatment period: 96 weeks • Safety follow-up: 4 weeks
Population	pwCF aged ≥12 years homozygous for the *F508del-CFTR* mutation (F/F)	pwCF aged ≥12 years heterozygous for the *F508del-CFTR* mutation and a CFTR mutation associated with residual CFTR function (F/RF)	pwCF aged ≥12 years homozygous or heterozygous for the *F508del-CFTR* mutation
Eligibility criteria for participants	**Inclusion criteria** • Patient (or legal guardian) signed and dated the informed consent form • Willing to comply with the treatment plan • 12 years of age or older • F/F genotype • Confirmed CF diagnosis • ppFEV1 ≥40% and ≤90% during screening • Stable CF disease • Willing to remain on a stable CF treatment regimen **Exclusion criteria** • History of any comorbidity that might confound the results or pose an additional risk to the patient • Abnormal laboratory values at screening (haemoglobin, AST, ALT, GGT, ALP, total bilirubin, renal function) • Acute upper or lower respiratory infection, PEx, or changes in therapy for pulmonary disease within 28 days before Day 1 • History of solid organ or haematological transplantation	**Inclusion criteria** • Patient (or legal guardian) signed and dated the informed consent form • Willing to comply with the treatment plan • 12 years of age or older • F/RF genotype • Stable CF disease • Willing to remain on a stable CF treatment regimen **Exclusion criteria** • History of any comorbidity that might confound the results or pose an additional risk to the patient • Abnormal laboratory values at screening (haemoglobin, AST, ALT, GGT, ALP, renal function) • Acute upper or lower respiratory infection, PEx, or changes in therapy for pulmonary disease within 28 days before Day 1 • History of solid organ or haematological transplantation • History of alcohol or drug abuse • Ongoing or prior participation in an investigational study within 30 days of screening • Use of restricted medications within the specified	**Inclusion criteria** • Patient (or legal guardian) signed and dated the informed consent form • Patient did not withdraw from parent study • Able to comply with the protocol requirements • Elect to enrol in Treatment Cohort • Completed study drug treatment period in a parent study • Willing to remain on a stable CF treatment regimen • Patients re-enrolling the Treatment Cohort must have previously received 4 weeks of study drug and completed the last required visit of another qualified Vertex study **Exclusion criteria** • History of any comorbidity that might confound the results or pose an additional risk to the patient • Pregnant or nursing females • Sexually active subjects of reproductive potential who are not willing to follow contraception requirements

Study	EVOLVE (study VX14-661-106, NCT02347657) (157, 221, 226)	EXPAND (study VX14-661-108, NCT02392234) (164, 227)	EXTEND OLE (study VX14-661-110, NCT02565914) (222, 223, 228)
	• History of alcohol or drug abuse • Ongoing or prior participation in an investigational study within 30 days of screening • Use of restricted medications within the specified window before 1st dose • Pregnant or nursing females • Patient or a close relative of the patient is the investigator or involved in the investigation team	window before 1st dose • Pregnant or nursing females • Patient or a close relative of the patient is the investigator or involved in the investigation team	• History of drug intolerance • Participation in an investigational drug trial other than the parent studies or other eligible Vertex studies investigating TEZ/IVA, or use of a commercially available CFTR modulator • Previous re-enrolment in the Treatment Cohort, after participating in other qualified Vertex Studies
Settings and locations where the data were collected	This trial was conducted at 91 sites in the United States, Canada, and Europe	This trial was conducted at 91 sites in Australia, Europe, Israel, and North America	This trial was conducted at 170 sites in Australia, Europe, Israel, and North America
Trial drugs	**Interventions** • TEZ/IVA (TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • PBO	**Interventions** • TEZ/IVA (TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • IVA: 150 mg Q12h • PBO	**Interventions** • TEZ/IVA (TEZ: 100 mg QD; IVA: 150 mg Q12h) **Comparators** • N/A
Permitted and disallowed concomitant medications	Subjects must remain on a stable medication regimen for CF from 28 days before Day 1 through the Safety Follow-up Visit. Patients may receive doses of prednisone (up to 10 mg/day) or prednisone (60 mg qd, up to 5 days). Information about bronchodilator use during the study will be collected and documented. Concomitant use of medications known to prolong the QT interval should be used with caution during the study	Subjects must remain on a stable medication regimen for CF from 28 days before Day 1 through the Safety Follow-up Visit. Patients may receive doses of prednisone (up to 10 mg/day) or prednisone (60 mg qd, up to 5 days). Information about bronchodilator use during the study will be collected and documented. Concomitant use of medications known to prolong the QT interval should be used with caution during the study	Subjects must remain on a stable medication regimen for CF for at least 28 days before Day 1. Subjects must not initiate long-term treatment with new medication from 28 days before Day 1 through the Safety Follow-up Visit unless approved. No restrictions on the concomitant use of corticosteroids. Information about bronchodilator use during the study will be collected and documented
Brief description of reported outcomes specified in the decision problem	**Primary outcome** • $ppFEV_1$ (absolute change) **Secondary outcomes** • $ppFEV_1$ (relative change) • PEx • BMI • CFQ-R RD	**Primary outcome** • $ppFEV_1$ (absolute change) **Secondary outcomes** • CFQ-R RD • Safety and tolerability • $ppFEV_1$ (relative change) • PEx • BMI	**Primary outcome** • Safety and tolerability **Secondary outcomes** • $ppFEV_1$ • PEx • BMI • CFQ-R RD
Primary outcomes	• absolute change in $ppFEV_1$ from baseline through Week 24	• absolute change in $ppFEV_1$ from baseline to Week 4/8 average	• safety and tolerability as assessed by number of subjects with AEs and SAEs from Day 1 up to Week 100)
Key secondary outcomes (including scoring methods and timings of assessments)	• relative change in $ppFEV_1$ from baseline through Week 24 • number of PEx through Week 24 • absolute change in BMI from baseline at Week 24 • absolute change in CFQ-R RD score from baseline through Week 24	• absolute change in CFQ-R RD score from baseline to Week 4/8 average • safety and tolerability assessments • relative change in $ppFEV_1$ from baseline to Week 4/8 average • absolute change in SwCl from baseline to Week 4/8 average	• absolute change in $ppFEV_1$ from baseline at Week 96 • relative change in $ppFEV_1$ from baseline at Week 96 • number of PEx from baseline up to Week 96 • absolute change in BMI from baseline at Week 96 • absolute change in BMI z-score from baseline at Week 96 (<20 years)

Study	EVOLVE (study VX14-661-106, NCT02347657) (157, 221, 226)	EXPAND (study VX14-661-108, NCT02392234) (164, 227)	EXTEND OLE (study VX14-661-110, NCT02565914) (222, 223, 228)
			• absolute change in CFQ-R RD score from baseline at Week 96 • absolute change in body weight from baseline at Week 96 • absolute change in body weight z-score from baseline at Week 96 (<20 years) • absolute change in height z-score from baseline at Week 96 (<20 years) • time-to-first PEx at Week 96 • PK parameters
Other secondary outcomes	• absolute change in SwCl from baseline through Week 24 • absolute change in BMI z-score from baseline at Week 24 • absolute change in body weight from baseline at Week 24	• rate of pulmonary exacerbations • absolute change in the FE-1 level from baseline to Week 4/8 average • absolute change in the immunoreactive trypsinogen level from baseline to Week 8 • PK parameters • absolute change in the BMI from baseline at Week 8	N/A
Trial supports application for marketing authorisation?	Yes	Yes	Yes
Trial used in the economic model?	Yes	Yes	Yes
Rationale for use/non-use in the model	Supported marketing authorisation in relevant patient population	Supported marketing authorisation in relevant patient population	Provides long-term outcomes of the pivotal trials, study 661-106 and study 661-108, in the relevant patient population

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire-revised; CFTR, cystic fibrosis transmembrane conductance regulator; FE-1, fecal elastase-1; F/F, homozygous for the *F508del-CFTR* mutation; GGT, gamma-glutamyl transferase; IVA, ivacaftor; PEx, pulmonary exacerbation; PK, pharmacokinetics; $ppFEV_{1,}$ percent predicted forced expiratory volume over one second; Q12h, once every 12 hours; QD, once daily; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

Table 26. Baseline characteristics of patients in TEZ/IVA studies, ≥12 years

Baseline characteristic	EVOLVE (study VX14-661-106, NCT02347657) (157)		EXPAND (study VX14-661-108, NCT02392234) (164)			EXTEND OLE (study VX14-661-110, NCT02565914) (222)	
	TEZ/IVA (N=248)	PBO (N=256)	TEZ/IVA (N=132)	IVA (N=81)	PBO (N=80)	106/110 F/F (N=459)	108/110 F/RF (N=226)
Age, mean (SD)	26.9 (11.2)	25.7 (9.5)	35.6 (13.5)	36.3 (15.2)	32.6 (13.9)	26.1 (10.4)	35.1 (14.2)
Sex, n (%)	F=121 (48.8)	F=125 (48.8)	F=48 (58)	F=40 (49)	F=46 (58)	F=222 (48%)	F=121 (54%)
Geographical region, n (%)	North America 59 (23.8) Europe 189 (76.2)	North America 68 (26.6) Europe 188 (73.4)	North America 45 (54) Europe† 38 (46)	North America 36 (44) Europe† 45 (56)	North America 39 (49) Europe† 41 (51)	–	–
Genotype, n (%)	F/F 248 (100.0)	F/F 256 (100.0)	F/RF 132 (100.0)	F/RF 81 (100.0)	F/RF 80 (100.0)	F/F 459 (100.0)	F/RF 226 (100.0)
BMI kg/m^2, mean (SD)	20.96 (2.95)	21.12 (2.88)	23.6 (4.6)	24.5 (5.5)	24.6 (5.0)	21.00 (2.94)	24.21 (5.00)
ppFEV$_1$, mean (SD)	59.6 (14.7)	60.4 (15.7)	61.8 (14.9)	62.8 (14.6)	62.1 (14.0)	60.0 (15.1)	62.2 (14.5)
Distribution, n (%) <40% 40 to <70% 70 to ≤90% >90% Missing data	 23 (9.3) 157 (63.3) 65 (26.2) 2 (0.8) 1 (0.4)	 24 (9.4) 152 (59.4) 73 (28.5) 7 (2.7) 0	 8 (10) 48 (58) 25 (30) 2 (2) –	 8 (10) 46 (57) 26 (32) 1 (1) –	 6 (8) 48 (60) 25 (31) 1 (1) –	 42 (9) 283 (62) 125 (27) 8 (2) –	 20 (9) 132 (58) 70 (31) 4 (2) –
SwCl concentration mmol/L, mean (SD)	101.3 (10.9)	100.5 (10.2)	64.1 (28.9)	74.9 (24.3)	70.7 (24.0)	–	–
CFQ-R RD score, mean (SD)	70.1 (16.8)	69.9 (16.6)	66.5 (17.9)	70.0 (17.7)	67.8 (17.5)	–	–
Pseudomonas aeruginosa-positive within previous 2 years, n (%)	185 (74.6)	182 (71.1)	52 (63)	45 (56)	48 (60)	–	–

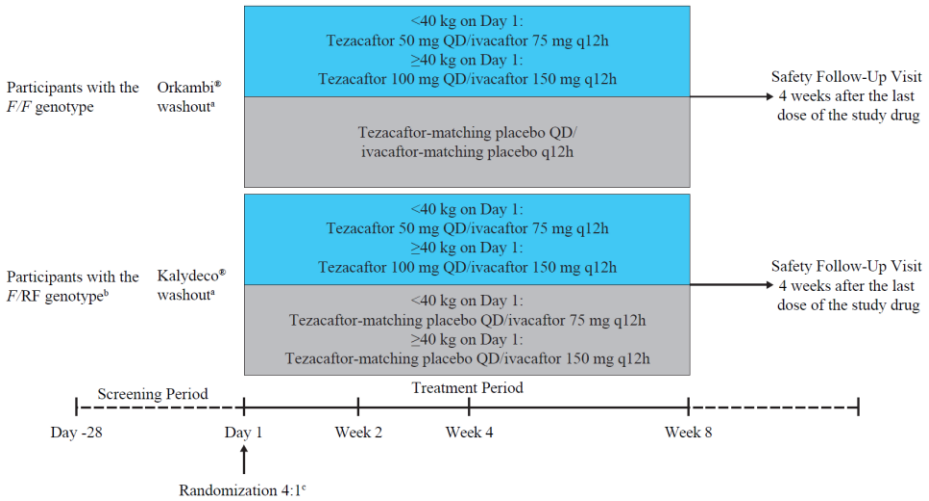
†Israel and Australia were categorised under Europe.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; IVA, ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.2.3.2 CF patients aged 6 to 11 years

Table 27 summarises the trial methodology of relevant TEZ/IVA clinical trials in pwCF aged 6 to 11 years of age, while Table 28 outlines the baseline characteristics of subjects enrolled in those trials.

Study 661-115 was a randomised, double-blind, PBO-controlled, parallel-group trial that evaluated the efficacy and safety of TEZ/IVA in CF patients with F/F and F/RF genotypes aged 6 to 11 years. After a 28-day screening period, study participants were stratified by genotype (F/F vs F /RF) and randomised in a 4:1 ratio to either the TEZ/IVA group or the blinding group over a 8-week period, followed by safety follow-up visit 4 weeks after the last study drug dose (Figure 18). Participants who completed the Week 8 visit had the opportunity to enrol in a 96-week open-label TEZ/IVA extension study (VX17-661-116; NCT03537651) (165).

Figure 18. Study 661-115 trial design



Notes: [a]Participants taking commercially available CFTR modulators (LUM/IVA or IVA) were required to wash out for 28 days prior to the Day 1 Visit; [b]Up to 15 participants with an F/RF genotype could be enrolled; [c]Participants were stratified by genotype (F/F or F/RF) and then randomised 4:1 to the TEZ/IVA group or blinding group. Participants in the blinding group received PBO if they had the F/F genotype and TEZ-matched PBO and IVA if they had an F/RF genotype.
Abbreviations: F/F, homozygous for the *F508del-CFTR* mutation; F/RF, heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein; Q12h, once every 12 hours; QD, once daily.
Reference: Davies et al. (165)

Table 27. Comparative summary of trial methodology for TEZ/IVA studies, 6-11 years

Study	EMBRACE (study VX16-661-115, NCT03559062) (165, 229)
Genotype	F/F or F/RF
Trial design	Phase 3, double-blind, parallel-group study evaluating the efficacy and safety of TEZ/IVA in subjects aged 6 to 11 years with CF with F/F or F/RF genotypes
Duration	• Treatment period: 8 weeks • Safety follow-up: 4 weeks
Population	pwCF aged 6 to 11 years homozygous or heterozygous for the *F508del-CFTR* Mutation with an eligible residual function mutation (F/F or F/RF)
Eligibility criteria for participants	**Inclusion Criteria** • Patient's authorised representative signed and dated the informed consent form • Willing and able to comply with scheduled visits, treatment plan and other study procedures • 6 to 11 years of age • Body weight ≥15 kg • F/F or F/RF genotype • Confirmed CF diagnosis • $ppFEV_1$ ≥70% at screening • $LCI_{2.5}$ ≥7.5 • Stable CF disease • Willing to remain on a stable CF treatment regimen • Able to swallow tablets • Negative serum pregnancy test at screening (female patients of childbearing potential) • Meet contraception requirements (sexually active patients of childbearing potential) • Able to understand protocol requirements and restrictions **Exclusion Criteria** • History of any comorbidity that may confound study results or pose additional risks • Abnormal laboratory values at screening (haemoglobin, AST, ALT, GGT, ALP, total bilirubin, liver function, renal function) • Respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before the first dose of study drug • Colonization with organisms associated with a more rapid decline in pulmonary status • Standard 12-lead ECG demonstrating QTc >450 msec • History of solid organ or haematological transplantation • Ongoing or prior participation in an investigational study or use of commercially available CFTR modulator that does not align with study protocol • Use of restricted medications or food as defined in the study protocol • Pregnant and nursing females • Participant or close relative of participant is the investigator or involved in the investigating team
Settings and locations where the data were collected	This trial was conducted at 27 sites in Australia and Europe
Trial drugs	**Interventions** • TEZ/IVA (TEZ: 50 mg QD; IVA: 75 mg Q12h [patients weighing <40 kg]; TEZ: 100 mg QD; IVA: 150 mg Q12h [patients weighing ≥40 kg]) **Comparators** • PBO (F/F genotype) • IVA (F/RF genotype) (PBO; IVA: 75 mg Q12h [patients weighing <40 kg]; PBO; IVA: 150 mg Q12h [patients weighing ≥40 kg])
Permitted and disallowed concomitant medications	Subjects should remain on a stable medication regimen for CF from 28 days before Day 1 through Week 8 or through the safety follow-up visit (if applicable). Patients may receive doses of prednisone or prednisolone of up to 10 mg/day chronically or 60 mg QD, up to 5 days. Information about bronchodilator use during the study will be collected and documented. Concomitant use of medications known to prolong the QT interval should be used with caution during the study
Reported outcomes specified in the decision problem	**Primary outcome** • $LCI_{2.5}$ **Secondary outcomes** • CFQ-R RD • Safety and tolerability • $ppFEV_1$ • BMI
Primary outcomes	• absolute change in $LCI_{2.5}$ from baseline through Week 8
Key secondary outcomes (including scoring methods and timings of assessments)	• absolute change in SwCl from baseline at Week 8 • absolute change in CFQ-R RD score from baseline through Week 8 • safety and tolerability assessments
Other secondary outcomes	• absolute change in $LCI_{5.0}$ from baseline through Week 8 • absolute change in $ppFEV_1$ from baseline through Week 8 • absolute change in BMI from baseline at Week 8

Study	EMBRACE (study VX16-661-115, NCT03559062) (165, 229)
	• absolute change in BMI z-score from baseline at Week 8 • absolute change in weight from baseline at Week 8 • absolute change in weight z-score from baseline at Week 8 • absolute change in height from baseline at Week 8 • absolute change in height z-score from baseline at Week 8 • drug acceptability at Week 2 • PK parameters • absolute change in FE-1 levels from baseline at Week 8 • absolute change in IRT levels from baseline at Week 8
Trial supports application for marketing authorisation?	Yes
Trial used in the economic model?	Yes
Rationale for use/non-use in the model	Supported marketing authorisation in relevant patient population
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire-revised; CFTR cystic fibrosis transmembrane conductance regulator; ECG, electrocardiogram; FE-1, fecal elastase-1; F/F, homozygous for the *F508del-CFTR* mutation; F/RF, heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein; GGT, gamma-glutamyl transferase; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; IRT, immunoreactive trypsinogen; PBO, placebo; PK, pharmacokinetics; $ppFEV_1$, percent predicted forced expiratory volume over one second; Q12h, once every 12 hours; QD, once daily; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.	

Table 28. Baseline characteristics of patients in TEZ/IVA studies, 6 – 11 years

Baseline characteristic	EMBRACE (study VX16-661-115, NCT03559062) (165)
	TEZ/IVA (N=54)
Age, mean (SD)	8.5 (1.7)
Sex, n (%)	F=29 (53.7)
Genotype, n (%)	F/F 42 (77.8) F/RF 12 (22.2)
Weight group, n (%) <40kg ≥40 kg	 52 (96.3) 2 (3.7)
Weight, mean (SD), kg	28.9 (6.7)
Weight z-score, mean (SD)	−0.28 (0.72)
Height, mean (SD), cm	133.1 (11.9)
Height z-score, mean (SD)	−0.13 (0.96)
BMI, mean (SD), kg/m^2	16.13 (1.66)
BMI z-score, mean (SD)	−0.25 (0.85)
$ppFEV_1$, mean (SD)	86.5 (12.9)
SwCl, mean (SD), mmol/L	99.2 (19.5)
CFQ-R RD score, mean (SD)	84.6 (11.4)
$LCI_{2.5}$, mean (SD)	9.56 (2.06)
Abbreviations: BMI, body mass index; IVA, ivacaftor; $LCI_{2.5}$,lung clearance index at 2.5; $ppFEV_1$, percent predicted forced expiratory volume over one second; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor	

B.2.2.4 Real-world evidence

A Data Collection Agreement (DCA) is in place between the NHS Commissioning Board, NICE, the UK CF Trust and Vertex Pharmaceuticals to record and report data on the real-world use and outcomes of LUM/IVA, TEZ/IVA and IVA/TEZ/ELX (5). The goal of the DCA is to address clinical uncertainties in the evidence base for the three CFTRms, including:

- long-term (more than 1 year) treatment effects on absolute $ppFEV_1$
- the impact of treatment on lung function decline
- discontinuation rates of Vertex therapies and reasons for discontinuation

- compliance rates of Vertex therapies
- comparative outcomes for different disease severities
- comparative treatment pathway costs
- patient and caregiver quality of life impact, including patient age-related differences
- the rate of PEx

These were therefore included as outcomes in the RWE studies that were designed to address the DCA i.e., study VX20-CFD-004 (MAGNIFY), study VX20-CFD-005 (TRAJECTORY) and a UK real-world, long-term outcomes of CFTRm (IA2) study using data from the UK CF registry (UKCFR). Evidence from non-randomised, real-world studies MAGNIFY and TRAJECTORY provided utility values for health-states defined by $ppFEV_1$, treatment-specific utilities for CF patients and their caregivers, respectively. Results from these studies are therefore relevant to the decision problem considered in the cost-effectiveness analysis (Section B.3). Evidence from the UK CF registry (UKCFR) was also used to support inputs in the model. Table 29 summarises the methodology of RWE studies, while Table 30 outlines the baseline characteristics of subjects enrolled in those studies.

Detailed methods and results of these three studies are presented in Sections B.2.2 to B.2.5.

B.2.2.4.1 Study VX20-CFD-004 (MAGNIFY)

Study VX20-CFD-004 [redacted] (Figure 19) [redacted]

[redacted]

(Figure 19, Table 29) (230):

[redacted]

Figure 19. Study VX20-CFD-004 design

[redacted].

Abbreviations: CGRO, caregiver-reported outcome; PRO, patient-reported outcome.
Source: Vertex, Data on File (230)

[redacted]

B.2.2.4.2 Study VX20-CFD-005 (TRAJECTORY)

[redacted]. Results from this IA are presented in Section B.2.5.

B.2.2.4.3 UKCFR study

[redacted]

Figure 20 [redacted]

Figure 20. UKCFR study design

[redacted]

Source: Vertex, data on file (8)

[redacted]

Table 29. Comparative summary of methodology of RWE studies

Study	MAGNIFY (study VX20-CFD-004 Part B) IA1 (230)	TRAJECTORY (study VX20-CFD-005, 2022) IA1 (231)	UKCFR study IA2 (8)
Genotype	[redacted]	[redacted]	[redacted]
Study design	[redacted]	[redacted]	[redacted]
Duration	[redacted]	[redacted]	[redacted]
Population	[redacted]	[redacted]	[redacted]
Eligibility criteria for participants	[redacted]	[redacted]	[redacted]

Study	MAGNIFY (study VX20-CFD-004 Part B) IA1 (230)	TRAJECTORY (study VX20-CFD-005, 2022) IA1 (231)	UKCFR study IA2 (8)
	[redacted]	[redacted]	[redacted]
Settings and locations where the data were collected	[redacted]	[redacted]	[redacted]
Drugs	[redacted]	[redacted]	[redacted]
Permitted and disallowed concomitant medications	[redacted]	[redacted]	[redacted]
Outcomes requested in the DCA investigated in the study[c]	[redacted]	[redacted]	[redacted]

Study	MAGNIFY (study VX20-CFD-004 Part B) IA1 (230)	TRAJECTORY (study VX20-CFD-005, 2022) IA1 (231)	UKCFR study IA2 (8)
Brief description of reported outcomes specified in the decision problem			
Primary outcomes	•		
Key secondary outcomes (including scoring methods and timings of assessments)	N/A		

Study	MAGNIFY (study VX20-CFD-004 Part B) IA1 (230)	TRAJECTORY (study VX20-CFD-005, 2022) IA1 (231)	UKCFR study IA2 (8)
		[redacted]	[redacted]
Other secondary outcomes	N/A	[redacted]	[redacted]
Study supports application for marketing authorisation?	No	No	No
Study used in the economic model?	Yes	Yes	Not directly; however the results are used to validate model inputs.
Rationale for use/non-use in the model	[redacted]	[redacted]	[redacted]

Study	MAGNIFY (study VX20-CFD-004 Part B) IA1 (230)	TRAJECTORY (study VX20-CFD-005, 2022) IA1 (231)	UKCFR study IA2 (8)
			[redacted]
[redacted] These refer to all study outcomes including those not described in this dossier and those for which results have not yet been posted.			

Abbreviations: BMI, body mass index; CarerQoL, Care-Related Quality of Life of Caregivers; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CGRO, caregiver-reported outcome; CFTRm, cystic fibrosis transmembrane conductance regulator modulators; EMR, electronic medical records; ELX, elexacaftor; IA2, second interim analysis; ICF, informed consent form; IA, interim analysis; IVA, ivacaftor; LUM, lumacaftor; MF, minimal function; N/A, not applicable; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; PRO, patient reported outcome; RF, residual function; SF-12, 12-Item Short Form Health Survey; TEZ, tezacaftor; VAS,visual analog scale; WPAI+CIQ:SHP, Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Specific Health Problem.

Table 30: Patient demographics and baseline characteristics in RWE studies

		MAGNIFY (study VX20-CFD-004 Part B)[a] IA1 (230)		TRAJECTORY (study VX20-CFD-005, 2022)[b] IA1 (231)			UKCFR study IA1 (8)		
		Patients [redacted]	Caregivers [redacted]	Patients 12 to 13 Years of Age at study Baseline	Patients ≥14 Years of Age at study Baseline [redacted]	IVA/TEZ/ELX [redacted]	IVA/TEZ /ELX [redacted]	LUM/IVA [redacted]	TEZ/IVA [redacted]
Age at treatment initiation (MAGNIFY)/study baseline (TRAJECTORY) /at CFTRm initiation (UKCFR) (years)	n	[redacted]							
	Mean (SD)								
	Median (Q1, Q3)								
Sex, n (%)	Male								
	Female								
Country, n (%)	UK								
	Germany								
	Spain								
Weight (kg)	N								
	Mean (SD)								
	Median (Q1, Q3)								
Weight z-score for patients < 18 years	N								
	mean (SD)								
	N								

		MAGNIFY (study VX20-CFD-004 Part B)[a] IA1 (230)		TRAJECTORY (study VX20-CFD-005, 2022)[b] IA1 (231)			UKCFR study IA1 (8)		
		Patients	Caregivers	Patients 12 to 13 Years of Age at study Baseline	Patients ≥14 Years of Age at study Baseline	IVA/TEZ/ELX	IVA/TEZ /ELX	LUM/IVA	TEZ/IVA
Height z-score for patients < 18 years	mean (SD)								
Height (cm)	N								
	Mean (SD)								
	Median (Q1, Q3)								
BMI (kg/m^2) [c]	N								
	Mean (SD)								
	Median (Q1, Q3)								
Time from CF diagnosis to study baseline (years)	N								
	Mean (SD)								
	Median (Q1, Q3)								
Previous CFTRm use, n (%)	Yes								
	No								
	Missing								
Genotype, n (%)	F/F								
	F/MF								
	F/RF								
	F/G								
	F/Other								
	non-F/MF								
	non-F/G								
ppFEV$_1$	N								
	Mean (SD)								
	Median (Q1, Q3)								
ppFEV$_1$ category, N (%)	<40								
	≥40 to <70								
	≥70								
	≥70 to ≤90								
	>90								

	MAGNIFY (study VX20-CFD-004 Part B)[a] IA1 (230)		TRAJECTORY (study VX20-CFD-005, 2022)[b] IA1 (231)			UKCFR study IA1 (8)		
	Patients [redacted]	Caregivers [redacted]	Patients 12 to 13 Years of Age at study Baseline [redacted]	Patients ≥14 Years of Age at study Baseline [redacted]	IVA/TEZ/ELX [redacted]	IVA/TEZ/ELX [redacted]	LUM/IVA [redacted]	TEZ/IVA [redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] [redacted] [b] [redacted]

Abbreviations: BMI, body mass index; CFQ-R RD, Cystic Fibrosis Questionnaire-Revised Respiratory Domain; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; F/F, homozygous for the *F508del*-CFTR mutation; F/Gating, 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 function IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; N/A, not applicable; NR, not reported; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; Q, quartile; SD, standard deviation.

B.2.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analyses conducted in relevant trials for each of the three interventions under appraisal are shown in Appendix M.

B.2.4 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment and CONSORT diagrams of relevant trials for each of the three interventions under appraisal are presented in Appendix D.

B.2.5 Clinical effectiveness results of the relevant trials

B.2.5.1 IVA/TEZ/ELX

B.2.5.1.1 CF patients ≥12 years of age

B.2.5.1.1.1 Study 445-102

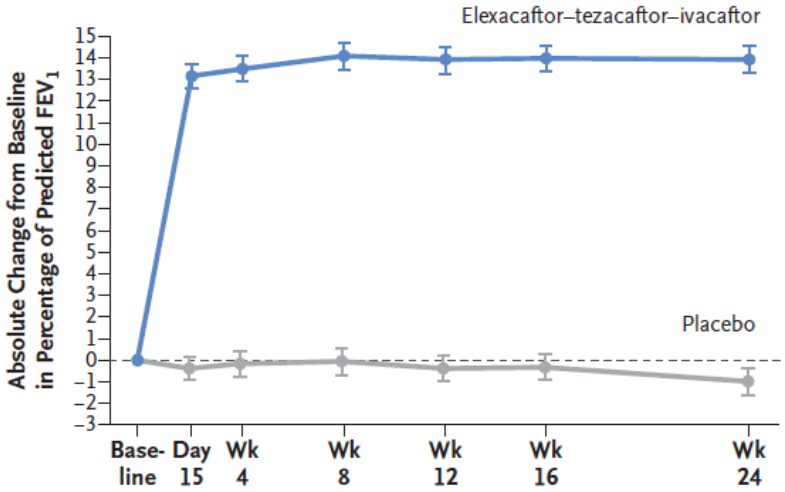
Study 445-102 was designed to demonstrate the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele. Most of the enrolled patients (n=314, ~78%) had a Class I MF mutation (minimal function) on the other *CFTR allele* including nonsense mutations, canonical splice mutations and frameshift mutations that result in no CFTR protein production and are consequently unresponsive to IVA/TEZ/ELX. The remaining 22% of enrolled patients had missense or in-frame deletions. A 24-week treatment duration was selected to allow for the collection of PBO-controlled safety data and data for outcomes that require longer treatment durations to demonstrate an effect (e.g., PEx and changes in nutritional status) (7, 192).

Primary efficacy endpoint: absolute change in $ppFEV_1$ from baseline

Treatment with IVA/TEZ/ELX resulted in a statistically significant improvement in the absolute change in $ppFEV_1$ at Week 4 from baseline compared to PBO (Global endpoint), assessed at the IA, with the least squares (LS) mean treatment difference vs PBO of 13.8 points (95% CI: 12.1 to 15.4; P<0.0001). A sustained improvement in $ppFEV_1$ was seen through Week 24 (European endpoint), with the LS mean treatment difference of 14.3 points relative to PBO (95% CI: 12.7 to 15.8; P<0.0001) (Figure 21).

Results of the sensitivity analysis performed using the multiple imputation method, were consistent with the primary analysis (LS mean difference through Week 24 of 14.3 [95% CI: 12.8 to 15.8; P<0.0001]). Forced expiratory volume over one second (FEV_1) is a strong predictor of clinical status in CF (7). Although the minimal clinically important difference (MCID) has not been established, given the association of $ppFEV_1$ with survival in pwCF (232), any significant difference between PBO and active treatment is potentially clinically relevant (233). The EMA considers a treatment effect equivalent to the average annual loss in FEV_1 as clinically relevant (1-3 percentage points annually) (233, 234).

Figure 21. MMRM analysis of absolute change from baseline in $ppFEV_1$ by visit (FAS) – study 445-102



Note: Least-squares means at each visit are shown, and the I bars represent standard error. Baseline was defined as the most recent non-missing measurement before the first dose of study drug. MMRM included final data from all available visits, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline $ppFEV_1$, age group at screening (<18, ≥18 years of age), and sex (male, female) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24 because the treatment effect was not expected to reach steady state at Day 15. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: FAS, Full Analysis Set; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; MMRM, mixed effects model for repeated measures.
Reference: Middleton et al. (7)

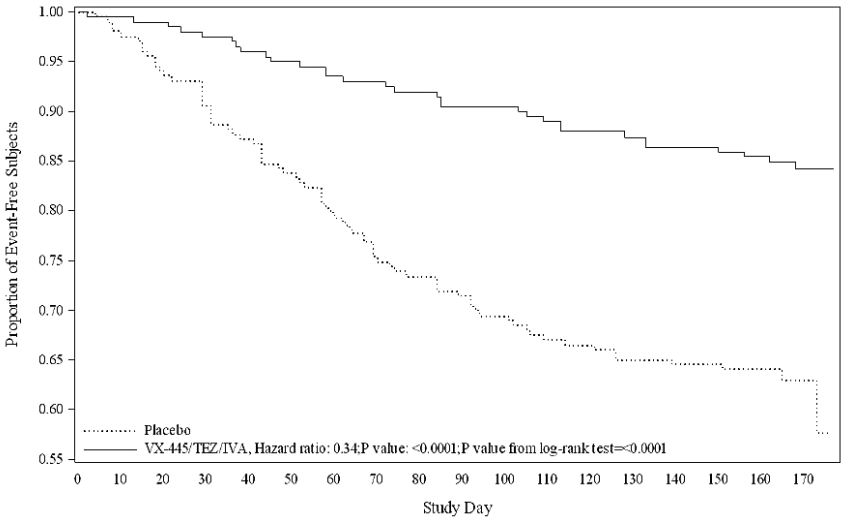
Key secondary efficacy endpoint: number of PEx through Week 24

Treatment with IVA/TEZ/ELX resulted in a significantly lower rate of PEx through Week 24, including severe events leading to hospitalisation or treatment with intravenous (IV) antibiotics, compared to PBO. A PEx rate was 63% lower in the IVA/TEZ/ELX group compared to the PBO group (rate ratio [RR]: 0.37; 95% CI: 0.25 to 0.55; P<0.0001). The annualised event rate was 0.37 in the IVA/TEZ/ELX group vs 0.98 in the PBO group (7).

Other secondary efficacy endpoint: time-to-first PEx through Week 24

Time-to-first PEx was significantly prolonged in the IVA/TEZ/ELX group compared with the PBO group (hazard ratio [HR]: 0.34; 95% CI: 0.22 to 0.52; P<0.0001) (7). Figure 22 shows the Kaplan Meier curve for time-to first PEx: the probability of event free survival during the analysis period of 24 weeks was 0.842 for IVA/TEZ/ELX and 0.629 for PBO group, P<0.0001 (194).

Figure 22. Kaplan-Meier plot for time-to-first pulmonary exacerbation (FAS) – study 445-102



Note: PEx was defined as any new or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms.
Abbreviations: FAS, Full Analysis Set; IVA, ivacaftor; PEx, pulmonary exacerbation; TEZ, tezacaftor.
Reference: Vertex, Data on File (194)

Additional variables for PEx and hospitalisation

The rate of PEx requiring hospitalisation was 71% lower in the IVA/TEZ/ELX group than the PBO group (RR: 0.29; 95% CI: 0.14 to 0.61). The annual event rate was 0.07 in the IVA/TEZ/ELX group vs 0.24 in the PBO group (194).

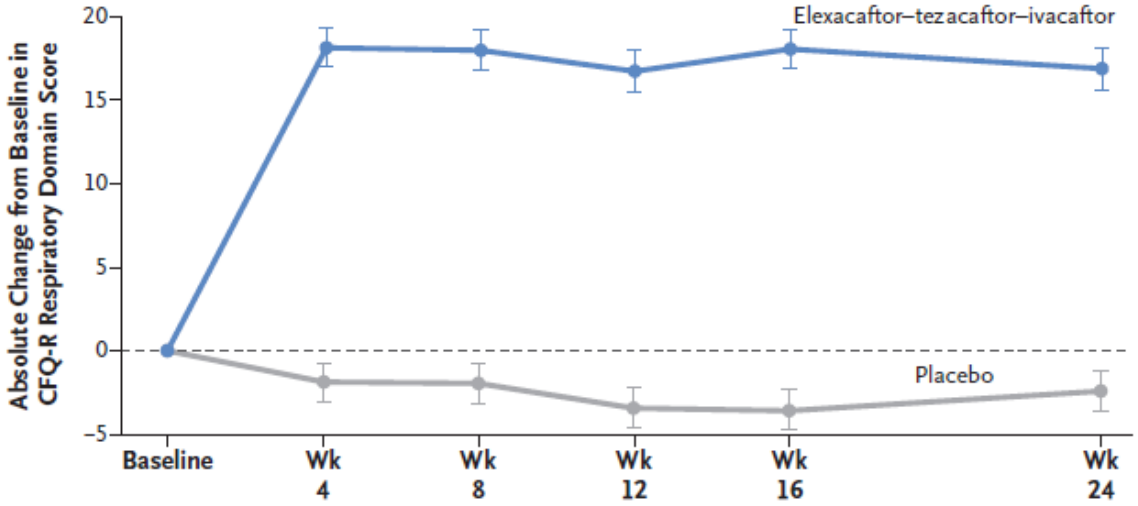
The rate of PEx requiring IV antibiotic therapy was 78% lower in the IVA/TEZ/ELX group than the PBO group (RR: 0.22; 95% CI: 0.11 to 0.43). The annual event rate was 0.08 in the IVA/TEZ/ELX group vs 0.36 in the PBO group (194).

Key secondary efficacy endpoint: absolute change in CFQ-R respiratory domain scores from baseline

Treatment with IVA/TEZ/ELX resulted in statistically significant improvements in the CFQ-R respiratory domain (RD) score from baseline through Week 24 compared to PBO (Figure 23) (7). Improvements in CFQ-R RD score exceeding the MCID (4 points)

were seen by Week 4 and were sustained through Week 24 (7, 235), with mean treatment difference relative to PBO of 20.1 points at Week 4 (95% CI: 16.9 to 23.2; P<0.0001) and 20.2 points through Week 24 (95% CI: 17.5 to 23.0; P<0.001) (7).

Figure 23. Absolute change from baseline in CFQ-R respiratory domain scores – study 445-102



Note: least-squares means at each visit are shown, and the I bars indicate the corresponding standard error; the dashed line indicates no change from baseline. Absolute change from baseline in the respiratory domain score on the CFQ-R, based on a mixed-effects model for repeated measures. Scores are normalised to range from 0 to 100 points, with higher scores indicating a higher patient-reported quality of life regarding respiratory symptoms; the minimum clinically important difference is 4 points.
Reference: Middleton et al. (7)

Other secondary efficacy endpoint: absolute change in CFQ-R non-RD scores from baseline through Week 24

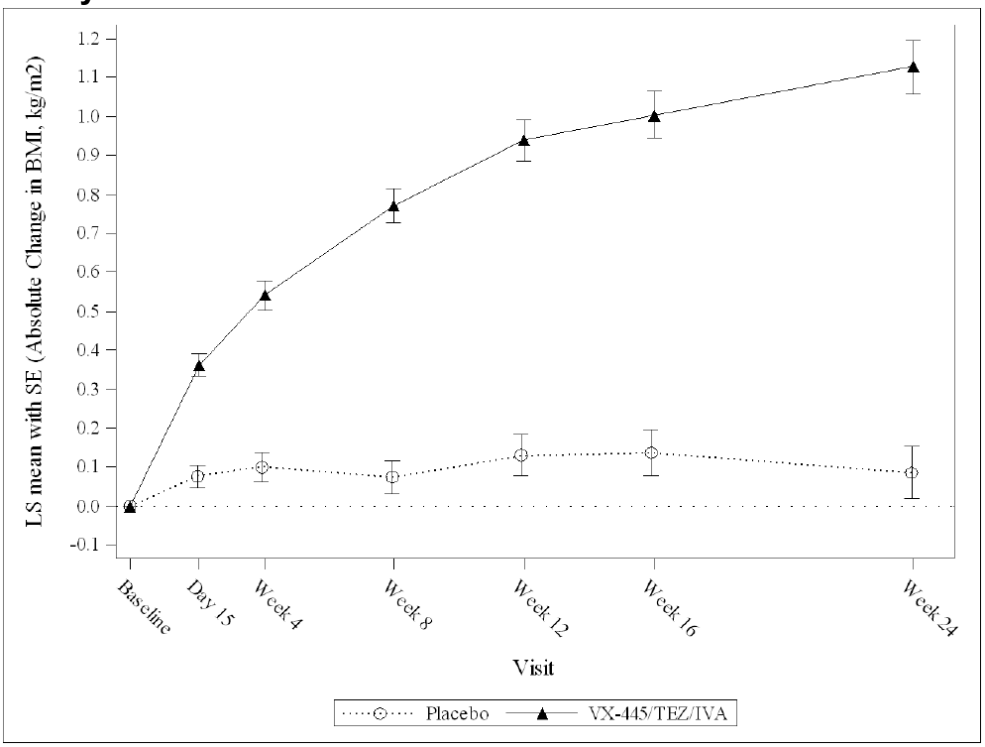
[redacted]Table 31[redacted]

Secondary efficacy endpoints: absolute change in nutritional parameters (BMI, BMI z-score, weight) from baseline at Week 24

Treatment with IVA/TEZ/ELX resulted in a statistically significant improvement in BMI from baseline at Week 24 relative to PBO [Figure 24, (194)], with a LS mean treatment difference of 1.04 kg/m^2 between the two treatment groups (95% CI: 0.85 to 1.23; P<0.001). Consistent with this increase, BMI z-score and body weight were

significantly increased in the IVA/TEZ/ELX group compared with the PBO group at Week 24 (LS mean treatment differences: 0.30; 95% CI: 0.17 to 0.43; P<0.0001, and +2.9 kg; 95% CI: 2.3 to 3.4; P<0.0001, respectively) (7).

Figure 24. MMRM analysis of absolute change from baseline in BMI by visit (FAS) – study 445-102



Note: The I bars represent standard error. Baseline was defined as the most recent non-missing measurement before the first dose of study drug. MMRM included final data from all available visits, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline ppFEV$_1$, age group at screening (<18, ≥18 years of age), and sex (male, female) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Reference: Vertex, Data on File (194)

Summary of the efficacy outcomes of study 445-102 are shown in Table 31.

Table 31. Summary results of AURORA F/MF (study 445-102)

AURORA F/MF (study VX17-445-102, NCT03525444)* (7, 194)			
	IVA/TEZ/ELX N=200	**PBO N=203**	**Difference or rate ratio (95% CI)† P Value**
Primary outcome			
Absolute change in ppFEV$_1$ from baseline at Week 4 (Global) (95% CI)‡	13.6 (12.4 to 14.8)	−0.2 (−1.3 to 1.0)	13.8 (12.1 to 15.4) <0.001
Absolute change in ppFEV$_1$ from baseline through Week 24 (Europe) (95% CI)	13.9 (12.8 to 15.0)	−0.4 (−1.5 to 0.7)	14.3 (12.7 to 15.8) <0.001
Key secondary outcome			
Number of PEx through Week 24	41	113	
Estimated annualised PEx event rate§	0.37	0.98	0.37 (0.25 to 0.55) <0.001
Absolute change in CFQ-R RD score from baseline through Week 24 (95% CI)¶	17.5 (15.6 to 19.5)	-2.7 (-4.6 to -0.8)	20.2 (17.5 to 23.0) <0.001
Absolute change in BMI from baseline at Week 24 (95% CI), kg/m^2	1.13 (0.99 to 1.26)	0.09 (−0.05 to 0.22)	1.04 (0.85 to 1.23) <0.001
Absolute change in CFQ-R RD score from baseline at Week 4 (95% CI)	18.1 (15.9 to 20.4)	−1.9 (−4.2 to 0.3)	20.1 (16.9 to 23.2) <0.001
Additional secondary outcomes			

Time to first PEx through Week 24 (Kaplan-Meier probability of not having PEx through 24 weeks) (95% CI)	0.842 (0.783 to 0.886)	0.629 (0.558 to 0.692)	0.34 (0.22 to 0.52) <0.0001
Absolute change in BMI z-score from baseline at Week 24 (95% CI)**	0.34 (0.25 to 0.44)	0.04 (-0.05 to 0.14)	0.30 (0.17 to 0.43)
Absolute change in body weight from baseline at Week 24 (95% CI), kg	3.4 (3.0 to 3.8)	0.5 (0.2 to 0.9)	2.9 (2.3 to 3.4)

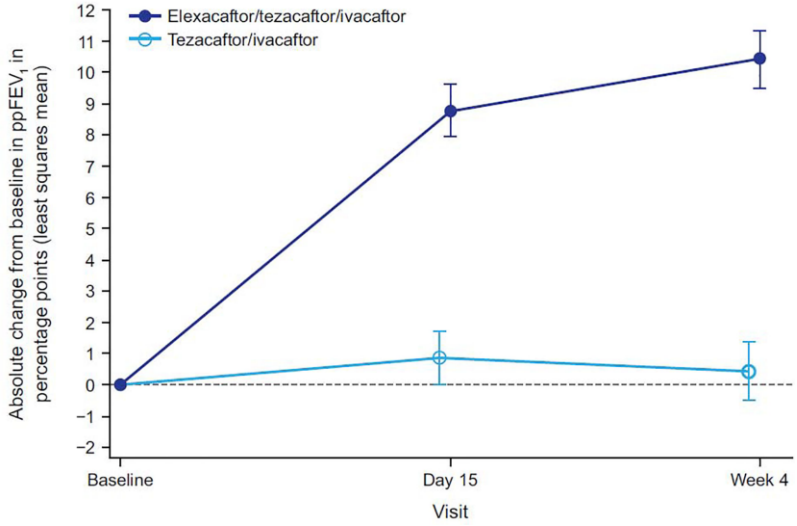
*Data are least-squares means with 95% CIs, except for PEx through Week 24, for which the number of events and the annualised estimated event rate are shown; †The difference is the least-squares mean difference between the IVA/TEZ/ELX group and the PBO group based on a MMRM, except for the number of PEx, for which the rate ratio is shown; and the time-to-first pulmonary exacerbation, for which the Kaplan-Meier estimate and hazard ratio based on a Cox proportional hazard regression model is shown; ‡The primary endpoint (Global) was assessed at the prespecified interim analysis at Week 4, which included all patients who underwent randomisation and received at least one dose of IVA/TEZ/ELX or PBO; §The analysis was based on a negative binomial-regression model (48 weeks per year was used to calculate the event rate); ¶For the CFQ-R RD score (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms), the minimum clinically important difference is 4 points; **Data included only patients who were age 20 years or younger at baseline (74 patients in the PBO group and 71 in the IVA/TEZ/ELX group).
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; MMRM, mixed-effects model for repeated measures; PBO, placebo; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.5.1.1.2 Study 445-103

Primary efficacy endpoint: absolute change in $ppFEV_1$ from baseline at Week 4

A statistically significant and rapid improvement in $ppFEV_1$ from baseline at Week 4 was observed with IVA/TEZ/ELX compared to TEZ/IVA, with an LS mean treatment difference of 10.0 percentage points (95% CI: 7.4 to 12.6; P<0.0001) (Figure 25) (170). These improvements were observed as early as Day 15, with a LS mean difference of 7.9 percentage points (95% CI: 5.5 to 10.3). Results of the sensitivity analysis performed using the multiple imputation method, were consistent with the primary analysis (LS mean difference at Week 4 of 9.3; 95% CI: 6.8 to 11.7, P<0.0001) (186).

Figure 25. Absolute change over time in ppFEV$_1$ from baseline – study 445-103



Note: Data are least squares means based on a mixed-effects model for repeated measures. Error bars indicate standard errors. The dashed line indicates no change from baseline (measured at the end of the TEZ/IVA run-in).
Abbreviations: ppFEV$_1$, percentage predicted forced expiratory volume in 1 s.
Reference: Heijerman et al. (170)

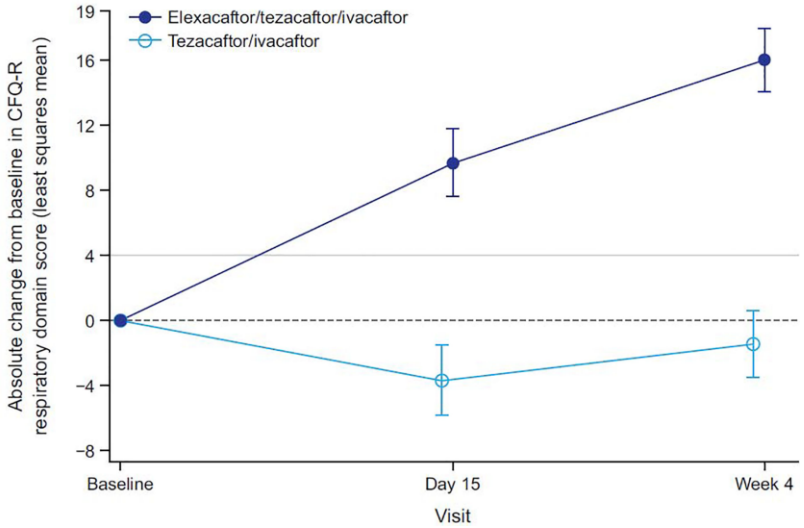
Notably, in previous trials, TEZ/IVA treatment led to significant improvements in ppFEV$_1$ relative to PBO in pwCF with an F/F genotype (+4.0 through Week 24, P<0.001) (157). Accordingly, any improvements in ppFEV$_1$ following IVA/TEZ/ELX treatment are above and in addition to those achievable with this currently approved modulator with demonstrated clinical efficacy in F/F patients.

Secondary efficacy endpoints

Key secondary efficacy endpoint: absolute change in CFQ-R respiratory domain scores from baseline at Week 4

Treatment with IVA/TEZ/ELX resulted in a statistically significant increase in CFQ-R RD scores from baseline at Week 4 compared to TEZ/IVA, with a LS mean treatment difference of 17.4 points (95% CI: 11.8 to 23.0; P<0.0001) (Figure 26). Given that the MCID in stable CF is a 4-point improvement, the observed treatment difference constitutes a clinically meaningful improvement in quality of life (170).

Figure 26. Absolute change from baseline in CFQ-R respiratory domain scores – study 445-103



Note: Scores range from 0 to 100, with higher scores indicating a higher participant-reported quality of life with regard to respiratory status. Data are least squares mean based on a mixed-effects model for repeated measures. Error bars indicate standard errors. The dashed line indicates no change from baseline.
Reference: Heijerman et al. (170)

Additional efficacy endpoint: absolute change in CFQ-R non-RD scores from baseline at Week 4

[redacted] (Table 32) (186).

Other secondary efficacy endpoint: Number of PEx

Although not assessed as an efficacy outcome in this 4-week study, there was a numerical reduction in reported AEs of infective PEx, as defined in the protocol, in the IVA/TEZ/ELX group compared with the TEZ/IVA group (2% vs 12%) (170).

Other secondary efficacy endpoints: absolute change in nutritional parameters (BMI, body weight) from baseline at Week 4

At Week 4, treatment with IVA/TEZ/ELX resulted in LS mean increase in BMI of 0.60 kg/m² (95% CI: 0.41 to 0.79; nominal P<0.0001) and a LS mean body weight increase of 1.6 kg (95% CI: 1.0 to 2.1; nominal P<0.0001) compared with TEZ/IVA (186) (170).

Summary of the results of efficacy outcomes of study 445-103 are shown in Table 32.

Table 32. Summary results of AURORA F/F (study 445-103)

AURORA F/F (study VX17-445-103, NCT03525548)* (170, 186)			
	IVA/TEZ/ELX N=55	**TEZ/IVA N=52**	**Difference (95% CI)† P Value**
Primary outcome			
Absolute change in $ppFEV_1$ from baseline at Week 4, (95% CI)	10.4 (8.6 to 12.2)	0.4 (–1.4 to 2.3)	10.0 (7.4 to 12.6) <0.0001
Key secondary outcome			
Absolute change in CFQ-R RD score from baseline at Week 4 (95% CI)	16.0 (12.1 to 19.9)	–1.4 (–5.4 to 2.6)	17.4 (11.8 to 23.0) <0.0001
Additional secondary outcomes			
Absolute change in BMI from baseline at Week 4 (95% CI), kg/m^2	[redacted]	[redacted]	0.60 (0.41 to 0.79) <0.0001¶
Absolute change in body weight from baseline at Week 4 (95% CI), kg	[redacted]	[redacted]	1.6 (1.0 to 2.1) <0.0001¶
[redacted]			

*Data are least squares means with 95% CIs; †Least squares mean difference between the IVA/TEZ/ELX group and the TEZ/IVA group on the basis of the MMRM. Baseline was defined as the end of the 4-week TEZ/IVA run-in period; ¶nominal P value.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; MMRM, mixed-effects model for repeated measures; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.5.1.1.3 Study 445-105 IA4

Primary efficacy endpoint: safety and tolerability

For results on safety and tolerability, please refer to Section B.2.9.

Secondary efficacy endpoints

Efficacy results at 144 weeks are available for participants that crossed over from study 445-102 (24-week study) and study 445-103 (a 4-week study). Patients from studies 445-102 and study 445-103 who transitioned to study 445-105 showed improvements in clinical outcomes consistent with those seen in the IVA/TEZ/ELX groups of studies 445-102 and 445-103, demonstrating sustainability and reproducibility of effect (188).

The annualised mean rate of change in $ppFEV_1$, a relevant measure of lung function decline, was assessed in an ad-hoc analysis. A positive annualised mean rate of change in $ppFEV_1$ was estimated (0.07 percentage points per 48 weeks; 95% CI: −0.12 to 0.26) when both genotype groups (F/MF and F/F) were pooled, indicating that patients treated with IVA/TEZ/ELX had no loss of pulmonary function through the 144-week treatment period. In participants with F/MF and F/F genotypes, the rates of change in $ppFEV_1$ were 0.08 (95% CI: −0.14 to 0.30) and 0.03 (95% CI: −0.33 to 0.39) percentage points per 48 weeks, respectively (236).

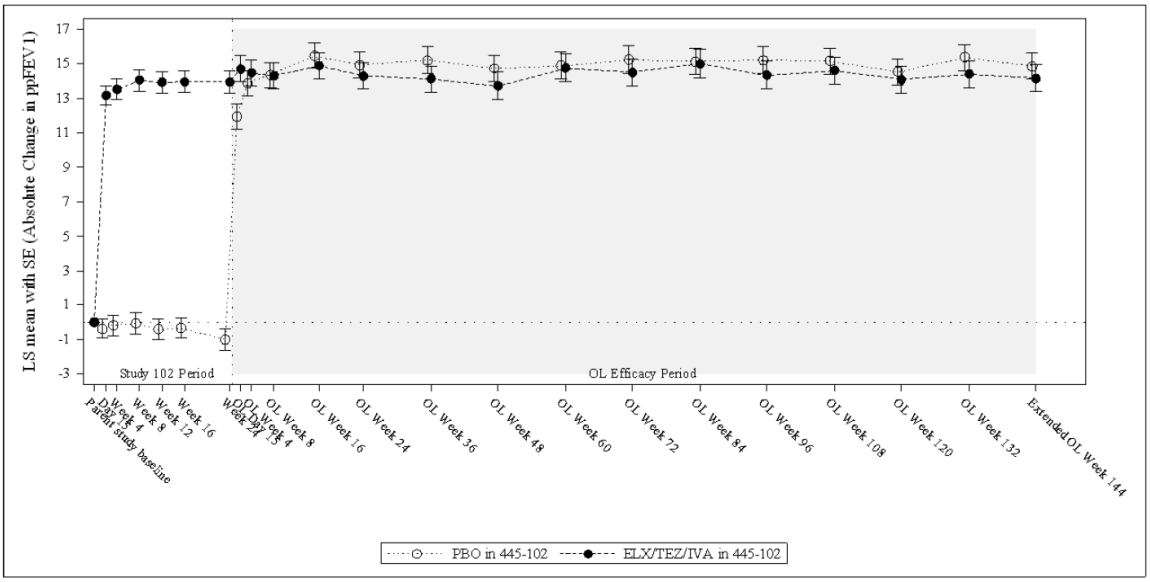
Patients with F/MF genotype (enrolled from parent study 445-102, AURORA F/MF)

Secondary efficacy endpoint: absolute change in $ppFEV_1$ from parent study baseline at extended Week 144 (IA4)

For patients who received PBO in the parent study, rapid improvements in $ppFEV_1$ were observed and sustained through Week 144 (LS mean absolute change from parent study baseline at Extended OL Week 144 of 14.8 percentage points; 95% CI: 13.3 to 16.3), after initiation with IVA/TEZ/ELX (Figure 27) (188).

For patients with F/MF genotype in the IVA/TEZ/ELX group of study 445-102, improvements in $ppFEV_1$ were sustained through Week 144 with an LS mean absolute change from parent study baseline at Extended OL Week 144 of 14.1 percentage points (95% CI: 12.6 to 15.6) (Figure 27) (188).

Figure 27. MMRM analysis of absolute change from parent study baseline in ppFEV$_1$ (%) at each visit up to extended OL Week 144 (study 445-102 FAS and OL-FAS) – study 445-105 IA4, F/MF



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomised in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV$_1$, age group at screening of the parent study (<18 vs ≥18 years), and sex (male vs female) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; LS, least squares; OL, open label; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Vertex, Data on File (188)

Secondary efficacy endpoint: number of PEx

In patients who received PBO in the parent study, the PEx event rate per year was 0.98, whereas an estimated PEx event rate per year in study 445-105 of 0.20 (95% CI: 0.16 to 0.24) was observed for all F/MF subjects treated with IVA/TEZ/ELX (7, 188).

Secondary efficacy endpoints: absolute change in nutritional parameters (BMI, BMI z-score, weight) from parent study baseline at extended Week 144 (IA4)

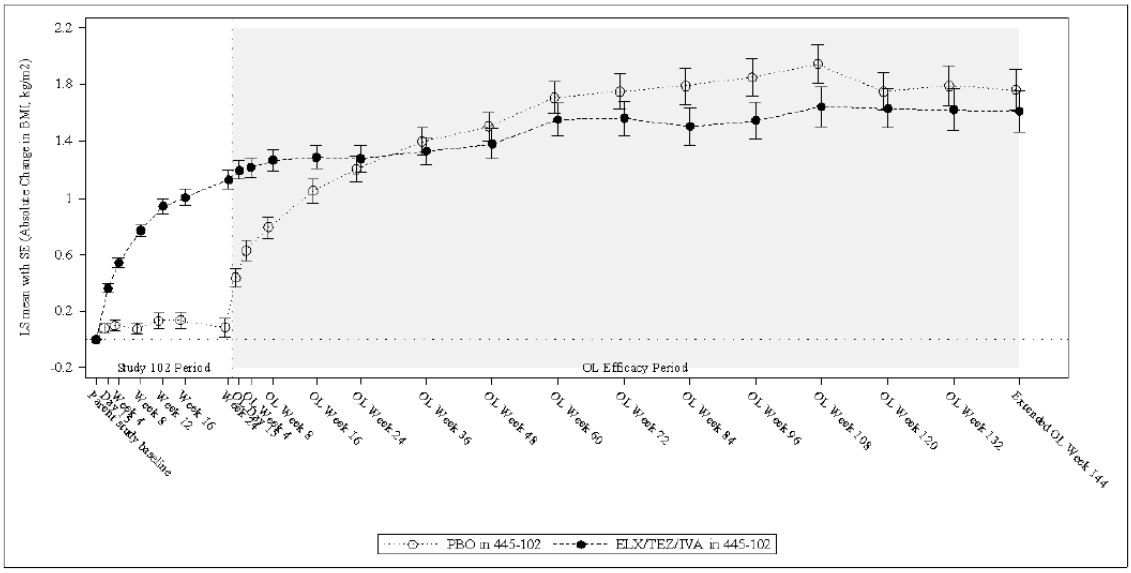
For subjects who received PBO in the parent study, rapid improvements in BMI and [redacted] were observed and sustained through Week 144. The LS mean absolute change in BMI and [redacted] from parent study baseline at Extended OL Week 144 were 1.76 kg/m2 (95% CI: 1.48 to 2.05) (Figure 28) and [redacted] (188).

With regards to patients who initially received IVA/TEZ/ELX in the parent study, improvements in BMI and [redacted] continued through Week 144, with LS mean

absolute changes from parent study baseline at Extended OL Week 144 of 1.61 kg/m^2 (95% CI: 1.32 to 1.90) (Figure 28) and [redacted](188).

[redacted]

Figure 28. MMRM analysis of absolute change from parent study baseline in BMI (kg/m^2) at each visit up to extended OL Week 144 (study 445-102 FAS and OL-FAS) – study 445-105 IA4, F/MF



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV$_1$, age group at screening of the parent study (<18 vs ≥18 years), and sex (male vs female) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: BMI, body mass index; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor.
Reference: Vertex, Data on File (188)

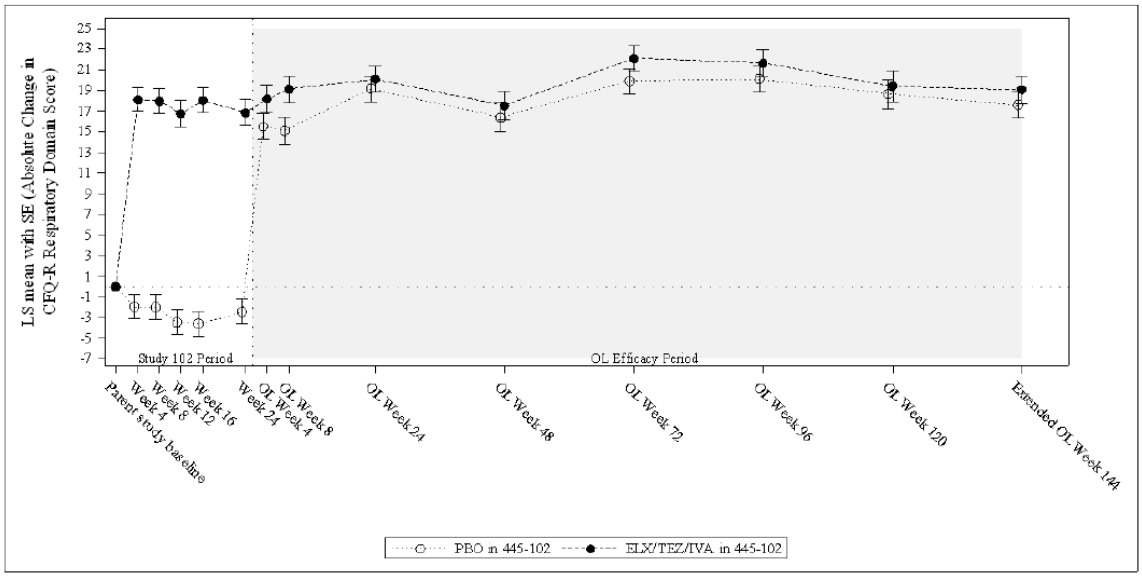
Secondary efficacy endpoint: absolute change in CFQ-R respiratory domain from parent study baseline at extended Week 144 (IA4)

Rapid improvements in CFQ-R RD score were observed and sustained through Week 144 in patients who received PBO in study 445-102, after initiation of IVA/TEZ/ELX (LS mean absolute change from parent study baseline at extended OL Week 144 17.6 points; 95% CI: 14.9 to 20.2) (Figure 29) (188).

For subjects who received IVA/TEZ/ELX in the parent study, improvements in CFQ-R RD score were sustained through Week 144, with an LS mean absolute change from

parent study baseline at Extended OL Week 144 of 19.1 points (95% CI: 16.4 to 21.8) (Figure 29) (188).

Figure 29. MMRM analysis of absolute change from parent study baseline in CFQ-R respiratory domain scores (points) at each visit up to extended OL Week 144 (study 445-102 FAS and OL-FAS) – study 445-105 IA4, F/MF



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, age group at screening of the parent study (<18 vs ≥18 years), and sex (male vs female) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: CFQ-R RD, Cystic Fibrosis Questionnaire–Revised respiratory domain; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Vertex, Data on File (188)

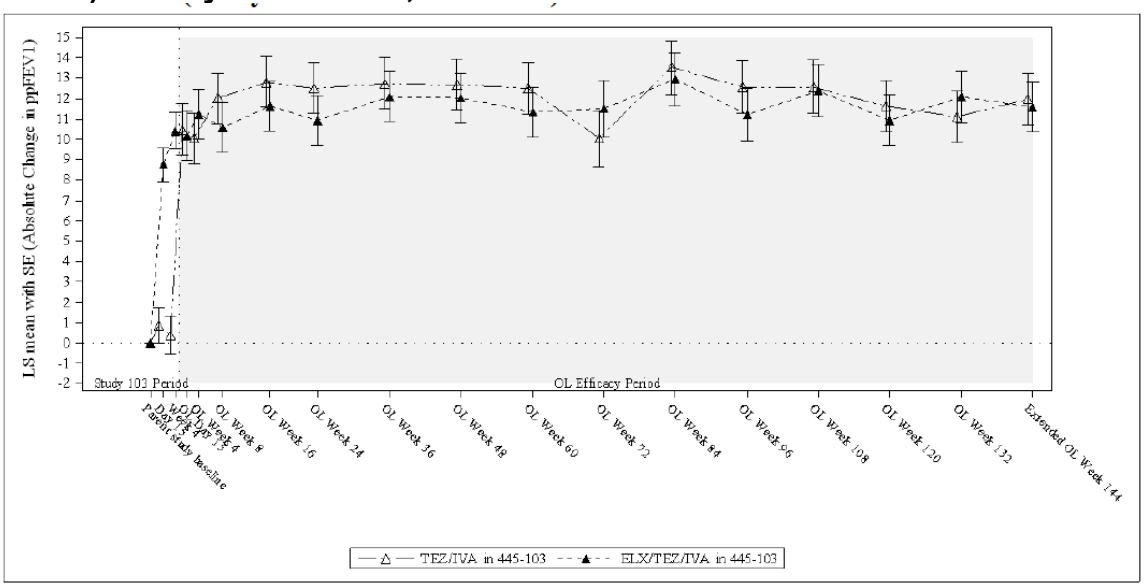
<u>Patients with F/F genotype (enrolled from parent study 445-103, AURORA F/F)</u>

Secondary efficacy endpoint: absolute change in $ppFEV_1$ from parent study baseline at extended Week 144 (IA4)

For patients who received TEZ/IVA in the parent study, rapid improvements in $ppFEV_1$ were observed and sustained through Week 144 (LS mean absolute change from parent study baseline at Extended OL Week 144 of 12.0 percentage points; 95% CI: 9.5 to 14.5), after initiation with IVA/TEZ/ELX (Figure 30) (188).

For patients with F/F genotype in the IVA/TEZ/ELX group of study 445-103, improvements in $ppFEV_1$ were sustained through Week 144 with an LS mean absolute change from parent study baseline at Extended OL Week 144 of 11.6 percentage points (95% CI: 9.1 to 14.0) (Figure 30) (188).

Figure 30. MMRM analysis of absolute change from parent study baseline in ppFEV$_1$ (%) at each visit up to extended OL Week 144 (study 445-103 FAS and OL-FAS) – study 445-105 IA4, F/F



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomised in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV$_1$ and age group at screening of the parent study (<18 vs ≥18 years) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; LS, least squares; OL, open label; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Vertex, Data on File (188)

Secondary efficacy endpoint: number of PEx

The estimated PEx event rate per year for F/F subjects was 0.18 (95% CI: 0.12 to 0.26) (188).

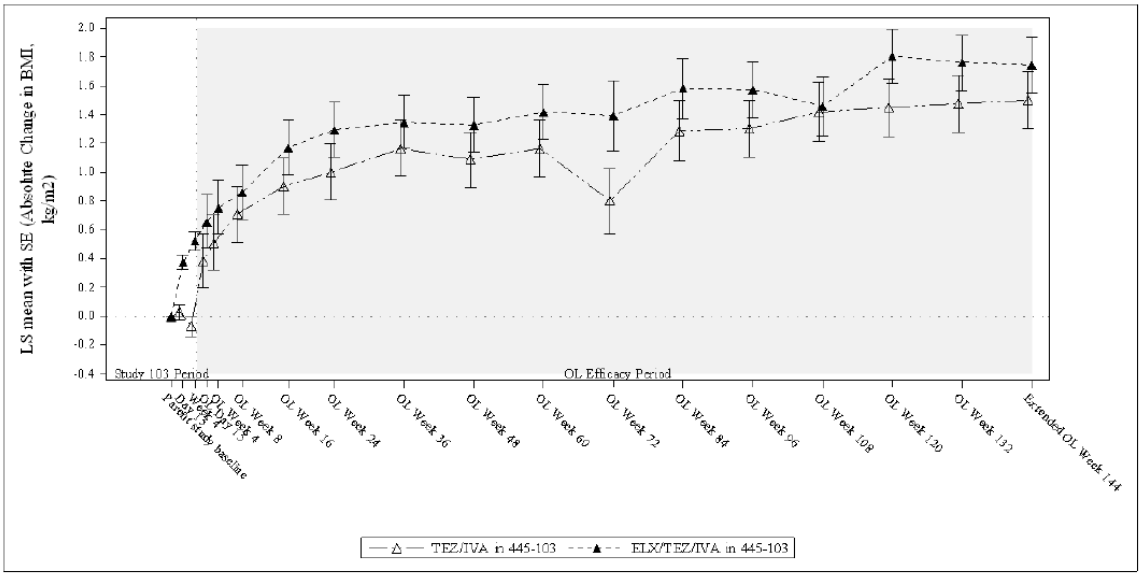
Secondary efficacy endpoints: absolute change in nutritional parameters (BMI, BMI z-score, weight) from parent study baseline at extended Week 144 (IA4)

For subjects who received TEZ/IVA in the parent study, rapid improvements in BMI [redacted] were observed and sustained through Week 144. The LS mean absolute change in BMI [redacted] from parent study baseline at extended OL Week 144 were 1.50 kg/m2 (95% CI: 1.11 to 1.89) (Figure 31) [redacted] (188).

With regards to patients who initially received IVA/TEZ/ELX in the parent study, improvements in BMI [redacted] continued through Week 144, with LS mean absolute changes from parent study baseline at Extended OL Week 144 of 1.74 kg/m^2 (95% CI: 1.36 to 2.12) (Figure 31) [redacted] (188).

[redacted]

Figure 31. MMRM analysis of absolute change from parent study baseline in BMI (kg/m^2) at each visit up to extended OL Week 144 (study 445-103 FAS and OL-FAS) – study 445-105 IA4, F/F



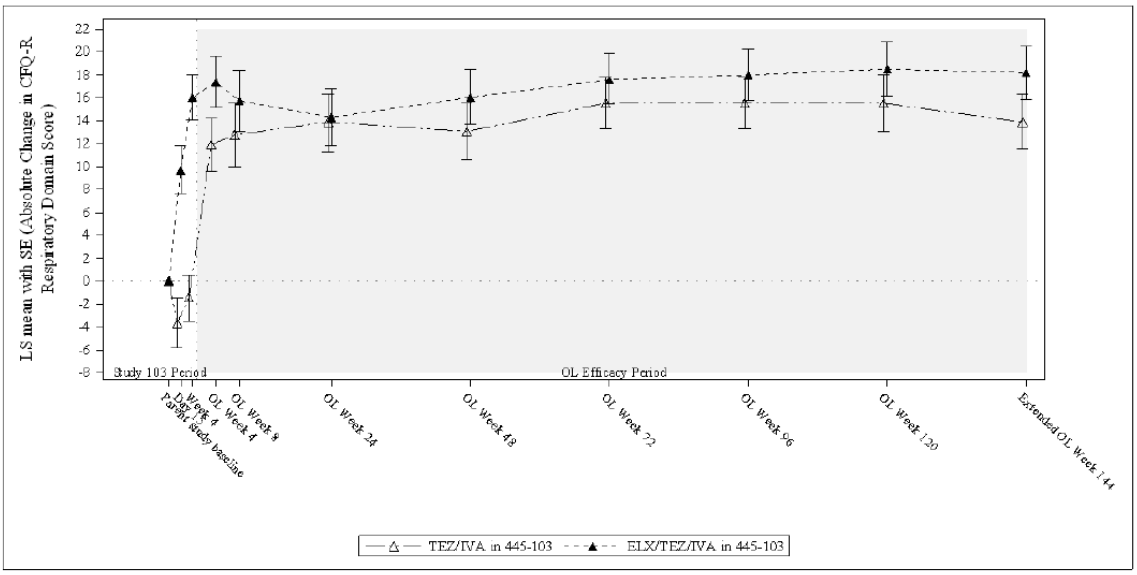
Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was similar to parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV1 and age group at screening of the parent study (<18 vs ≥18 years) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetric covariance structure was used to model the within-subject errors.
Abbreviations: BMI, body mass index; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor.
Reference: Vertex, Data on File (188)

Secondary efficacy endpoint: absolute change in CFQ-R respiratory domain from parent study baseline at extended Week 144 (IA4)

Rapid improvements in CFQ-R RD score were observed and sustained through Week 144 in patients who received TEZ/IVA in study 445-103, after initiation of IVA/TEZ/ELX (LS mean absolute change from parent study baseline at extended OL Week 144 of 13.9 points; 95% CI: 9.2 to 18.6) (Figure 32) (188).

For subjects who received IVA/TEZ/ELX in the parent study, improvements in CFQ-R RD score were sustained through Week 144, with an LS mean absolute change from parent study baseline at Extended OL Week 144 of 18.2 points (95% CI: 13.6 to 22.7) (Figure 32) (188).

Figure 32. MMRM analysis of absolute change from parent study baseline in CFQ-R respiratory domain scores (points) at each visit up to extended OL Week 144 (study 445-103 FAS and OL-FAS) – study 445-105 IA4, F/F



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to Extended OL Week 144, with treatment (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, age group at screening of the parent study (<18 vs ≥18 years), and sex (male vs female) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: CFQ-R RD, Cystic Fibrosis Questionnaire–Revised respiratory domain; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; OL, open-label; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Vertex, Data on File (188)

Summary of the results of efficacy outcomes of study 445-105 IA4 are shown in Table 33.

Table 33. Summary results of AURORA OLE (study 445-105 IA4)

AURORA OLE (study VX17-445-105 IA4, NCT03525574) (188, 236)				
	F/MF (Parent study 445-102)		F/F (Parent study 445-103)	
	PBO to IVA/TEZ/ELX (N=203)	IVA/TEZ/ELX to IVA/TEZ/ELX (N=200)	TEZ/IVA to IVA/TEZ/ELX (N=52)	IVA/TEZ/ELX to IVA/TEZ/ELX (N=55)
Primary outcome				
Safety and tolerability	Table 69			
Secondary outcomes				
Absolute change in $ppFEV_1$ from parent study baseline at extended OL Week 144 (95% CI)	14.8 (13.3 to 16.3)	14.1 (12.6 to 15.6)	12.0 (9.5 to 14.5)	11.6 (9.1 to 14.0)
Number of PEx	[redacted]		[redacted]	
Estimated PEx event rate per year (95% CI)	0.20 (0.16 to 0.24)		0.18 (0.12 to 0.26)	
Time to first PEx during the cumulative TC Efficacy Period (probability of event-free survival, Kaplan-Meier estimate) (95% CI)	[redacted]		[redacted]	
Absolute change in BMI from parent study baseline at extended OL Week 144 (95% CI), kg/m^2	1.76 (1.48 to 2.05)	1.61 (1.32 to 1.90)	1.50 (1.11 to 1.89)	1.74 (1.36 to 2.12)
Absolute change in BMI z-score from parent study baseline at extended OL Week 144[a] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in body weight from parent study baseline at extended OL Week 144 (95% CI), kg	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in CFQ-R RD score from parent study baseline at extended OL Week 144 (95% CI)	17.6 (14.9 to 20.2)	19.1 (16.4 to 21.8)	13.9 (9.2 to 18.6)	18.2 (13.6 to 22.7)

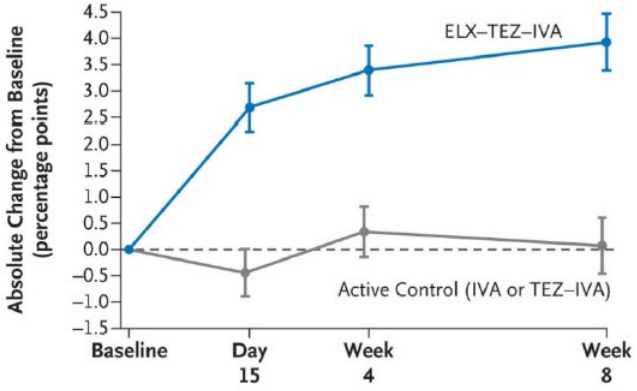
Note: Results are least-squares (LS) mean absolute change (95% CI), except as noted; Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For further details on secondary efficacy endpoints, refer to respective sections in the CSR. The analysis visit window for Extended OL Week 144 Visit included the Week 144 Visit and all subsequent scheduled or unscheduled visits. [a] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TC, triple combination; TEZ, tezacaftor.

B.2.5.1.1.4 Study 445-104

Primary efficacy endpoint: absolute change in $ppFEV_1$ from baseline through Week 8 for IVA/TEZ/ELX group

Patients who received treatment with IVA/TEZ/ELX showed a statistically significant improvement in $ppFEV_1$ from baseline through Week 8, with a LS mean within-group absolute change of 3.7% (95% CI: 2.8 to 4.6; P<0.0001) (Figure 33) (168). [redacted] Results of the sensitivity analysis performed using the multiple imputation method, were consistent with the primary analysis (237).

Figure 33. Absolute change from baseline at each visit in ppFEV$_1$ – study 445-104



No. of Patients				
ELX–TEZ–IVA	132	110	101	98
Active Control (IVA or TEZ–IVA)	126	106	97	96

Note: Data are least-squares means; I bars indicate standard errors; the dashed line at 0 corresponds to no change from baseline; sample size shown below the x-axis represent the number of participants at the timepoint with data that could be evaluated. Absolute change from baseline at each visit in the ppFEV$_1$ on the basis of a mixed-effects model for repeated measures.
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Barry et al. (168)

Secondary efficacy endpoints

Key secondary efficacy endpoint: absolute change in ppFEV$_1$ from baseline through Week 8 for IVA/TEZ/ELX group vs active control

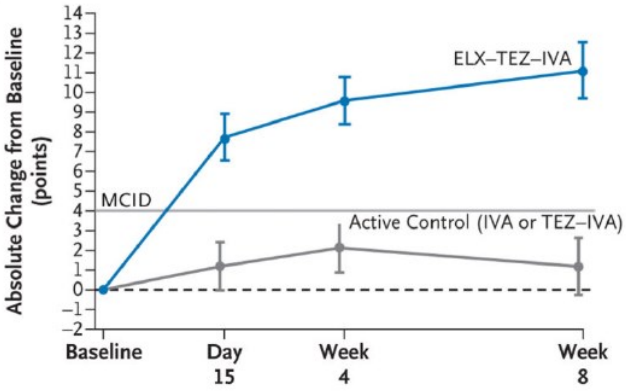
One of the key secondary endpoints was the absolute change in ppFEV$_1$ from baseline through Week 8 in IVA/TEZ/ELX group compared to the control group; the between-group difference was 3.5 percentage points (95% CI: 2.2 to 4.7; P<0.0001). These results demonstrate the greater improvement in lung function provided by IVA/TEZ/ELX treatment compared to IVA or TEZ/IVA (168). The between-group improvements in ppFEV$_1$ were achieved rapidly by Day 15 of treatment (LS mean difference: +3.1; 95% CI: 1.9 to 4.4; P<0.0001) and were sustained through the treatment period. A sensitivity analysis was performed using the multiple imputation method, and results were consistent with the primary analysis of this endpoint (237).

Other secondary efficacy endpoints: absolute change in CFQ-R respiratory domain scores from baseline through Week 8 for IVA/TEX/ELX and vs control

Absolute change in CFQ-R RD score from baseline through Week 8 (average of Week 4 and Week 8 measurements) was also analysed using a MMRM. Treatment with IVA/TEZ/ELX resulted in a LS mean absolute change from baseline through Week 8 in the CFQ-R RD score of 10.3 points (95% CI: 8.0 to 12.7; P<0.0001), while the

absolute change observed in the active control group was 1.6 points (95% CI: −0.8 to 4.1), reflecting a between-group difference of 8.7 points (95% CI: 5.3 to 12.1; P<0.0001) (Figure 34) (168).

Figure 34. Absolute change from baseline at each visit in CFQ-R respiratory domain scores – study 445-104



No. of Patients				
ELX–TEZ–IVA	132	120	125	128
Active Control (IVA or TEZ–IVA)	126	123	120	119

Note: Scores are normalised to range from 0 to 100 points, with higher scores indicating a higher patient-reported quality of life regarding respiratory symptoms; the minimum clinically important difference is 4 points and is indicated in the plot by the straight gray line. Data are least-squares means; I bars indicate standard errors; the dashed line at 0 corresponds to no change from baseline; sample size shown below the x-axis represent the number of participants at the timepoint with data that could be evaluated. absolute change from baseline at each visit in the score on the respiratory domain of the CFQ-R on the basis of a mixed-effects model for repeated measures.
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Barry et al. (168)

Additional efficacy endpoint: absolute change in CFQ-R non-RD scores from baseline through Week 8

[redacted]

Figure 35. MMRM analysis of absolute change from baseline in CFQ-R domain scores through Week 8 for IVA/TEZ/ELX vs control group (points, 95% CI) – study 445-104

Abbreviations: CFQ-R, cystic fibrosis questionnaire – revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; LS, least squares; MMRM, mixed effects model for repeated measures; TEZ, tezacaftor.
Reference: Vertex, Data on File (237)

Additional efficacy endpoint: absolute change in nutritional parameters (BMI,) from baseline at Week 8

Absolute change in BMI and from baseline at Week 8 were assessed as exploratory endpoints (196, 237).

Number of PEx

In study 445-104, PEx was collected as a safety outcome, since an excessively large number of patients would be required to demonstrate a treatment effect on the rate of PEx given that patients were already receiving a CFTRm. Although not assessed as an efficacy outcome, a numerical reduction in reported AEs of infective PEx in the IVA/TEZ/ELX group vs the control group was observed (2.3% vs 10.3% (168) (see Section B.2.9). The evidence of a sustained and robust effect of IVA/TEZ/ELX on PEx in patients with a single *F508del-CFTR* allele, demonstrated in studies 445-102 and

445-105 IA4, was considered by the EMA as relevant for patients with a single *F508del-CFTR* allele plus a gating or a RF allele (7, 188). Summary of the results of efficacy outcomes of study 445-104 are shown in Table 34.

Table 34. Summary results of AURORA F/RF F/G (study 445-104)

AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168, 237)			
	IVA/TEZ/ELX (N=132)	**Control (IVA or TEZ/IVA) (N=126)**	**Difference (95% CI)[†] P Value**
Primary outcome			
Absolute change in ppFEV$_1$ for IVA/TEZ/ELX from baseline through to Week 8 (95% CI)	3.7 (2.8 to 4.6)	N/A	N/A
Key Secondary outcomes[¶]			
Absolute change in ppFEV$_1$ for IVA/TEZ/ELX compared to control group from baseline through Week 8 (95% CI)	3.7 (2.8 to 4.6)	0.2 (-0.7 to 1.1)	3.5 (2.2 to 4.7) <0.0001
Additional secondary outcomes			
Absolute change in CFQ-R RD score for IVA/TEZ/ELX from baseline through Week 8 (95% CI)[a]	10.3 (8.0 to 12.7)	N/A	N/A
Absolute change in CFQ-R RD score for IVA/TEZ/ELX compared to control group from baseline through Week 8 (95% CI)[a]	10.3 (8.0 to 12.7)	1.6 (-0.8 to 4.1)	8.7 (5.3 to 12.1) <0.0001
Absolute change in BMI from baseline at Week 8 (95% CI), kg/m^2	[redacted]	[redacted]	[redacted]
[redacted][b]	[redacted]	[redacted]	NR

[†]The difference is the least squares mean difference between the IVA/TEZ/ELX group and the control group (IVA or TEZ/IVA) on the basis of the MMRM, with 95% CIs; [a]The scaled CFQ-R domain scores from the Children Ages 12 and 13 Version and Adolescent and Adults Version were pooled for analysis; [b] Results are mean absolute change (SD) presented with summary statistics; [¶]Key secondary endpoints, in hierarchical order, were the absolute change in SwCl from baseline through Week 8 in the IVA/TEZ/ELX group, the absolute change in the ppFEV$_1$ from baseline through Week 8 for IVA/TEZ/ELX compared with active control, and the absolute change in SwCl from baseline through Week 8 for IVA/TEZ/ELX as compared with active control.
Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; MMRM, mixed-effects model for repeated measures; N/A, not applicable; NR, not reported; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.5.1.1.5 Study 445-110

Primary efficacy endpoint: safety and tolerability

Since the primary outcome of the study was safety and tolerability, please refer to Section B.2.9.

Secondary efficacy endpoints

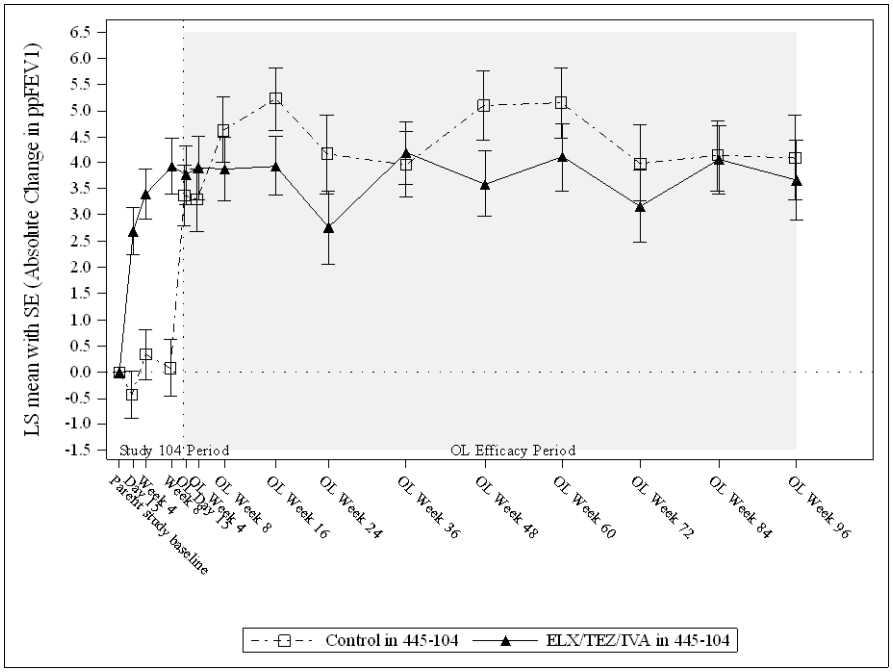
Secondary efficacy endpoint: absolute change in ppFEV$_1$ from parent study baseline at OL Week 96

Patients in the active comparator group of 445-104 experienced rapid improvements in ppFEV$_1$ which were sustained through Week 96 after initiation of IVA/TEZ/ELX in

study 445-110, with an LS mean absolute change from parent study baseline at OL Week 96 of 4.1 percentage points (95% CI: 2.5 to 5.7) (Figure 36) (190, 191).

For pwCF treated with IVA/TEZ/ELX in the parent study, the LS mean absolute change from parent study baseline at OL Week 96 was 3.7 percentage points (95% CI: 2.2 to 5.2) (Figure 36) (190, 191).

Figure 36. MMRM analysis of absolute change from parent study baseline in ppFEV$_1$ (%) at each visit up to OL Week 96 (study 104 FAS and OL FAS for Part A) – study 445-110



Note: The y-axis corresponds to the LS means from the MMRM model. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For parent study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV$_1$, parent study SwCl, and comparator group of the parent study (IVA vs TEZ/IVA) as covariates. A Kenward Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed effects model for repeated measures; OL, open-label; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Chmiel et al. (190)

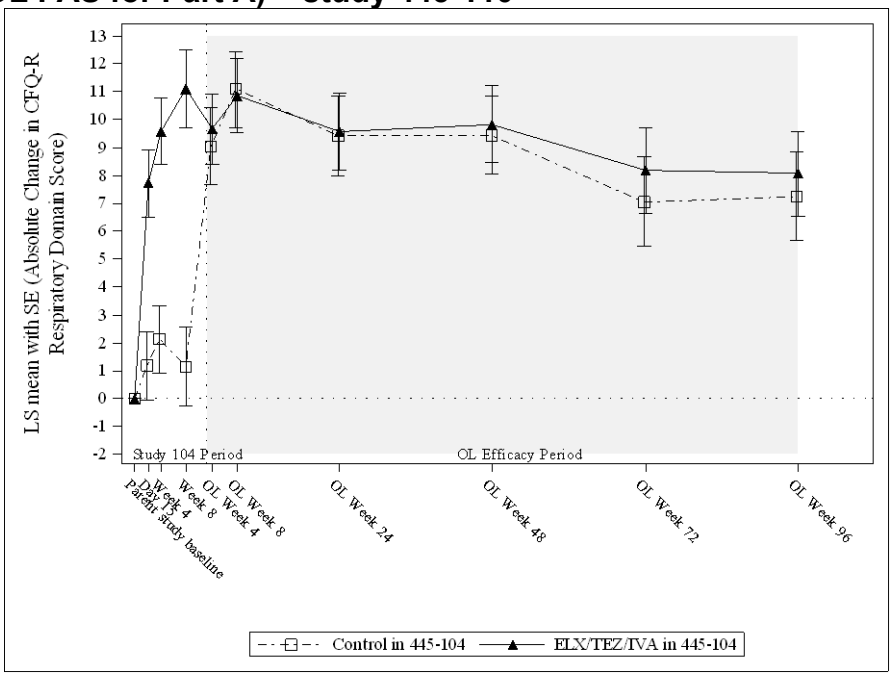
Secondary efficacy endpoint: absolute change in CFQ-R respiratory domain scores from parent study baseline at OL Week 96

Patients who received active control in study 445-104 experienced improvements in CFQ-R RD score after initiation of IVA/TEZ/ELX in study 445-110, with LS mean absolute change from parent study baseline at OL Week 96 of 7.2 points; 95% CI: 4.1 to 10.4) (Figure 37) (190, 191).

For those already on IVA/TEZ/ELX in the parent study, improvements in CFQ-R RD continued through Week 96 of treatment, with an LS mean absolute change from

parent study baseline at OL Week 96 of 8.1 points (95% CI: 5.1 to 11.1) (Figure 37) (190, 191).

Figure 37. MMRM analysis of absolute change from parent study baseline in CFQ-R respiratory domain scores at each visit up to OL Week 96 (study 104 FAS and OL FAS for Part A) – study 445-110



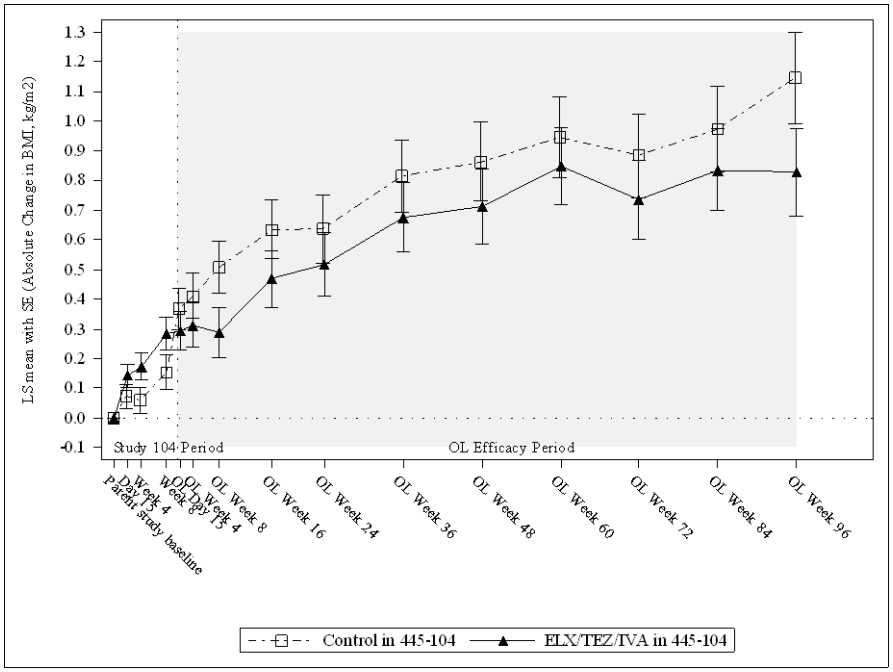
Note: The y-axis corresponds to the LS means from the MMRM model. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline SwCl, and comparator group (IVA vs TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. The model was applied to CFQ-R data obtained in clinic and at home. The CFQ-R RD score from the Children Ages 12 and 13 Version and Adolescent and Adults Version were pooled for analysis.
Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire–Revised; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed effects model for repeated measures; OL, open-label; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; RD, respiratory domain; TEZ, tezacaftor.
Reference: Chmiel et al. (190)

Secondary efficacy endpoints: absolute change in nutritional parameters (BMI, BMI z-score, weight) from parent study baseline at OL Week 96

After initiation of IVA/TEZ/ELX in study 445-110, patients who initially received active control treatment in 445-104 experienced rapid increases in BMI and body weight which were maintained through OL Week 96. The LS mean absolute changes in BMI and body weight from parent study baseline at OL Week 96 were 1.15 kg/m^2 (95% CI: 0.84 to 1.45) (Figure 38) and 3.6 kg (95% CI: 2.7 to 4.6), respectively (190). [redacted]

In patients continuing on IVA/TEZ/ELX from the parent study, sustained increases in BMI, body weight [redacted] were observed through OL Week 96, with LS mean absolute changes from parent study baseline at Extended OL Week 96 of 0.83 kg/m^2 (95% CI: 0.54 to 1.11) (Figure 38), 2.9 kg (95% CI: 2.0 to 3.8) and [redacted] (190, 191).

Figure 38. MMRM analysis of absolute change from parent study baseline in BMI (kg/m^2) at each visit up to OL Week 96 (study 104 FAS and OL FAS for Part A) – study 445-110



Note: The y-axis corresponds to the LS means from the MMRM model. Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline ppFEV$_1$, parent study baseline SwCl, and comparator group of the parent study (IVA vs TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.
Abbreviations: BMI, body mass index; ELX, elexacaftor; FAS, Full Analysis Set; IVA, ivacaftor; LS, least squares; MMRM, mixed effects model for repeated measures; OL, open-label; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.
Reference: Chmiel et al. (190)

Additional efficacy endpoint: absolute change in CFQ-R non-RD scores from parent study baseline at OL Week 96

[redacted]

Summary of the efficacy outcomes of study 445-110 are shown in **Table 35**.

Table 35. Summary results of AURORA F/RF F/G OLE (study 445-110)

AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (190, 191)		
	Control to IVA/TEZ/ELX (N=121)	**IVA/TEZ/ELX to IVA/TEZ/ELX (N=130)**
Primary outcome		
Safety and tolerability	Table 69	
Key secondary outcomes		
Absolute change in $ppFEV_1$ from parent study baseline at OL Week 96 (95% CI)	4.1 (2.5 to 5.7)	3.7 (2.2 to 5.2)
Absolute change in CFQ-R RD score from parent study baseline at OL Week 96 (95% CI)	7.2 (4.1 to 10.4)	8.1 (5.1 to 11.1)
Absolute change in BMI from parent study baseline at OL Week 96 (95% CI), kg/m^2	1.15 (0.84 to 1.45)	0.83 (0.54 to 1.11)
Absolute change in BMI z-score from parent study baseline at OL Week 96 (95% CI)[a]	[redacted]	[redacted]
Absolute change in body weight from parent study baseline at OL Week 96 (95% CI), kg	3.6 (2.7 to 4.6)	2.9 (2.0 to 3.8)
Additional secondary outcomes		
[redacted]		

Note: Results are least-squares (LS) mean absolute change (95% CI), except as noted; Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For further details on secondary efficacy endpoints, refer to respective sections in the abbreviated CSR. [redacted]

Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; OL, open-label; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; TEZ, tezacaftor.

B.2.5.1.2 CF patients aged 6 to 11 years

B.2.5.1.2.1 Study 445-106 Part B and OLE study 445-107 Part A

Since OLE 445-107 had just one parent phase 3 trial with a single arm design, results of both studies are presented together.

Primary efficacy endpoint: safety and tolerability

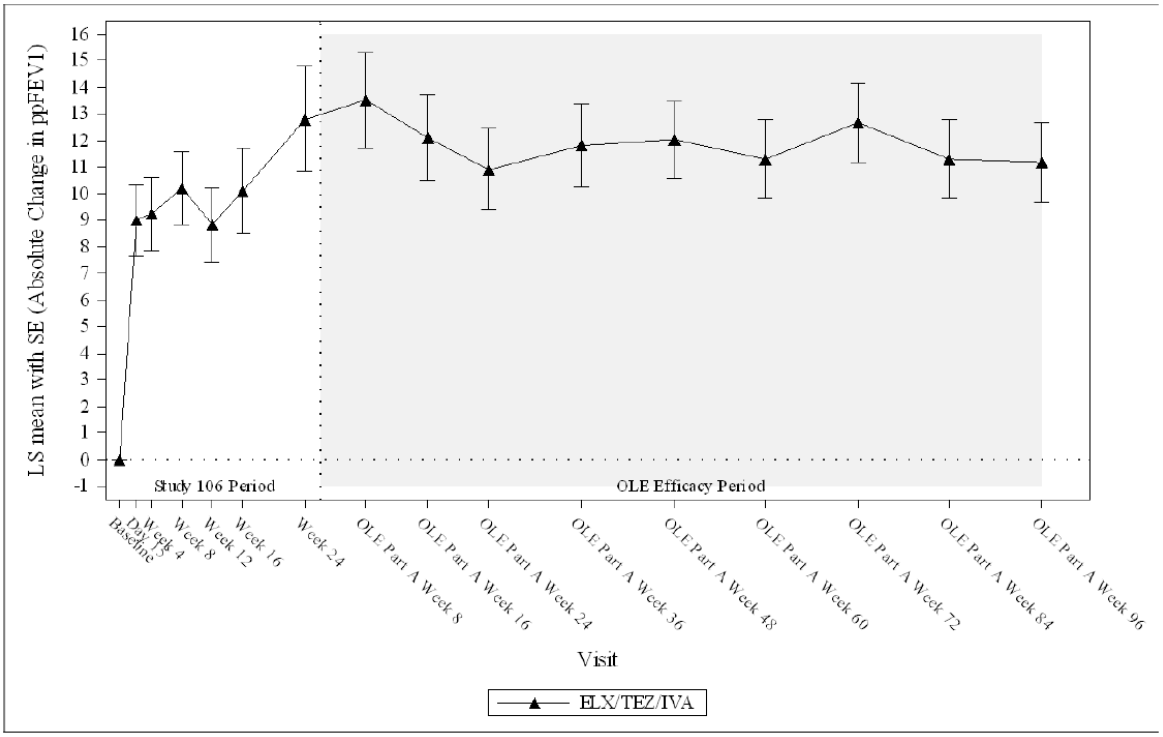
For information on safety and tolerability results, please refer to Section B.2.9.

Secondary efficacy endpoints

Secondary efficacy endpoint: absolute change in $ppFEV_1$ from baseline

Treatment with IVA/TEZ/ELX resulted in a within-group LS mean increase in ppFEV$_1$ from baseline through Week 24 of 10.2 percentage points (95% CI: 7.9 to 12.6; P<0.0001) (Table 36) (174). [redacted] (199). Although participants in 445-106 had well-preserved lung function at baseline compared to subjects in studies of pwCF aged 12+ years (mean baseline ppFEV$_1$ 88.8 vs 61.4 in 445-102), IVA/TEZ/ELX nevertheless led to significant improvements in ppFEV$_1$ as early as 2 to 4 weeks after initiation (174). The improvement was maintained through 96 weeks of additional treatment in 445-107 Part A: the LS mean absolute change in ppFEV$_1$ from baseline at Week 96 was 11.2 percentage points (95% CI: 8.3 to 14.2) (Figure 39) (201, 202).

Figure 39. Absolute change from parent study baseline in ppFEV$_1$ at each visit up to Week 96 (study 445-106 FAS and OLE-FAS for study 445-107 Part A) – study 445-106 Part B and 445-107 Part A



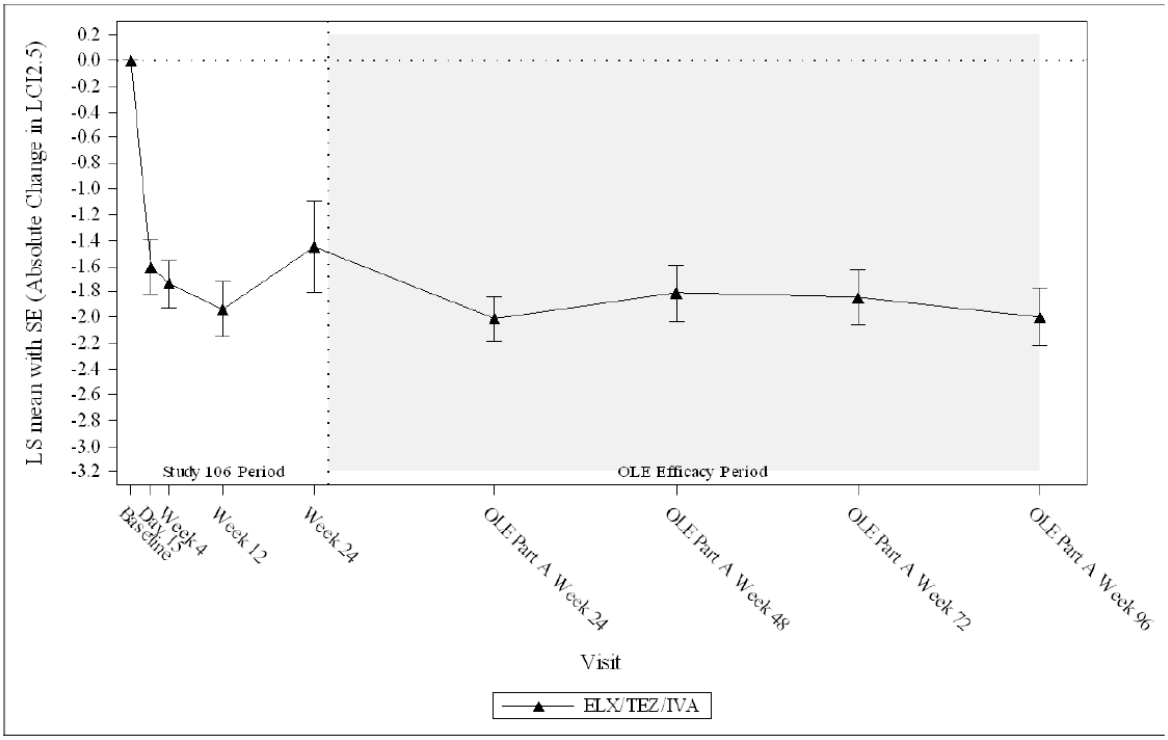
Note: The y-axis corresponds to the LS means from the MMRM models at the IA. The I bars represent standard error. Parent study baseline is defined as the most recent non missing measurement before the first dose of study drug in the Treatment Period of the parent study. For parent study period, MMRM is the same as parent study analysis [redacted]

Abbreviations: ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; OLE, open-label extension; ppFEV$_1$, percent predicted forced expiratory volume over 1 second; SE, standard error, TEZ, tezacaftor.
Reference: Wainwright,et al. (201)

Secondary efficacy endpoint: absolute change in LCI$_{2.5}$ from baseline

Treatment with IVA/TEZ/ELX resulted in a mean absolute change from baseline in lung clearance index at 2.5 of starting concentration ($LCI_{2.5}$) of -1.71 units (95% CI: -2.11 to -1.30; P<0.0001), with improvements observed from Week 4 and sustained through Week 24 and through an additional treatment period of 96 weeks (174, 201). The LS mean absolute change in $LCI_{2.5}$ from baseline at OL Week 96 was -2.00 units (95% CI: -2.45 to -1.55) (Figure 40) (201, 202).

Figure 40. Absolute change from parent study baseline in $LCI_{2.5}$ at each visit up to Week 96 (study 445-106 FAS and OLE-FAS for study 445-107 Part A) – study 445-106 Part B and 445-107 Part A



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. The I bars represent standard error. Parent study baseline is defined as the most recent non missing measurement before the first dose of study drug in the Treatment Period of the parent study. For parent study period, MMRM is the same as parent study analysis. [redacted]

Abbreviations: ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; LS, least squares; OLE, open-label extension; SE, standard error; TEZ, tezacaftor.
Reference: Wainwright,et al. (201)

The observed improvement is greater than the annual rate of deterioration in $LCI_{2.5}$ seen in observational studies of pre-school children with CF (+0.4 LCI units/year) or 6 to 11-year-olds (+0.21 units/year) naive to CFTRms and can be considered clinically relevant (238, 239).

Secondary efficacy endpoint: number of PEx and CF-related hospitalisation

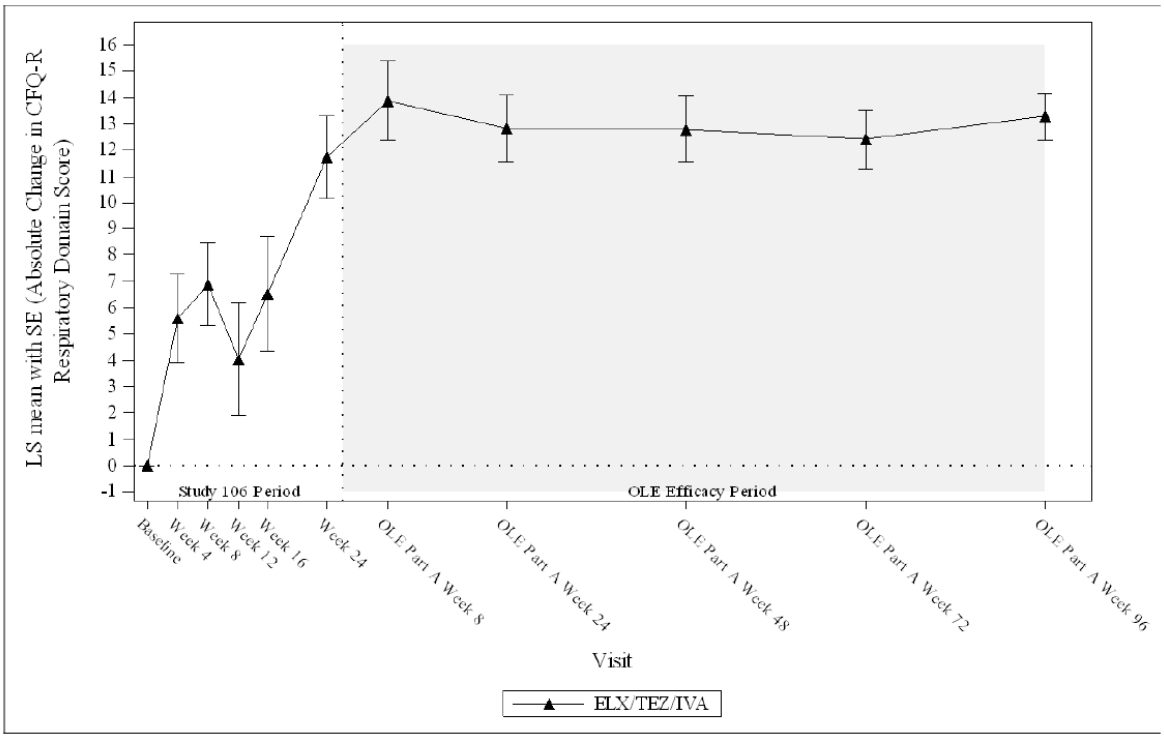
A total of four patients (6.1%) experienced a PEx during follow-up (one event each), resulting in an annualised event rate of 0.12 PEx (199). An even lower PEx annualised event rate of 0.04 was observed in the OL 96-week treatment period (201, 202).

Event rates for PEx requiring hospitalisation and/or IV antibiotic therapy were each 0.03 events/year in study 445-106 Part B and 0.01 events/year in study 445-107 Part A (199, 201, 202). [redacted] Annual event rates for planned and unplanned CF-related hospitalisations during the cumulative treatment period of study 445-107 were each 0.01 events/year (201, 202).

Secondary efficacy endpoint: absolute change in CFQ-R respiratory domain scores from baseline

CFQ-R RD (child's version) scores improved through Week 24 and exceeded the MCID of 4 points (235), with a LS mean absolute change from baseline through Week 24 of 7.0 points (95% CI: 4.7 to 9.2; P<0.0001), with improvements seen since Week 4 (174). These improvements were maintained up to extended Week 96 of study 445-107 Part A, with a LS mean absolute change from baseline of 13.3 points (95% CI: 11.4 to 15.1) (Figure 41) (201, 202).

Figure 41. Absolute change from parent study baseline in CFQ-R respiratory domain (child's version) at each visit up to Week 96 (study 445-106 FAS and OLE-FAS for study 445-107 Part A) – study 445-106 Part B and 445-107 Part A



Note: The y-axis corresponds to the LS means from the MMRM models at the IA. The I bars represent standard error. Parent study baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For parent study period, MMRM is the same as parent study analysis. [redacted]

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire – Revised; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; OLE, open-label extension; RD, respiratory domain; SE, standard error; TEZ, tezacaftor.
Reference: Wainwright,et al. (201)

Secondary efficacy endpoints: absolute change in nutritional parameters (BMI, BMI z-score, weight, weight z-score) from baseline

An MMRM analysis was used to assess the absolute change from baseline in BMI, BMI z-score, weight and weight z-score at Week 24. An increase over the 24-week treatment period in BMI (LS mean absolute change at Week 24 of 1.02; 95% CI: 0.76 to 1.28; P<0.0001), BMI z-score (LS mean absolute change at Week 24 of 0.37; 95% CI: 0.26 to 0.48; P<0.0001), weight (LS mean absolute change at Week 24 of 3.0; 95% CI: 2.5 to 3.5; P<0.0001) and weight z-score (LS mean absolute change at Week 24 of 0.25; 95% CI: 0.16 to 0.33; P<0.0001) without reaching a plateau was observed (174). The absolute changes from baseline in BMI, BMI z-score, weight and weight z-score after 96 weeks of additional treatment in the OLE study were [redacted] (Figure 42), 0.24 (95% CI: 0.11 to 0.37), [redacted] and 0.23 (95% CI 0.10 to 0.35), respectively (201, 202).

Figure 42. Absolute change from parent study baseline in BMI at each visit up to Week 96 (study 445-106 FAS and OLE-FAS for study 445-107 Part A) – study 445-106 Part B and 445-107 Part A

Note: The y-axis corresponds to the LS means from the MMRM models at the IA. The I bars represent standard error. Parent study baseline is defined as the most recent non missing measurement before the first dose of study drug in the parent study. - For parent study period, MMRM is the same as parent study analysis.

Abbreviations: BMI, body mass index; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; OLE, open-label extension;; SE, standard error; TEZ, tezacaftor.
Reference: Vertex, Data on File (202)

Additional efficacy endpoint: absolute change in CFQ-R non-RD scores from baseline

Summary of the results of efficacy outcomes of studies 445-106 Part B and 445-107 Part A are shown in Table 36.

Table 36. Summary results of AURORA 6-11 (study 445-106 Part B) and AURORA 6-11 OLE (study 445-107 Part A)

	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779)[a] (174, 201)		AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790)[b] (201, 202)
	IVA/TEZ/ELX N=66	p value	IVA/TEZ/ELX [redacted]
Primary outcome			
Safety and tolerability	Table 70	N/A	Table 70
Key secondary outcomes			
Absolute change in ppFEV$_1$ from baseline (95% CI)	10.2 (7.9 to 12.6)	<0.001[†]	11.2 (8.3 to 14.2)
Absolute change in CFQ-R RD score from baseline (95% CI)	7.0 (4.7 to 9.2)		13.3 (11.4 to 15.1)
Absolute change in BMI from baseline (95% CI), kg/m^2	1.02 (0.76 to 1.28)		[redacted]
Absolute change in BMI z-score (95% CI)	0.37 (0.26 to 0.48)		0.24 (0.11 to 0.37)
Absolute change in weight from baseline (95% CI), kg	3.0 (2.5 to 3.5)		[redacted]
Absolute change in weight z-score from baseline (95% CI)	0.25 (0.16 to 0.33)		0.23 (0.10 to 0.35)
Absolute change in LCI$_{2.5}$ from baseline (95% CI)	-1.71 (-2.11 to -1.30)		-2.00 (-2.45 to -1.55)
Number of PEx, n	4	–	7
Estimated annualised PEx event rate	0.12	–	0.04
Number of CF-related hospitalisations, n	0	–	1
Time frame	Through Week 24		[redacted]

Note: Results are LS means (95% CI), except as noted; [a]All patients in the full analysis set; [†]Nominal P value; [b] Parent study baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For parent study period, MMRM is the same as parent study analysis. [redacted]

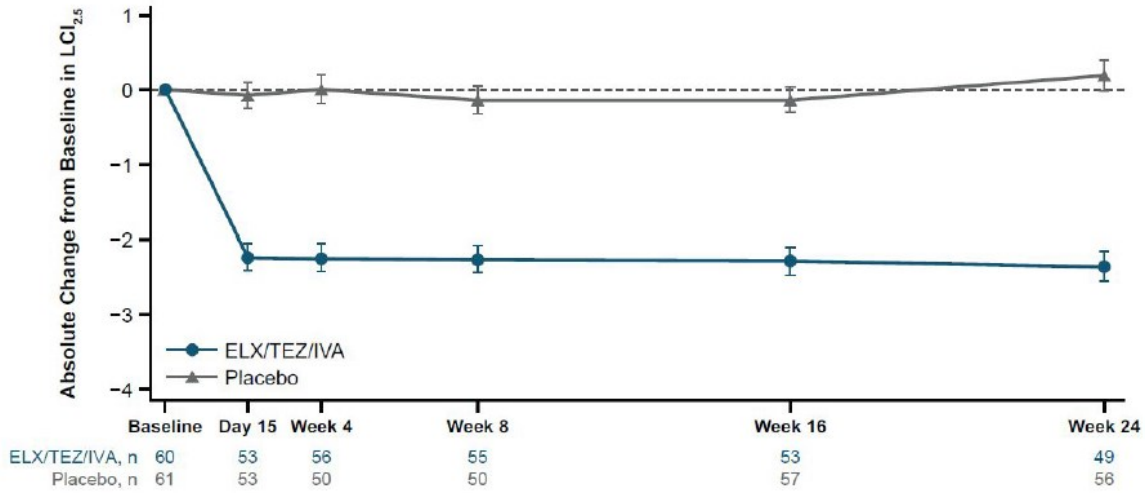
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; LCI$_{2.5}$, lung clearance index at 2.5; LS, least-squares; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor

B.2.5.1.2.2 Study 445-116

Primary efficacy endpoint: absolute change in LCI$_{2.5}$ from baseline through Week 24

By Day 15, treatment with IVA/TEZ/ELX led to a significant reduction of LCI$_{2.5}$ from baseline which was maintained through Week 24 (LS mean within-group change: -2.29; 95% CI: -2.60 to -1.97) (Figure 43). Compared to PBO, treatment with IVA/TEZ/ELX resulted in rapid, sustained and statistically significant improvements through Week 24 (LS mean difference: -2.26; 95% CI: -2.71 to -1.81; P<0.0001) (204). This observed reduction is, in absolute value, greater than the annual rate of deterioration in LCI$_{2.5}$ previously observed among pwCF of similar age (i.e., +0.21 to +0.4 LCI units/year) and could therefore be considered clinically relevant (238, 239). The improvement (i.e., reduction) in LCI$_{2.5}$ may correlate with prolonged survival or reduced risk of lung transplantation (240).

Figure 43. Absolute change in $LCI_{2.5}$ from baseline at each visit – study 445-116



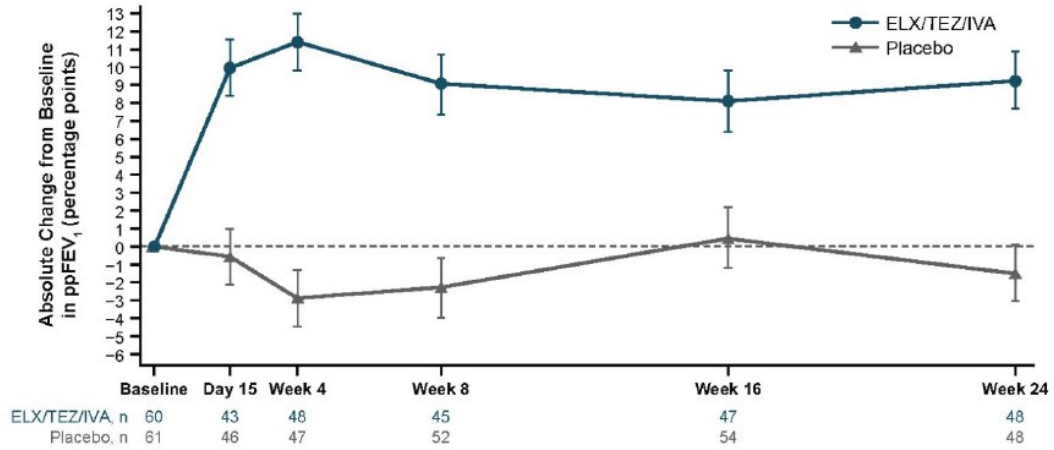
Note: Data are least-squares means based on a mixed-effects model for repeated measures; I-bars indicate standard error of the mean; and the dashed horizontal line corresponds to the baseline. Sample size shown below the X axis is the number of children at the timepoint with evaluable in-clinic data. Absolute change in $LCI_{2.5}$ from baseline at each visit. Lower values indicate decreased airway obstruction and improved homogeneity of ventilation.
Abbreviations: ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LCI2.5, lung clearance index at 2.5; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error; TEZ, tezacaftor.
Reference: Mall et al. (204)

Secondary efficacy endpoints

Secondary efficacy endpoint: absolute change in $ppFEV_1$ from baseline through Week 24

The LS mean change in $ppFEV_1$ from baseline through Week 24 of IVA/TEZ/ELX treatment was 9.5 percentage points (95% CI: 6.6 to 12.4). In contrast, $ppFEV_1$ decreased by -1.5 percentage points from baseline in the PBO group (95% CI: -4.4 to 1.4), reflecting a between-group difference of 11.0 percentage points (95% CI: 6.9 to 15.1; nominal P<0.0001) (Figure 44) (204). This treatment effect exceeds the average annual loss in $ppFEV_1$ (1 to 3 percentage points) and is likely clinically relevant (233). Furthermore, the improvements were of similar magnitude to those observed in other phase 3/3b IVA/TEZ/ELX trials in pwCF aged 6 or older (445-106 and 445-107) demonstrating reproducibility of effect.

Figure 44. Absolute change in ppFEV$_1$ from baseline at each visit – study 445-116

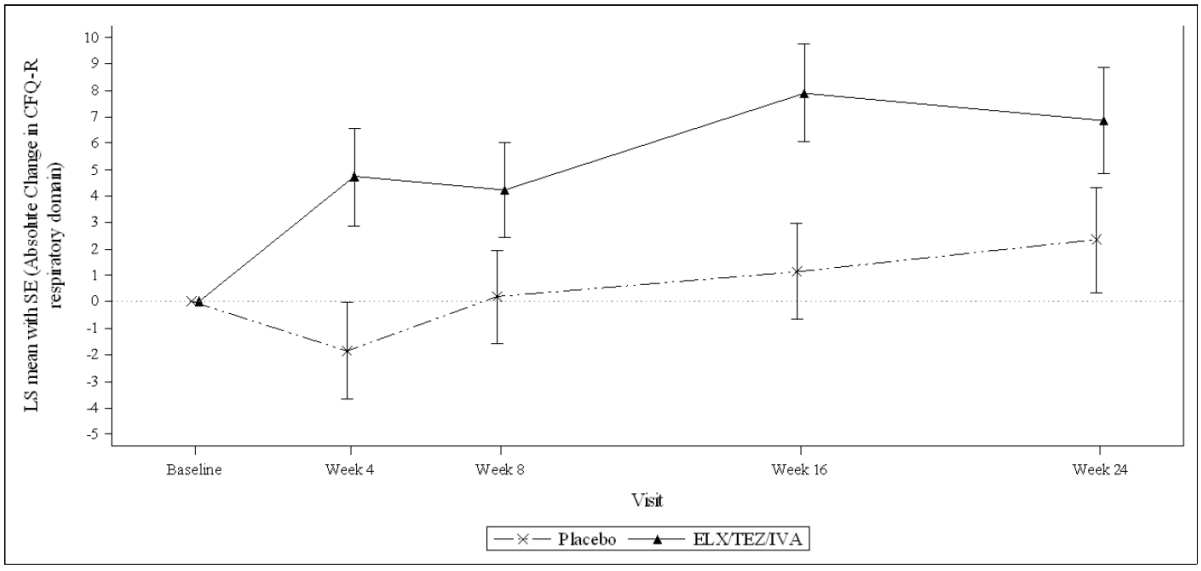


Note: Data are least-squares means based on a mixed-effects model for repeated measures; I-bars indicate standard error of the mean; and the dashed horizontal line corresponds to the baseline. Sample size shown below the X axis is the number of children at the timepoint with evaluable in-clinic data. Absolute change in ppFEV$_1$ from baseline at each visit.
Abbreviations: ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV$_1$, percent predicted forced expiratory volume over 1 second; SE, standard error; TEZ, tezacaftor.
Reference: Mall et al. (204)

Secondary efficacy endpoint: absolute change in CFQ-R scores from baseline through Week 24

IVA/TEZ/ELX treatment resulted in a mean increase in CFQ-R RD score from baseline through Week 24 of 5.9 points (95% CI: 2.8 to 9.1) compared with a mean increase of 0.5 points (95% CI, −2.7 to 3.6) in children receiving PBO; between-group treatment difference of +5.5 points (95% CI: 1.0 to 10.0; nominal P=0.0174) from baseline through Week 24 exceeds the 4-point threshold for a clinically meaningful improvement (Figure 45) (204, 235).

Figure 45. Absolute change in CFQ-R (child's version) respiratory domain scores from baseline at each visit – study 445-116



Note: Data are least-squares means based on a mixed-effects model for repeated measures; I-bars indicate standard error of the mean; and the dashed horizontal line corresponds to the baseline. Sample size shown below the X axis is the number of children at the timepoint with evaluable in-clinic data. Absolute change in the respiratory domain score on the CFQ-R (child's version) from baseline at each visit; scores normalized to a 100-point range, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms.
Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; RD, respiratory domain; SE, standard error; TEZ, tezacaftor.
Reference: Vertex, Data on File

Summary of the efficacy outcomes of study 445-116 are shown in Table 37.

Table 37. Summary results of GALILEO (study 445-116)

GALILEO (study VX19-445-116, NCT04353817) (204)			
	IVA/TEZ/ELX N=60	**PBO N=61**	**Difference (95% CI) P value**
Primary outcome			
Absolute change in $LCI_{2.5}$ from baseline through Week 24 (95% CI)	−2.29 (−2.60 to −1.97)	−0.02 (−0.34 to 0.29)	−2.26 (−2.71 to −1.81) <0.0001
Secondary outcomes			
Absolute change in $ppFEV_1$ from baseline through Week 24 (95% CI)	9.5 (6.6 to 12.4)	−1.5 (−4.4 to 1.4)	11.0 (6.9 to 15.1) <0.0001†
Absolute change in CFQ-R RD score from baseline through Week 24 (95% CI)	5.9 (2.8 to 9.1)	0.5 (−2.7 to 3.6)	5.5 (1.0 to 10.0) P=0.0174†
Results are least-squares (LS) mean absolute change (95% CI); †P values are considered to be nominal. Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; LS, least-squares; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.			

B.2.5.2 LUM/IVA

B.2.5.2.1 CF patients ≥12 years of age

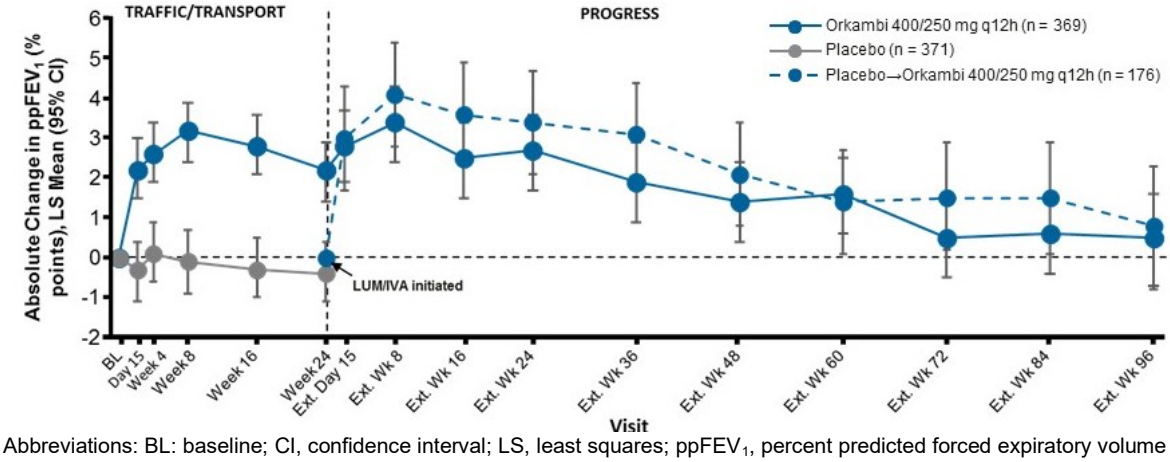
B.2.5.2.1.1 Studies 809-103, 809-104 and 809-105

Studies 809-103 and 809-104 were very similar in design and hence it was possible to pool the results and increase the statistical power; eligible patients who completed either 809-103 or 809-104 were enrolled in OLE 809-105. The outcomes investigated

in study 809-105 overlapped with those of 809-103 and 809-104 and provided evidence of the longer-term benefits. Hence these studies are described simultaneously in the sections that follow. The availability of commercial LUM/IVA contributed to increase in proportion of missing data between Week 72 and 96 of study 809-105; thus, the main efficacy analyses were done for visits up to extension Week 72, with sensitivity analyses done for visits up to extension Week 96.

In study 809-103 and study 809-104 the difference between LUM/IVA and PBO with respect to the **primary endpoint**, defined as the **absolute change from baseline in ppFEV$_1$ at Week 24** (assessed as the average treatment effect at Week 16 and at Week 24), was statistically significant in both studies (2.6, P<0.001 and 3.0, P<0.001 respectively) and in the pooled analysis (2.8 percentage points, P<0.001) (Table 38) (158). There was a consistent improvement in ppFEV$_1$ from as early as Day 15 (Figure 46) (Table 38). Improvements were rapid in onset and sustained through 24 weeks in the LUM/IVA group (155).

Figure 46 Absolute change in ppFEV$_1$ with up to 120 weeks of treatment



Abbreviations: BL: baseline; CI, confidence interval; LS, least squares; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours.
Adapted from Konstan et al.(155)

Patients who received LUM/IVA in study 809-103 and study 809-104 maintained the improvement in ppFEV$_1$ through a total of up to 120 weeks of treatment in the rollover study (Figure 46) (155).

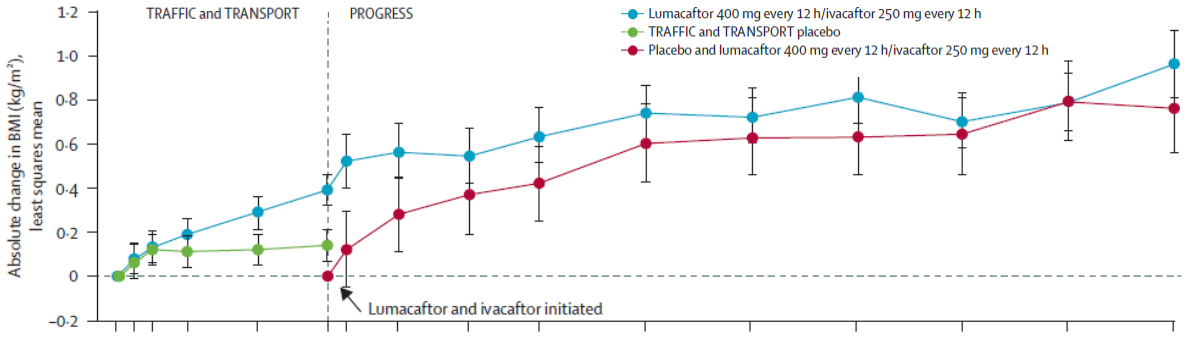
Key secondary endpoints of studies 809-103 and 809-104 included **relative change in ppFEV$_1$ at Week 24** (assessed as the average treatment effect at Week 16 and at Week 24), **absolute change from baseline in BMI at Week 24**, **absolute change from baseline in CFQ-R RD score at Week 24**, **response** defined as ≥5% increase

in average relative change from baseline in percent predicted FEV_1 at Week 16 and at Week 24 and lastly the **number of PEx through Week 24**.

Relative change in ppFEV$_1$ at Week 24 confirmed the superiority of LUM/IVA vs PBO in improving lung function, yielding statistically significant results in the LUM/IVA group in both studies and the pooled analysis (158), which were maintained through to 96 weeks of treatment in study 809-105 (Table 39) (155). The pooled analysis also showed a significantly larger proportion of patients with a relative improvement of ≥5% in the LUM/IVA group compared with the PBO group (39% vs 22%) with an OR of 2.2 (95% CI: 1.6 to 3.1; P<0.001) at Week 24, favouring the LUM/IVA group.

There was a non-statistically significant difference between the **absolute change from baseline in BMI** in those treated with LUM/IVA compared to PBO at Week 24 in study 809-103. However, in both study 809-104 and the pooled analysis, patients in the LUM/IVA group had statistically significant improvements in BMI from baseline at Week 24 compared with PBO (Figure 47).

Figure 47. Absolute change in BMI in study 809-103, study 809-104 and study 809-105

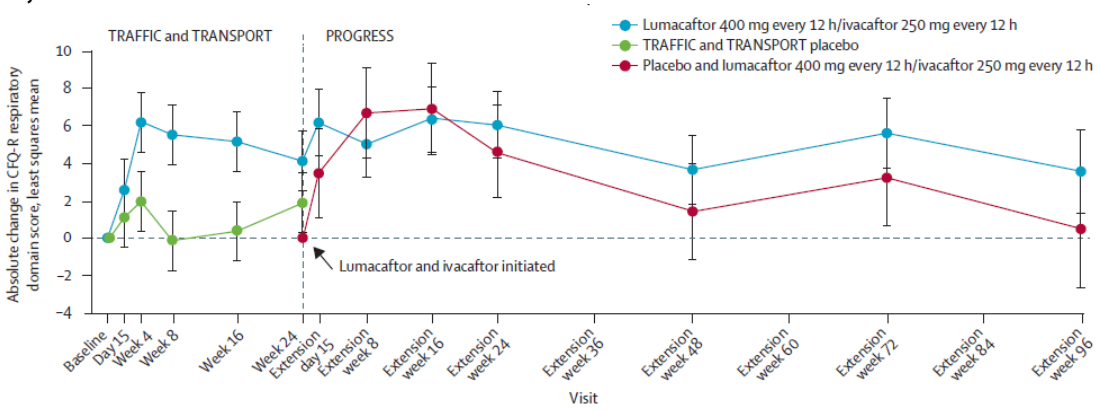


TRAFFIC is study 809-103, TRANSPORT is study 809-104 and PROGRESS is study 809-105
Abbreviations: BMI, body mass index.
Reference: Konstan et al. (155)

As shown in Figure 47, when patients who had received active treatment with LUM/IVA entered study 809-105, the improvements in BMI observed in studies 809-103 and 809-104 continued (155). The LS mean absolute change in BMI from baseline of the parent studies at Week 72 of study 809-105 was 0.69 kg/m^2 (95% CI: 0.56 to 0.81) for those that continued treatment with the LUM/IVA (23). Patients who had received PBO in the parent studies demonstrated improvements in BMI upon receiving active treatment in study 809-105 consistent with those observed in the active treatment group (pooled analysis) from 809-103 and 809-104 (158, 241).

The pooled analysis of studies 809-103 and 809-104 showed a numerical **improvement in the CFQ-R RD score** in the LUM/IVA group compared with the PBO group although the improvement was not statistically significant at Week 24. The difference between LUM/IVA and PBO in the CFQ-R RD score was statistically significant at all other time-points (Week 4, 8, 16). When compared to baseline, patients treated with LUM/IVA achieved an MCID of over 4 points at all specified time-points. In study 809-105, the improvement in mean RD score from baseline at Week 72 was statistically significant in patients that transitioned from PBO to LUM/IVA and in those that continued treatment with LUM/IVA from the parent study (baseline is that of the parent studies). This score remained above pre-treatment baseline in both groups up to extension Week 96 (although the change from baseline at Week 96 was not statistically significant in patients who transitioned to LUM/IVA from PBO) (Figure 48).

Figure 48. Absolute change in CFQ-R respiratory domain score in studies 809-103, 809-104 and 809-105



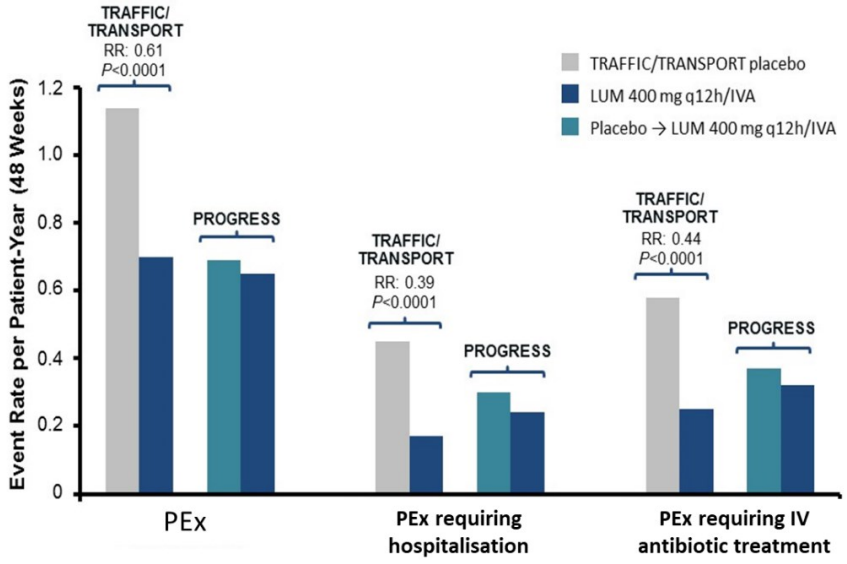
TRAFFIC is study 809-103, TRANSPORT is study 809-104 and PROGRESS is study 809-105
Abbreviations: CFQ-R, Cystic fibrosis questionnaire-revised.
Reference: Konstan et al. (155)

[redacted] on the single utility index analysis of the EuroQol 5-dimension 3-level (EQ-5D-3L) results. [redacted] (20).

The **number of PEx** was lower in the LUM/IVA group compared with the PBO group in both 809-103 and 809-104. The RRs showed a treatment effect that favoured

LUM/IVA vs PBO in both 809-103 (RR: 0.66, P=0.02) and 809-104 (RR: 0.57, P<0.001) (158). The annualised PEx rate through extension Week 96 remained lower in the LUM/IVA group (0.65 [95% CI: 0.56 to 0.75] than the event rate observed in the PBO group during studies 809-103 or 809-104 (1.14 [95% CI: 0.97 to 1.34]) (155, 158).

Figure 49. Annualised PEx rate with up to 120 weeks of treatment

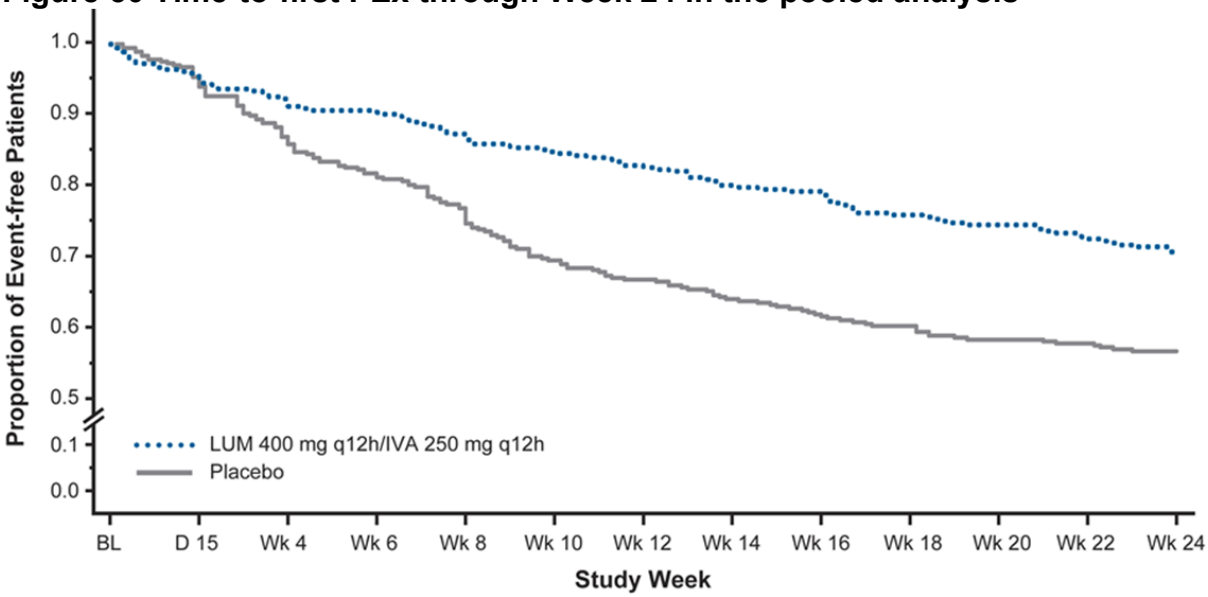


Note: TRAFFIC (study 809-103) /TRANSPORT (study 809-104) results estimated from 24 weeks of observation. PROGRESS (study 809-105) LUM/IVA group calculated from patients who received up to 120 weeks of LUM/IVA, including during TRAFFIC/TRANSPORT. PROGRESS PBO→ LUM/IVA group calculated from patients who received up to 96 weeks of LUM/IVA only, not including TRAFFIC/TRANSPORT events.
Abbreviations: PEx, pulmonary exacerbation; RR, rate ratio; q12h, every 12 hours
Adapted from Konstan et al. Rate ratios taken from Wainwright et al. (155, 158)

The annualised rate of PEx requiring hospitalisation or IV antibiotic treatment followed the same trend with subjects receiving LUM/IVA over the parent and extension study periods having fewer such severe episodes per year than those patients receiving PBO (Figure 49 and Table 38) (241).

According to the pooled analysis of time-to-first PEx, the proportion of patients free of PEx was significantly greater among those receiving LUM/IVA vs PBO (Figure 50) (158). In both study 809-103 and study 809-104, the risk of having at least one PEx was lower in the LUM/IVA group compared with the PBO group (RR, 0.64, P=0.0512 and 0.44, P=0.0002 respectively) and the pooled analysis (RR, 0.5327, P<0.001) (242, 243).

Figure 50 Time-to-first PEx through Week 24 in the pooled analysis



Abbreviations: BL, baseline; PEx, pulmonary exacerbation; q12h, every 12 hours.
Adapted from Wainwright et al. (158)

Mean total durations of PEx, including severe episodes requiring hospitalisation or IV antibiotics, were shorter in the LUM/IVA group vs the PBO group: in the pooled analysis of 809-103 and 809-104, the mean number of days patients were hospitalised for a PEx was 2.48 days and 7.64 days in the LUM/IVA group and PBO group, respectively (P<0.0001). Mean number of days on IV antibiotic therapy for a PEx was 3.79 days and 10.13 days in the LUM/IVA group and PBO group, respectively (P<0.0001). Duration of PEx was not an outcome in the study 809-105.

In summary, the pooled analysis of studies 809-103 and 809-104, together with the additional data from the extension study 809-105, showed that treatment with LUM/IVA is associated with reduced rates of all PEx, including those requiring hospitalisation and/or IV antibiotics and increased time to first PEx as compared with PBO in pwCF aged 12 years or older homozygous for the *F508del-CFTR* mutation. These outcomes are clinically meaningful to patients and their carers, as the avoidance of PEx improves long term prognosis.

Table 38. Summary results of TRAFFIC (study 809-103) and TRANSPORT (study 809-104) (A)

	TRAFFIC (study VX12-809-103), NCT01807923) (158, 243)			TRANSPORT (study VX12-809-104, NCT01807949) (158, 242)			Pooled analysis (158)		
	PBO N=184	LUM (400 mg q12h)/ IVA (250 mg q12h) N=182	Difference or rate ratio P value	PBO N=186	LUM (400 mg q12h)/ IVA (250 mg q12h) N=187	Difference or rate ratio P value	PBO N=371	LUM (400 mg q12h)/ IVA (250 mg q12h) N=369	Difference or rate ratio P value
Primary outcome									
Absolute change from baseline at Week 24, $ppFEV_1$, Mean, percentage points	-0.44 (P=0.40)	2.2 (P<0.0001)	2.6 (P<0.001)	-0.15 (P=0.77)	2.9 (P<0.001)	3.0 (P<0.001)	–0.32 (P=0.40)	2.5 (P<0.001)	2.8 (P<0.001)
Key secondary outcomes									
Relative change from baseline at Week 24, $ppFEV_1$, Mean, %	-0.34 (P=0.71)	4.0 (P<0.001)	4.3 (P<0.001)	0.0 (P=0.10)	5.3 (P<0.001)	5.3 (P<0.001)	–0.17 (P=0.80)	4.6 (P<0.001)	4.8 (P<0.001)
Absolute change from baseline in BMI at Week 24, Mean (kg/m^2)	0.19 (P=0.007)	0.32 (P<0.001)	0.13 (P=0.19)	0.07 (P=0.29)	0.43 (P<0.001)	0.36 (P<0.001)	0.13 (P=0.007)	0.37 (P<0.001)	0.24 (P<0.001)
Absolute change from baseline at Week 24 in CFQ-R-RD, Mean	1.1 (P=0.34)	2.6 (P=0.03)	1.5 (P=0.36)	2.8 (P=0.02)	5.7 (P<0.001)	2.9 (P=0.07)	1.9 (P=0.02)	4.1 (P<0.001)	2.2 (P=0.05)
Absolute change from baseline in weight at Week 24, Mean (kg)	0.93 (P<0.001)	1.23 (P<0.001)	0.30 P=0.2992	0.44 (0.0196)	1.38 (0.187)	0.95 (0.0003)	-	-	-
Number of PEx through Week 24	112	73	-	139	79	-	251	152	-
Estimated annualised PEx event rate	1.07	0.71	0.66 (P=0.02)	1.18	0.67	0.57 (P<0.001)	1.14	0.70	0.61 (P<0.001)
Number of PEx requiring hospitalisation through Week 24	[redacted]	[redacted]	-	[redacted]	[redacted]	-	-	-	-
Estimated annualised event rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Number of PEx requiring intravenous antibiotic therapy through Week 24	[redacted]	[redacted]	-	[redacted]	[redacted]	-	-	-	-
Estimated annualised event rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Reported means are least square means
Changes in $ppFEV_1$ are calculated by averaging means at weeks 16 and 24
Abbreviations: BMI, body mass index; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; $ppFEV_1$, percent predicted forced expiratory volume in the first second; h, hour; IVA, ivacaftor; kg, kilogram; LUM, lumacaftor; m^2, metre squared; mg, milligrams; PBO, placebo; $ppFEV_1$, percent predicted FEV_1; q, every; qd, once daily

Table 39. Summary results of PROGRESS (study 809-105) (B)

PROGRESS (VX12-809-105, NCT01931839) (155)			
Parameter		**PBO transitioned to LUM 400 mg q12h/IVA 250 mg q12h (N=176)**	**LUM 400 mg q12h/IVA 250 mg q12h (N=340)**
Primary outcome			
Safety		Table 71	
Secondary outcomes*			
$ppFEV_1$, absolute change from baseline (Wang-Hankinson), LS mean (95% CI), percentage points[1]	Extension Week 72	1.5 (0.2 to 2.9), P=0.0254	0.5 (–0.4 to 1.5), P=0.2806
	Extension Week 96	0.8 (–0.8 to 2.3), P=0.3495	0.5 (–0.7 to 1.6), P=0.4231
$ppFEV_1$, relative change from baseline (Wang-Hankinson), LS mean (95% CI), percentage points[1]	Extension Week 72	2.6 (0.2 to 5.0), P=0.0332	1.4 (–0.3 to 3.2), P=0.1074
	Extension Week 96	1.1 (–1.7 to 3.9), P=0.4415	1.2 (–0.8 to 3.3), P=0.2372
BMI, absolute change from baseline, LS mean (95% CI), kg/m2 [1]	Extension Week 72	0.62 (0.45 to 0.79), P<0.0001	0.69 (0.56 to 0.81), P<0.0001
	Extension Week 96	0.76 (0.56 to 0.97), P<0.0001	0.96 (0.81 to 1.11), P<0.0001
Weight absolute change from baseline, LS mean (95% CI), kg/m2 [1,2]	Extension Week 72	[redacted]	[redacted]
CFQ-R-RD score, absolute change from baseline, LS mean (95% CI)[1]	Extension Week 72	3.3 (0.7 to 5.9), P=0.0124	5.7 (3.8 to 7.5), P<0.0001
	Extension Week 96	0.5 (–2.7 to 3.6) P=0.7665	3.5 (1.3 to 5.8) P=0.0018
PEx events[3]	Number of events per patient year (95% CI)	0.69 (0.56 to 0.85)	0.65 (0.56 to 0.75)
	Number of events requiring hospitalisation per patient year (95% CI)	0.30 (0.22 to 0.40)	0.24 (0.19 to 0.29)
	Number of events requiring IV antibiotics per patient year (95% CI)	0.37 (0.29 to 0.49)	0.32 (0.26 to 0.38)
	Percentage of participants with at least 1 PEx, N (%)	[redacted]	[redacted]

The primary outcome was long term safety. These results can be seen in Section B.2.9.
Change from baseline data in study 809-105 are shown at extension Week 72 (the main efficacy analysis) and at extension Week 96 (sensitivity analysis). In the main efficacy analysis, patients who remained on lumacaftor/ivacaftor received up to 96 weeks of active treatment. Patients included in the sensitivity analysis received up to 120 weeks of active treatment with lumacaftor/ivacaftor
[1]For the LUM/IVA group, baseline from study 809-103 or study 809-104 was used; for the PBO transitioned to lumacaftor/ivacaftor group, baseline from study 809-105 was used. All p values are within treatment.
[redacted] and for the PBO transitioned to LUM/IVA and the LUM/IVA groups respectively
[2]The pulmonary exacerbations analyses for study 809-105 included events throughout the cumulative study period (study 809-103 or study 809-104 and study 809-105), such that the PBO transitioned to LUM/IVA group received up to 96 weeks of active treatment and the LUM/IVA group received up to 120 weeks of active treatment
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CF, cystic fibrosis; CFRD, Cystic fibrosis-related diabetes; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; CI, confidence interval; DIOS, distal intestinal obstruction syndrome; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in the first second; GLI, Global Lungs Initiative; IV, intravenous; IVA, ivacaftor; LUM, lumacaftor; LS, least squares; NA, not applicable; PEx, pulmonary exacerbation; q, every; qd, once daily RTI, respiratory tract infection; SAE, serious adverse event.

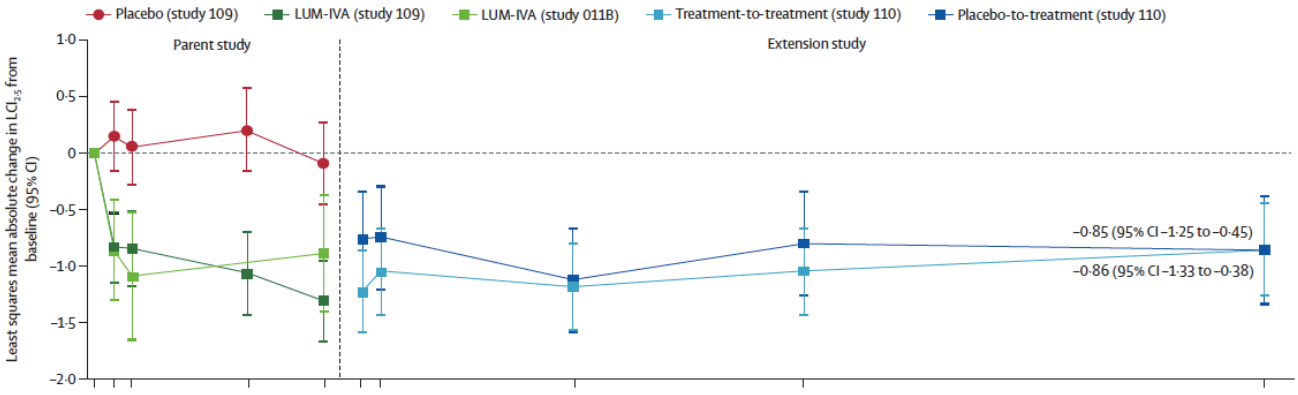
B.2.5.2.2 CF patients 6 to 11 years of age

B.2.5.2.2.1 Study 809-109 and study 809-110

Study 809-109 is one of the two parent studies of OLE 809-110, which enrolled eligible pwCF who completed either 809-109 or 809-011B (809-011B is not discussed in Section B.2 as it does not inform the CEM; for more detail on this study see appendix D). Although the primary endpoints of these studies were different, there was a significant overlap in endpoints because the objective of 809-110 was to assess the durability of treatment benefits seen in 809-109. Hence these studies are described simultaneously in this section.

Treatment with LUM/IVA in study 809-109 resulted in a statistically significant **reduction in $LCI_{2.5}$ from baseline** up to and including Week 24 compared with PBO (LS mean treatment difference: -1.1, 95% CI: -1.4 to -0.8, P<0.0001) (Table 40 and Table 41) (159). These improvements were sustained for patients continuing LUM/IVA throughout study 809-110 as can be seen in Figure 51 (156). The LS mean absolute change in $LCI_{2.5}$ from parent study baseline at Week 96 was -0.85 (95% CI: -1.25 to -0.45) in the patients continuing LUM/IVA and -0.86 (95% CI: -1.33 to -0.38) in the patients transitioning from PBO to LUM/IVA in 809-110 (156).

Figure 51 Absolute change from parent study baseline in $LCI_{2.5}$



Study 011B on the graph is not discussed in Section B.2.
as BL, baseline; CI, confidence interval; LCI, lung clearance index; LS, least squares; OL, open-label; RCT, randomised controlled trial. Reference: Chilvers et al. (156)

Secondary outcomes investigated in studies 809-109 and 809-110 included **changes from baseline in $LCI_{5.0}$, $ppFEV_1$, BMI, CFQ-R RD** and **frequency of PEx**. In study 809-109 treatment with LUM/IVA resulted in [redacted]

[redacted]

The rate of change in lung function endpoints, $LCI_{2.5}$ and $LCI_{5.0,}$ after the initiation of LUM/IVA was also investigated. $LCI_{2.5}$ and $LCI_{5.0}$ decreased rapidly (improved) by Day 15 after the initiation of LUM/IVA treatment, and these improvements were sustained up to Week 96 in study 809-110. Early improvements in $LCI_{2.5}$ and $LCI_{5.0}$ observed after the initiation of LUM/IVA treatment were durable throughout study 809-110; $LCI_{2.5}$ rate of change was -0.01 (95% CI: -0.12 to 0.09) and the $LCI_{5.0}$ rate of change was 0.00 (95% CI: -0.04 to 0.04).

Treatment with LUM/IVA also led to a statistically significant improvement in **absolute change in ppFEV$_1$** from baseline up to and including Week 24 compared with PBO in study 809-109 (LS mean treatment difference 2.4 percentage points [95% CI: 0.4 to 4.4], P=0.0182; Figure 52) (159). The LS mean treatment difference for the relative change in $ppFEV_1$ from baseline up to and including Week 24 was [redacted] (Table 40). (244). The improvement in $ppFEV_1$ was generally maintained over 96 weeks of treatment in study 809-110 (Figure 52). The $ppFEV_1$ rate of change from Day 15 after the first dose of LUM/IVA (in either the parent study or study 809-110) was also evaluated; $ppFEV_1$ remained stable or increased once subjects started treatment with LUM/IVA, resulting in a [redacted] (156).

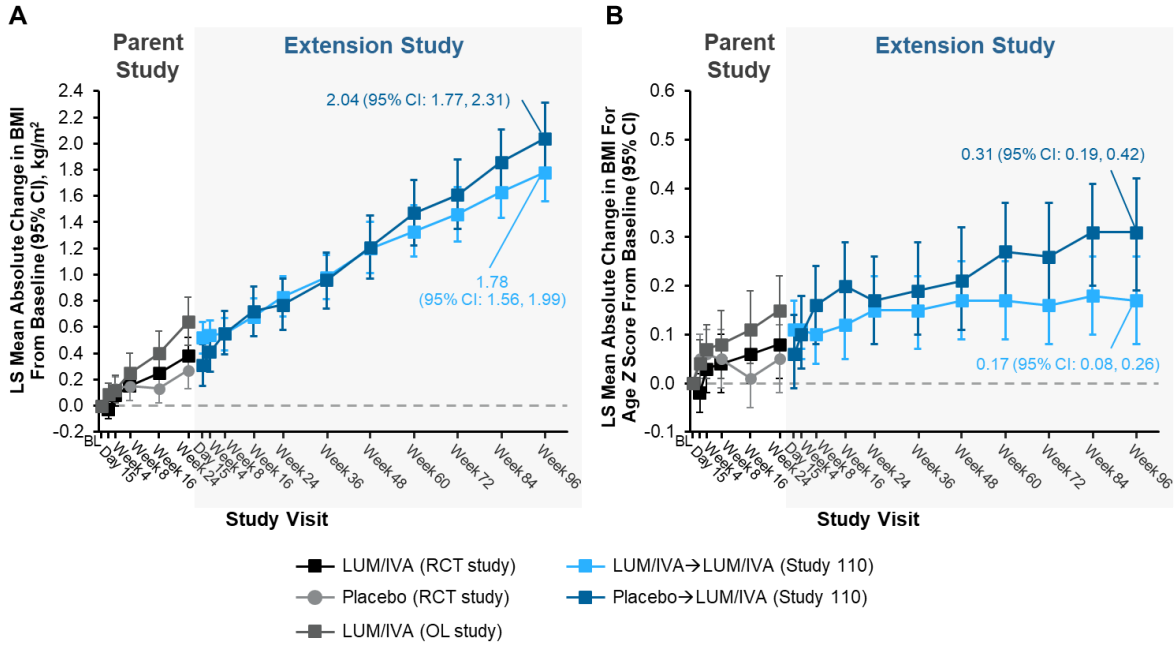
Figure 52. Absolute change from parent study baseline in ppFEV$_1$

Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; PBO, PBO; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.
Reference: Vertex, Data on File (215)

Patients treated with LUM/IVA experienced significant within-group **changes in BMI from baseline** at Week 24 of 0.4 kg/m^2 (95% CI: 0.3 to 0.5, P<0.0001), a clinically relevant effect in the rapidly growing population of 6-11 year olds (159). In contrast, in the PBO group, the within-group LS mean change was 0.3 kg/m^2 (95% CI: 0.1 to 0.4, P=0.0002). The treatment difference favoured LUM/IVA numerically but was not statistically significant (LS mean treatment difference, 0.1 kg/m^2 [95% CI: -0.1 to 0.3], P=0.2522) (159).

Patients' BMI increased throughout study 809-110 both in patients continuing LUM/IVA and in those transitioning to LUM/IVA from PBO (Figure 53) (156). The LS mean **absolute change in BMI** from parent study baseline at study 809-110 Week 96 was 1.78 kg/m^2 (95% CI: 1.56 to 1.99) in patients continuing LUM/IVA and 2.04 kg/m^2 (95% CI: 1.77 to 2.31) in the patients transitioning from PBO to LUM/IVA (156). Similarly, results of weight, height, and associated z-scores (including **BMI z-score**) demonstrated age-appropriate growth that continued in both treatment groups and was maintained through the 96 weeks of study 809-110 (156).

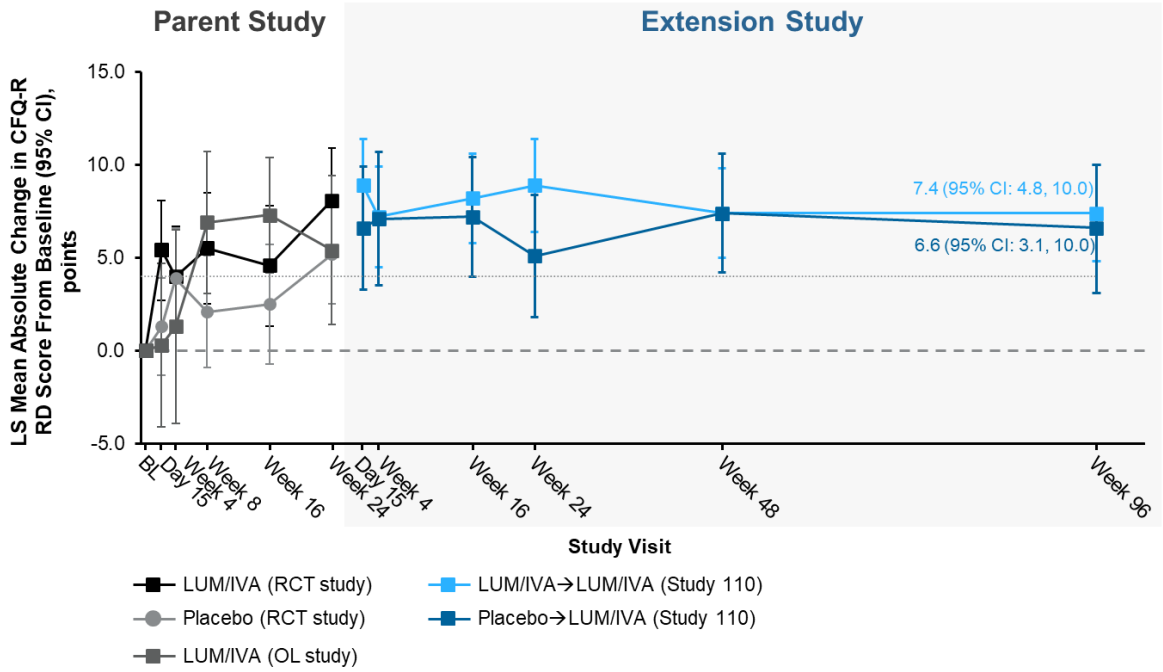
Figure 53. Absolute change from baseline of parent study in BMI (A) and BMI for age z-score (B)



The RCT study refers to study 809-109. The OL study refers to study 809-011B which is not discussed in Section B.2.
Abbreviations: BL, baseline; BMI, body mass index; CI, confidence interval; LS, least squares; OL, open-label; RCT, randomised controlled trial.
Reference: Chilvers et al.(156)

The LS **mean increase in CFQ-R RD score from baseline** up to and including Week 24 was 5.5 points (95% CI: 3.4 to 7.6, P<0.0001) for the LUM/IVA group and 3.0 points (95% CI 1.0 to 5.0, P=0.0035) for the PBO group (Figure 54) (159). LUM/IVA-treated patients achieved the MCID (235), whereas PBO-treated patients did not, but the treatment difference was not significant (2.5 points [95% CI: -0.1 to 5.1], P=0.0628) (159). Patients enrolled in 809-110 experienced clinically significant improvements in CFQ-R RD scores from parent study baseline: the LS mean absolute change from parent study baseline at Week 96 was 7.4 points (95% CI: 4.8 to 10.0) in patients continuing LUM/IVA and 6.6 points (95% CI: 3.1 to 10.0) in those transitioning from PBO to LUM/IVA (156).

Figure 54. Absolute change from parent baseline in CFQ-R Respiratory Domain score



The grey dotted line shows the minimal clinically important difference of 4.0.
The RCT study refers to study 809-109. The OL study refers to study 809-011B which is not discussed in Section B.2.
BL, baseline; CI, confidence interval; CFQ-R, Cystic Fibrosis Questionnaire-Revised; LS, least squares; OL, open-label; RCT, randomised controlled trial; RD, respiratory domain.
Reference: Chilvers (156)

Compared with subjects 12 years of age or older, the subjects in this study had relatively few PEx (244). **Outcomes related to PEx** were generally similar in the LUM/IVA and PBO groups. Analysis of time-to-first PEx through Week 24 showed event-free probability of [redacted]

The number (event rate per year) of PEx through Week 24 was [redacted] the LUM/IVA group and [redacted] in the PBO group. The RR for the LUM/IVA group vs the PBO group was [redacted] (244). The PEx results are described further in Table 41.

Table 40. Summary results of study 809-109

Study VX14-809-109 (NCT02514473) (159, 244)				
Parameter		**LUM/IVA*(N=103)**	**PBO (N=101)***	**Treatment difference vs PBO**
Primary outcome				
LS mean absolute change in $LCI_{2.5}$ up to and including Week 24 (95% CI)		−1.0 (−1.3 to −0.8) P<0.0001	0.1 (−0.2 to 0.3) P=0.5390	−1.1 (−1.4 to −0.8) P<0.0001
Secondary outcomes				
LS mean absolute change in BMI at Week 24 (95% CI)		0.4 (0.3 to 0.5) P<0.0001	0.3 (0.1 to 0.4) P=0.0002	0.1 (−0.1 to 0.3) P=0.2522
LS mean absolute change in BMI-for-age z-score at Week 24 (95% CI)		0.1 (0.0 to 0.2) P=0.0310	0.1 (−0.0 to 0.1) P=0.1739	0.0 (−0.1 to 0.1) P=0.5648
LS mean absolute change in weight at Week 24 (95% CI)		[redacted]	[redacted]	[redacted]
LS mean absolute change in weight for-age z-score at Week 24 (95% CI)		[redacted]	[redacted]	[redacted]
LS mean absolute change in CFQ-R-RD score up to and including Week 24 (95% CI)		5.5 (3.4 to 7.6) P<0.0001	3.0 (1.0 to 5.0) P=0.0035	2.5 (−0.1 to 5.1) P=0.0628
LS mean absolute change in $ppFEV_1$ up to and including Week 24 (95% CI)		1.1 (−0.4 to 2.6) P=0.1483	−1.3 (−2.8 to 0.2) P=0.0899	2.4 (0.4 to 4.4) P=0.0182
LS mean relative change in $ppFEV_1$ up to and including Week 24 (95% CI)		2.2 (0.3 to 4.1) P=0.0218	-0.9 (-2.8 to 1.0) P=0.3278	3.2 (0.6 to 5.7) P=0.0141
LS mean absolute change in $LCI_{5.0}$ from baseline through Week 24		[redacted]	[redacted]	[redacted]
Number of PEx events	Number of subjects with events	[redacted]	[redacted]	N/A
	Number of events	[redacted]	[redacted]	N/A
	Event rate per patient-year (95% CI)	[redacted]	[redacted]	N/A
	Rate ratio (95% CI)	N/A	N/A	[redacted]
Number of PEx requiring hospitalisation, event rate per year (95% CI)		[redacted]	[redacted]	N/A
Number of PEx requiring intravenous antibiotic therapy through Week 24		[redacted]	[redacted]	N/A

All endpoints shown are from baseline
*p values are within-group
Abbreviations: BMI, body mass index; CFQ-R-RD, cystic fibrosis questionnaire–revised-respiratory domain; CI, confidence interval; IVA, ivacaftor; $LCI_{2.5}$=lung clearance index $_{2.5}$; LUM, lumacaftor; N/A, not applicable; LS, least squares; PBO, placebo; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in the first second; SwCl, sweat chloride; TSQM, Treatment satisfaction questionnaire for medication

Table 41. Summary results of study 809-110

Study VX15-809-110 (NCT02544451) (156) (215)		
	Treatment-to treatment group	**PBO-to treatment group**
Primary outcome		
Safety	**Table 73**	
Secondary outcomes		
LS mean absolute change in $LCI_{2.5}$ from baseline at Week 96, LS mean (95% CI); N	-0.85 (-1.25 to -0.45); [redacted]	-0.86 (-1.33 to -0.38); [redacted]
LS mean absolute change in BMI from baseline at Week 96, LS mean (95% CI); N	1.78 (1.56 to 1.99); [redacted]	2.04 (1.77 to 2.31); [redacted]
LS mean absolute change in BMI-for-age z-score from baseline at Week 96, LS mean (95% CI); N	0.17 (0.08 to 0.26); [redacted]	0.31 (0.19 to 0.42) [redacted]
LS mean absolute change in CFQ-R RD score from baseline at Week 96, LS mean (95% CI); N	6.6 (3.1 to 10.0) [redacted]	7.4 (4.8 to 10.0) [redacted]
LS mean absolute change in $ppFEV_1$ (percentage points) from baseline at Week 96, LS mean (95% CI); N	[redacted]	[redacted]
LS mean relative change in $ppFEV_1$ from baseline at Week 96, LS mean (95% CI); N	[redacted]	[redacted]
LS mean absolute change in weight (kg) from baseline at Week 96, LS mean (95% CI); N	10.3 (9.6 to 11.0); [redacted]	11.0 (10.1 to 11.8); [redacted]
LS mean absolute change in weight-for-age z-score from baseline at Week 96, LS mean (95% CI); N	0.12 (0.04 to 0.20); [redacted]	0.24 (0.14 to 0.34); [redacted]
LS mean absolute change in $LCI_{5.0}$ from baseline at Week 96, LS mean (95% CI); N	[redacted]	[redacted]
Time-to-first PEx (days), Median (1st and 3rd quartiles)	[redacted]	[redacted]
Event of having at least 1 PEx, N (%) subjects	51 (49.5)*	31 (32.3)**
Number of PEx (per patient-year), Event rate per patient-year	0.45 (0.33, 0.61)*	0.30 (0.21, 0.43)**

*Subjects who received LUM/IVA in study 809-109 assessed over the Cumulative Study Period
**Subjects who received PBO in study 109 and began LUM/IVA treatment in study 110, assessed during the Current Study Period
Baseline refers to baseline in parent studies (study 809-109 and study 809-011B)
Because fewer than 50% of subjects in the PBO to treatment group had PEx, the median time-to-first PEx could not be estimated for these subjects (only 32.3% of subjects had events during study 809-110). Similarly, the 3rd quartile of time-to-first PEx could not be estimated for either group, because fewer than 75% of subjects in each group had events during the

Study VX15-809-110 (NCT02544451) (156) (215)		
	Treatment-to treatment group	PBO-to treatment group
LUM/IVA treatment period. Abbreviations: BMI, body mass index; kg, kilogram; LCI, lung clearance index; LS, least square; NE, not estimable; PBO, placebo; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in the first second.		

B.2.5.2.3 CF patients 2 to 5 years of age

B.2.5.2.3.1 Study 809-115B and study 809-116

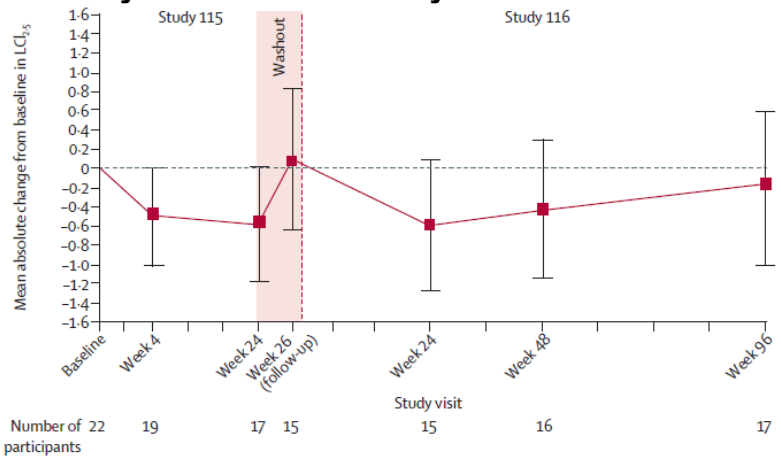
Study 809-116 enrolled eligible patients who completed single arm phase 3 study 809-115B. While the primary objective of both studies was safety, they had overlapping efficacy objectives (BMI, PEx, CF-related hospitalisations, ppFEV$_1$ and LCI$_{2.5}$) assessed at short term (through Week 24) in 809-115B and at longer term (Week 96) in 809-116. Hence both studies are described simultaneously here to illustrate the kinetics and duration of response.

No notable change from baseline was observed in ppFEV$_1$ at Week 24 in study 809-115B or at Week 96 in study 809-116; in study 809-115 the mean change in ppFEV$_1$ from baseline at Week 24 (n=12) was 0.5 percentage points (95% CI: –6.9 to 7.9) and in study 809-116 the mean absolute change in ppFEV$_1$ from parent study baseline at study 809-116 Week 96 was [redacted] (Table 42). However, given that only 12 and 13 subjects, respectively, had relevant spirometry measurements at baseline and the last study visit, which showed substantial intrapatient variability, definitive conclusions in this age group could not be reached (161, 162).

In study 809-115B an improvement (i.e., a reduction) in LCI$_{2.5}$ was observed among the 17 patients who completed the LCI sub study of study 809-115B. The overall mean absolute change from baseline at Week 24 was −0.58 (P=0.06) (Table 42) (162). After the 2-week washout period, LCI$_{2.5}$ returned to the approximate baseline levels (162). The improvement in LCI$_{2.5}$ observed among 2 to 5-year-olds treated with LUM/IVA in study 809-115 Part B is consistent with that experienced by patients aged 6 to 11 years of age

(162). In study 809-116 the mean absolute change in $LCI_{2.5}$ at Week 96 from baseline in the parent study was −0.20 (95% CI: -0.99 to 0.60) (Figure 55) (161, 167).

Figure 55. Absolute change in $LCI_{2.5}$ in study 809-115B and study 809-116



Abbreviations: $LCI_{2.5}$, Lung clearance index 2.5
Reference: Hoppe et al. (161)

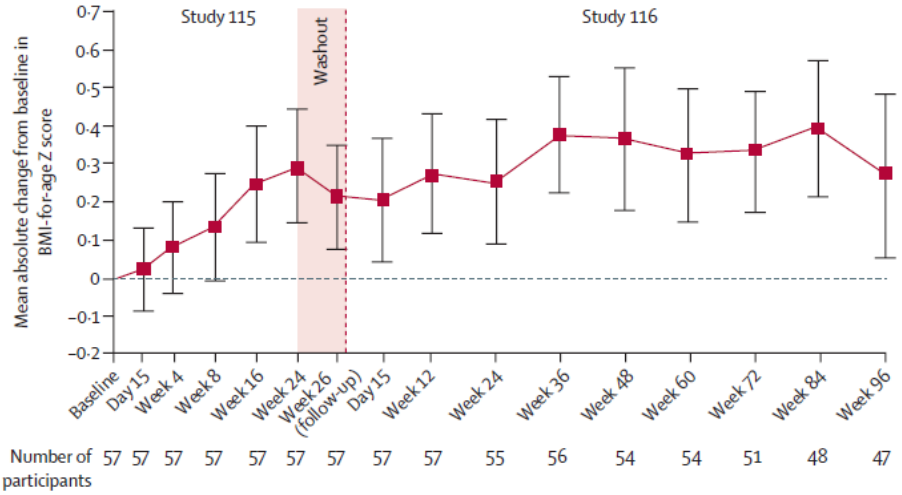
In study 809-115 Part B, a total of 18 patients (30%) experienced PEx through Week 24 (162). [redacted] both 809-115B and 809-116 experienced a PEx. In 809-115B the rate of PEx was 0.90 per patient-year, whereas in the pooled data from study 809-115B and 809-116 the event rate per patient-year was [redacted] (

Table 43) (167).

In study 809-115B the rate of CF-related hospitalisations was [redacted] whilst in the pooled data from study 809-115B and study 809-116 the rate of CF-related hospitalisations [redacted] (162).

In study 809-115B the mean absolute change in BMI from baseline at Week 24 was 0.27 kg/m² (95% CI: 0.07 to 0.47, P=0.0091) and in BMI z-score was 0.29 (95% CI: 0.14 to 0.45, P=0.0003) (Table 42) (162). These positive results were maintained in the long-term as evidenced by the extension study. At Week 96 of study 809-116 the mean absolute change from study 809-115B baseline in BMI was 0.30 kg/m² (95% CI: 0.06 to 0.65) and in BMI z-score was 0.27 (95% CI, 0.05 to 0.48) (161).

Figure 56. Absolute change in BMI-for-age z-score in study 809-115B and study 809-116



Abbreviations: BMI, body mass index
Reference: Hoppe et al. (161)

Table 42. Summary results of studies 809-115B and 809-116

	Study VX15-809-115 Part B (NCT02797132) (162, 245)[1]			Study VX16-809-116 (NCT03125395) (161)[2]		
	Mean absolute change from baseline at Week 24, LUM 100 mg/IVA 125 mg q12h	**Mean absolute change from baseline at Week 24, LUM 150 mg/IVA 188 mg q12h**	**Mean absolute change from baseline at Week 24, total**	**Mean at baseline in study 809-115B (SD)**	**Mean at Week 96 of study 809-116 (SD)**	**Mean absolute change from study 809-115B baseline at Week 96 in study 809-116 (95% CI)**
Primary outcome						
Safety	Table 74			Table 74		
Secondary outcomes						
BMI[3], kg/m^2	[redacted]	[redacted]	0.27 (0.75; 0.07 to 0.47; P= 0.0091); N=57	15.99 (1.05); N=57	16.23 (1.33); N=47	0.30 (–0.06 to 0.65); N=47
BMI-for-age z-score[3]	[redacted]	[redacted]	0.29 (0.57; 0.14 to 0.45; P=0.0003); N=57	0.16 (0.82); N=57	0.42 (0.77); N=47	0.27 (0.05 to 0.48); N=47
Weight[3], kg	[redacted]	[redacted]	1.4 (0.9; 1.2 to 1.7; P<0.0001); N=57	15.6 (2.8); N=57	21.8 (4.2); N=47	6.0 (5.4 to 6.6); N=47
Weight-for-age z-score[3]	[redacted]	[redacted]	0.26 (0.44; 0.15 to 0.38; <0.0001), N=57	–0.08 (0.82); N=57	0.18 (0.83); N=47	0.23 (0.07 to 0.40); N=47
$LCI_{2.5}$ (optional)	[redacted]	[redacted]	–0.58 (1.16; –1.17 to 0.02; P=0.06); N=17	8.81 (1.87); N=22	8.71 (1.65); N=21	–0.20 (–0.99 to 0.60); N=17
$ppFEV_1$	[redacted]	[redacted]	[redacted]	--	--	[redacted]

[1]Data are: mean (SD; 95% CI; P-value within treatment)
[2] Data are mean (SD) or mean (95% CI)
[3]Baseline for 809-116 value was defined as the most recent non-missing measurement before the first dose of study drug was taken in study 809-115B.
In study 809-116 The baseline value for LCI assessments was defined as the most recent non-missing values calculated from the technically acceptable replicates before the first dose of study drug was taken in study 809-115B.
In study 809-116 the optional LCI sub study set included 37 participants in study 809-115B and 31 participants in study 809-116.
In study 809-115 Part B nominal p values are reported.
Calculated from the children with data available at both time points.
Abbreviations: BMI, body-mass index; kg, kilogram; $LCI_{2.5}$, lung clearance index 2.5 (number of lung turnovers required to reduce the end tidal inert gas concentration to 2.5% of its starting value; SD, standard deviation

Table 43. Summary of PEx-related and CF-related hospitalisation endpoints from pooled data from study 809-115B and study 809-116

Study VX15-809-115B and study VX16-809-116 (NCT02797132 & NCT03125395) (167, 245)	
Secondary Endpoint	**N=60**
PEx	
Time-to-first PEx (days), median (1st and 3rd quartiles)	600.0 (98.0, NE)
Number of PEx through study 809-115B and 809-116	
Number of subjects with events	[redacted]
Total number of events	[redacted]
PEx event rate per patient-year (mean [SD])	[redacted]
CF-related Hospitalisations	
Number of CF-related hospitalisations through study 809-115B and 809-116	
Number of subjects with events	[redacted]
Total number of events	[redacted]
CF-related hospitalisations: Event rate per patient-year (mean [SD])	[redacted]

Notes: Number of PEx or CF-related hospitalisations through the cumulative study period normalized by total duration in patient-years for a subject: number of events for the subject/total number of patient-years for the corresponding subject. A patient-year is considered 48 weeks.
Abbreviations: CF, cystic fibrosis; N, total sample size; n: size of subsample; NE, not estimable; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in the first second; SD, standard deviation

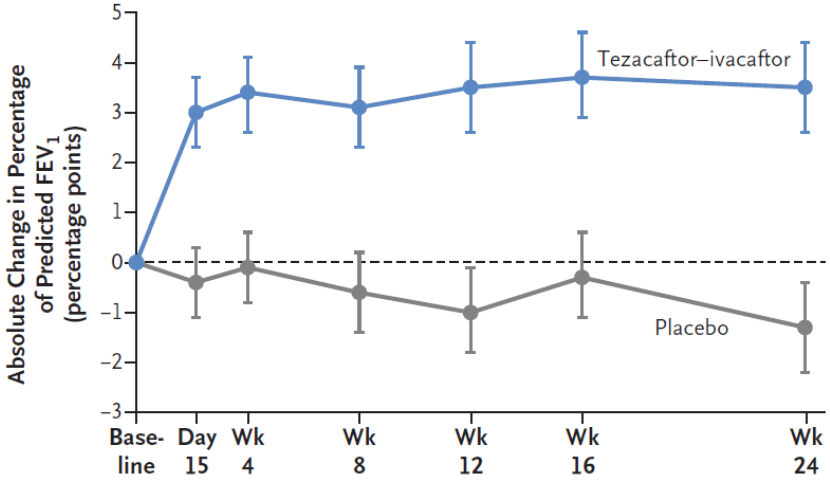
B.2.5.3 TEZ/IVA

B.2.5.3.1 CF patients ≥12 years of age

B.2.5.3.1.1 Study 661-106

In CF patients with F/F genotype, treatment with TEZ/IVA resulted in a significantly greater absolute change from baseline in $ppFEV_1$ than PBO (LS mean difference through 24 weeks, 4.0%; 95% CI: 3.1 to 4.8; P<0.001), with improvements observed as early as Day 15 and maintained through Week 24. Study 661-106 met its primary endpoint, with a LS mean difference between TEZ/IVA and PBO treatment groups in the relative change from baseline in $ppFEV_1$ through Week 24 was 6.8% (95% CI: 5.3 to 8.3; P<0.001) (Figure 57) (157).

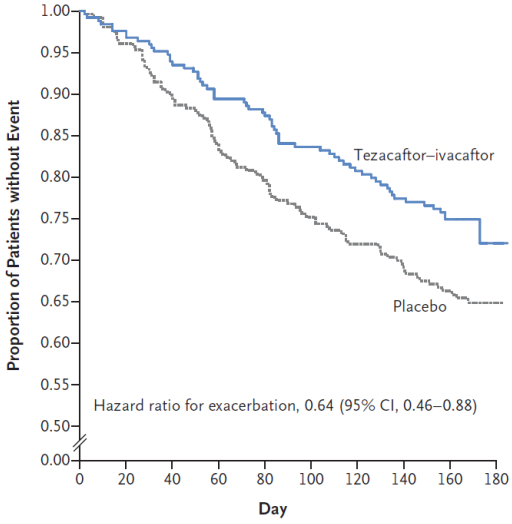
Figure 57. Absolute change from baseline in $ppFEV_1$ – study 661-106



Note: Data are least-squares means, and I bars indicate 95% confidence intervals. The dashed line indicates no change from baseline
Reference: Taylor-Cousar et al. (157)

An annualised estimated event rate of PEx was significantly lower in patients treated with TEZ/IVA than in PBO group (RR: 0.65; 95% CI: 0.48 to 0.88; P=0.005). The rate of PEx that required hospitalisation or treatment with IV antibiotic agents was also lower in the TEZ/IVA group compared to PBO (RR: [redacted]; RR: 0.53; 95% CI: 0.34 to 0.82; [redacted], respectively) (Figure 58) (157, 246).

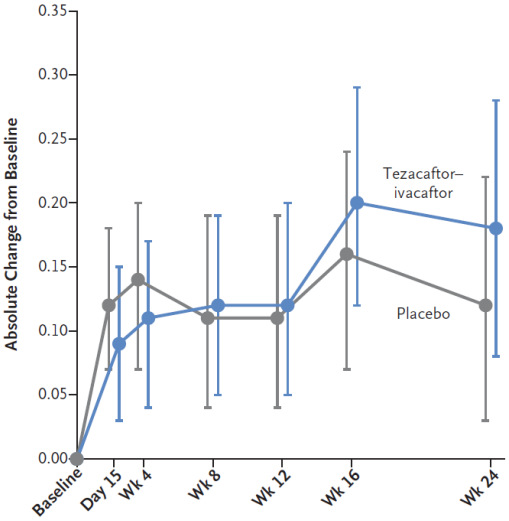
Figure 58. Proportion of patients free from exacerbation events – study 661-106



Reference: Taylor-Cousar et al. (157)

An increase in mean BMI from baseline was observed in both the TEZ/IVA and PBO groups at Week 24 (LS mean increase 0.18; 95% CI: 0.08 to 0.28 and 0.12; 95% CI: 0.03 to 0.22, respectively). Although the LS mean absolute change from baseline in BMI was numerically greater in the TEZ/IVA group than in the PBO group at Week 24, the treatment difference was not statistically significant (P=0.41) (Figure 59) (157).

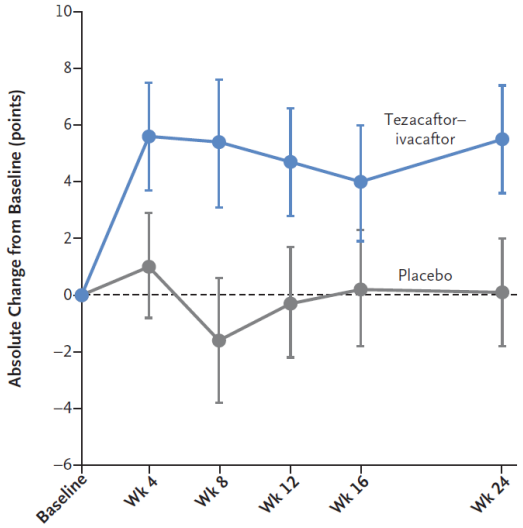
Figure 59. Absolute change from baseline in BMI – study 661-106



Note: data are least-squares means, and I bars indicate 95% confidence intervals.
Reference: Taylor-Cousar et al. (157)

Statistically significant improvement with TEZ/IVA treatment was also observed across all key secondary endpoints. Patients randomised to TEZ/IVA group experienced greater improvement in their CFQ-R RD score compared to those randomised to PBO, with the LS mean between-group difference through Week 24 of 5.1 points (95% CI: 3.2 to 7.0) (Figure 60) (157).

Figure 60. Absolute change from baseline in the respiratory domain score on the CFQ-R – study 661-106



Note: data are least-squares means, and I bars indicate 95% confidence intervals; the dashed line indicates no change from baseline; scores range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status.
Reference: Taylor-Cousar et al. (157)

Summary of the results of efficacy outcomes of study 661-106 are shown in Table 44.

Table 44. Summary results of EVOLVE (study 661-106)

EVOLVE (study VX14-661-106, NCT02347657) (157, 246)			
	TEZ/IVA N=248	**PBO N=256**	**Difference or rate/hazard ratio (95% CI) P Value**
Primary outcome			
Absolute change in $ppFEV_1$ from baseline through Week 24 (95% CI)	3.4 (2.7 to 4.0)	−0.6 (−1.3 to 0.0)	4.0 (3.1 to 4.8) <0.001
Key Secondary outcome			
Relative change in $ppFEV_1$ from baseline through Week 24 (95% CI)	6.3 (5.1 to 7.4)	−0.5 (−1.7 to 0.6)	6.8 (5.3 to 8.3) <0.001
Number of PEx through Week 24	78	122	—
Estimated annualised PEx event rate	0.64 (—)	0.99 (—)	0.65 (0.48 to 0.88)† 0.005
Time-to-first PEx	—	—	[redacted]
Absolute change in BMI from baseline at Week 24 (95% CI), kg/m^2	0.18 (0.08 to 0.28)	0.12 (0.03 to 0.22)	0.06 (−0.08 to 0.19) 0.41
Absolute change in CFQ-R RD score from baseline through Week 24 (95% CI)	5.0 (3.5 to 6.5)	−0.1 (−1.6 to 1.4)	5.1 (3.2 to 7.0) <0.0001‡

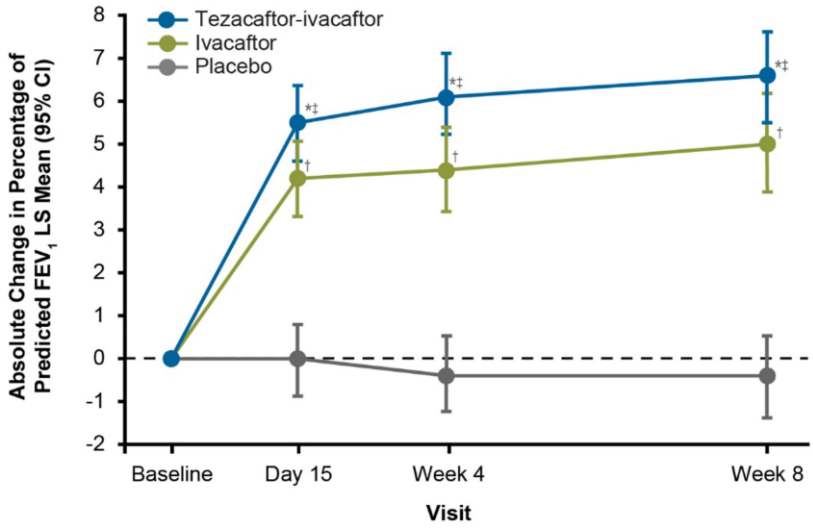
Note: Data are least-squares mean differences (95% CI), except as noted.
†The between-group difference is expressed as a rate ratio. The analysis was based on a negative binomial regression model (48 weeks per year was used to calculate the event rate).
¶[redacted]
‡[redacted]

Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; IVA, ivacaftor; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; TEZ, tezacaftor.

B.2.5.3.1.2 Study 661-108

In CF patients with F/RF genotype, treatment with TEZ/IVA resulted in statistically significant improvement compared to PBO in the absolute change in ppFEV$_1$ (primary endpoint), the study primary endpoint. The LS means treatment differences vs PBO from study baseline to the average of Week 4 and Week 8 of 6.8% (95% CI: 5.7 to 7.8; P<0.001) for TEZ/IVA and 4.7% (95% CI: 3.7 to 5.8; P<0.001) for IVA. These improvements were observed as early as Day 15 and were maintained through Week 8 of treatment (Figure 61) (164).

Figure 61. Absolute change from baseline in ppFEV$_1$ at each visit (MMRM Analysis, FAS) – study 661-108



Note: *P<0.0001 vs PBO and within group; †P<0.0001 vs PBO and within group; ‡P<0.05 TEZ/IVA vs IVA.
Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed-effects models for repeated measures; FEV$_1$, forced expiratory volume in 1 second.
Reference: Rowe et al. (164)

Similarly, for the key secondary endpoint of absolute change in CFQ-R RD score, statistically significant improvements were observed for TEZ/IVA and IVA compared with PBO, with the LS mean changes from study baseline to the average of Week 4 and Week 8 of 11.1 (95% CI: 8.7 to 13.6; P<0.001) and 9.7 (95% CI: 7.2 to 12.2; P<0.001) points for TEZ/IVA and PBO, respectively. The CFQ-R RD data were also analysed in terms of the percentage of patients who achieved a MCID of at least 4 points or more. 65.2% of patients in the TEZ/IVA group achieved the MCID, compared with 58.3% in the IVA group and 32.9% for PBO (164). [redacted]

[redacted] (247).

Results for the secondary endpoint of relative change in $ppFEV_1$ were consistent with the findings from the primary analysis (LS mean treatment difference 11.4; 95% CI: 9.6 to 13.2; P<0.001 and 8.1; 95% CI: 6.3 to 9.9; P<0.001] for TEZ/IVA and IVA vs PBO, respectively) (164).

Although a beneficial effect on PEx and BMI was not expected in this population treated over a short 8-week period, numerical improvements in both outcomes were observed. Treatment with TEZ/IVA was associated with a numerically lower rate of PEx per year compared to PBO (0.34 vs 0.63; RR: 0.54; 95% CI: 0.26 to 1,13; P=0.10). Increases in BMI at Week 8 were observed in both treatment groups and PBO (TEZ/IVA, 0.47 kg/m^2; IVA 0.47 kg/m^2; PBO, 0.18 kg/m^2). However, treatment effects were not statistically significant (164).

Summary of the results of efficacy outcomes of study 661-108 are shown in Table 45.

Table 45. Summary results of EXPAND (study 661-108)

EXPAND (study VX14-661-108, NCT02392234) (164, 247)			
	TEZ/IVA (N=161) vs PBO (N=161) P value	**TEZ/IVA (N=161) vs IVA (N=156) P value**	**IVA (N=156) vs PBO (N=161) P value**
Primary outcome*			
Absolute change in $ppFEV_1$ from baseline to Week 4/8 average (95% CI)	6.8 (5.7 to 7.8) P<0.001	2.1 (1.2 to 2.9) P<0.001	4.7 (3.7 to 5.8) P<0.001
Secondary outcomes*			
Absolute change in CFQ-R RD score from baseline to Week 4/8 average (95% CI)	11.1 (8.7 to 13.6) P<0.001	1.4 (−1.0 to 3.9) P=0.26	9.7 (7.2 to 12.2) P<0.001
Relative change in $ppFEV_1$ from baseline to Week 4/8 average§ (95% CI)	11.4 (9.6 to 13.2) P<0.001	3.3 (1.8 to 4.8) P<0.001	8.1 (6.3 to 9.9) P<0.001
Exploratory outcomes§			
	TEZ/IVA (N=161)	**IVA (N=156)**	**PBO (N=161)**
Number of PEx	11	9	20
Estimated annualised PEx event rate	0.34	0.29	0.63
Rate ratio vs PBO (95% CI)	0.54 (0.26 to 1.13) P=0.10	0.46 (0.21 to 1.01) P=0.05	–
Time-to-first PEx	[redacted]	[redacted]	[redacted]
Absolute change in the BMI from baseline at Week 8, mean (SD), kg/m^2	0.34 [redacted]	0.47 [redacted]	0.18 [redacted]

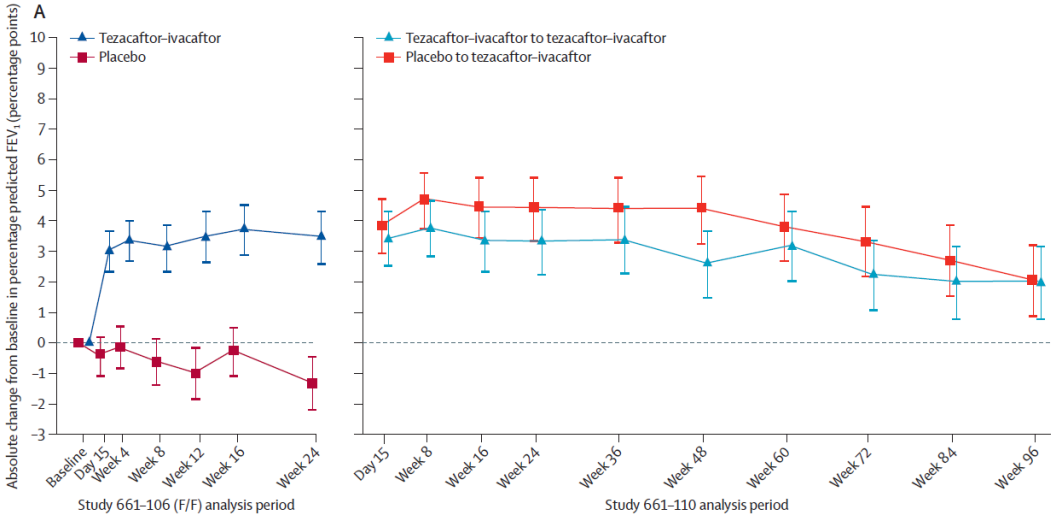
*Data are least-squares mean differences (95% CI); §Gatekeeping approach not applied to analyses of these endpoints, so no statistical significance can be claimed
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; IVA, ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; TEZ, tezacaftor.

B.2.5.3.1.3 Study 661-110

Patients with F/F genotype (enrolled from parent study 661-106, EVOLVE)

In the 106/110 (F/F) efficacy set, the improvement in ppFEV$_1$ in patients continuing treatment with TEZ/IVA was maintained through Week 96 in this OLE study, with the LS mean absolute change from baseline at Week 96 of 2.0% (95% CI: 0.7 to 3.2). Patients who received PBO in study 661-106 and transitioned to treatment with TEZ/IVA showed an increase in ppFEV$_1$ of a magnitude similar to that in those treated with TEZ/IVA in the parent study: the LS mean absolute change from baseline at Week 96 in ppFEV$_1$ was 2.1% (95% CI: 0.8 to 3.3) (Figure 62) (222). These data provide evidence supporting the sustained and consistent benefits of TEZ/IVA.

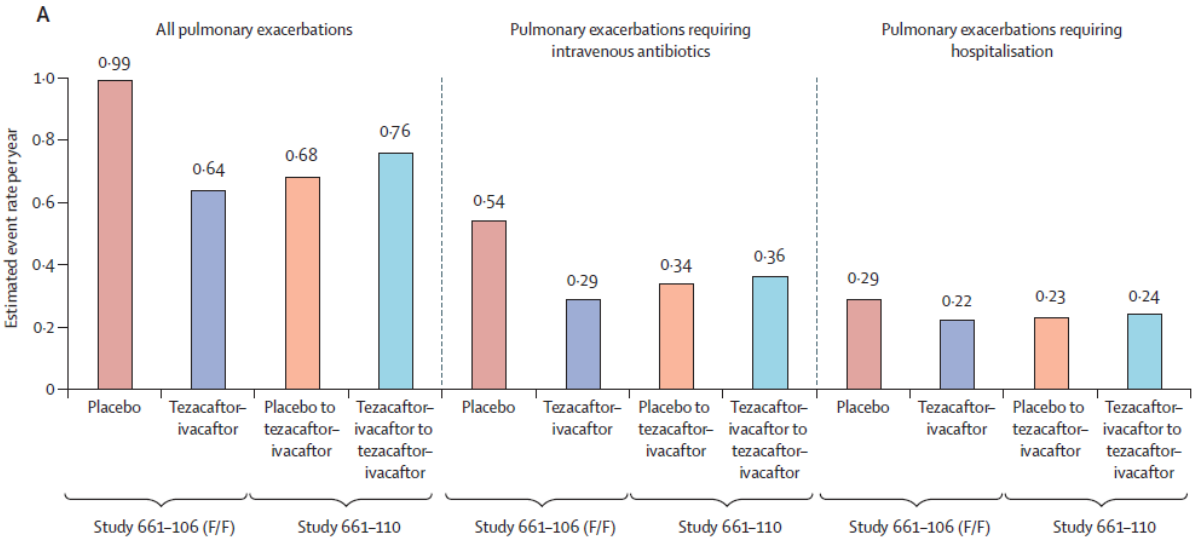
Figure 62. Absolute change from baseline in ppFEV$_1$ – study 661-110 (F/F)



Note: Datapoints are least squares mean and error bars are 95% CIs; the dashed line indicates no change from baseline; ppFEV$_1$ calculated using Wang and Hankinson equations; data from the PBO and TEZ/IVA groups in the 661-106 (F/F) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

Patients who transitioned from PBO to TEZ/IVA treatment showed reductions in PEx rates comparable to those observed in the TEZ/IVA group in study 661-106. For these patients, the estimated annualised event rates were 0.68 (95% CI: 0,55 to 0.83) for all PEx, 0.34 (95% CI: 0.25 to 0.44) for PEx requiring IV antibiotics and 0.23 (95% CI: 0.16 to 0.32) for PEx requiring hospitalisation. In the TEZ/IVA to TEZ/IVA group, these estimated annualised event rates were 0.76 (95% CI: 0.63 to 0.92), 0.36 (95% CI: 0.28 to 0.47), and 0.24 (95% CI: 0.18 to 0.32). The improvements in PEx rates observed in the parent study were generally maintained in this group of patients in study 661-110 (Figure 63) (222).

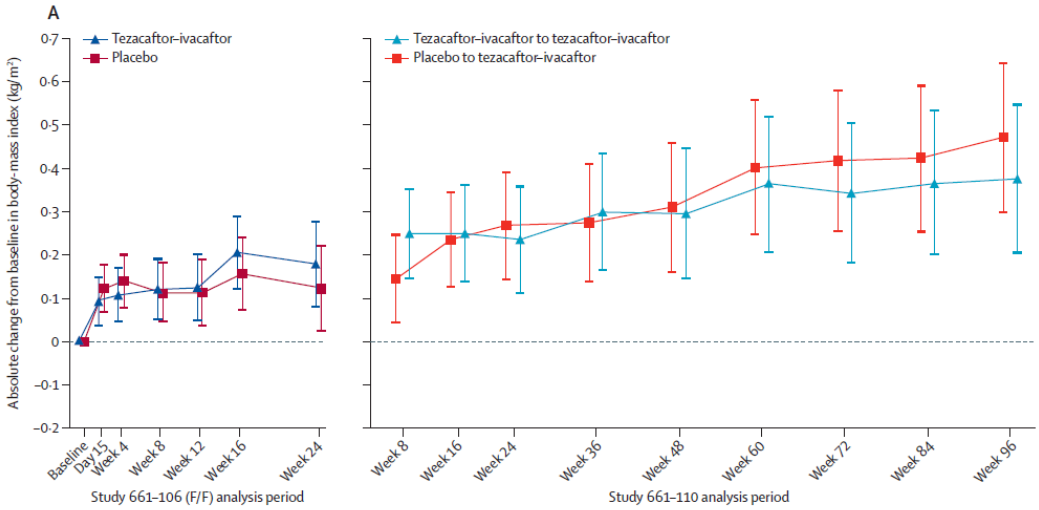
Figure 63. Pulmonary exacerbation rates – study 661-110 (661-106 [F/F] parent study)



Note: Annualised PEx rate was calculated based on 48 weeks in a year; PEx event rates in the PBO and TEZ/IVA groups in the 661-106 (F/F) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

Increases in BMI observed in the parent study were generally maintained during the treatment period, with observed LS means absolute changes from baseline at Week 96 of 0.47 (05% CI: 0.30 to 0.65) and 0.38 (95% CI: 0.20 to 0.55) in the PBO to TEZ/IVA and TEZ/IVA to TEZ/IVA treatment groups, respectively (Figure 64) (222).

Figure 64. Absolute change from baseline in BMI – study 661-110 (F/F)

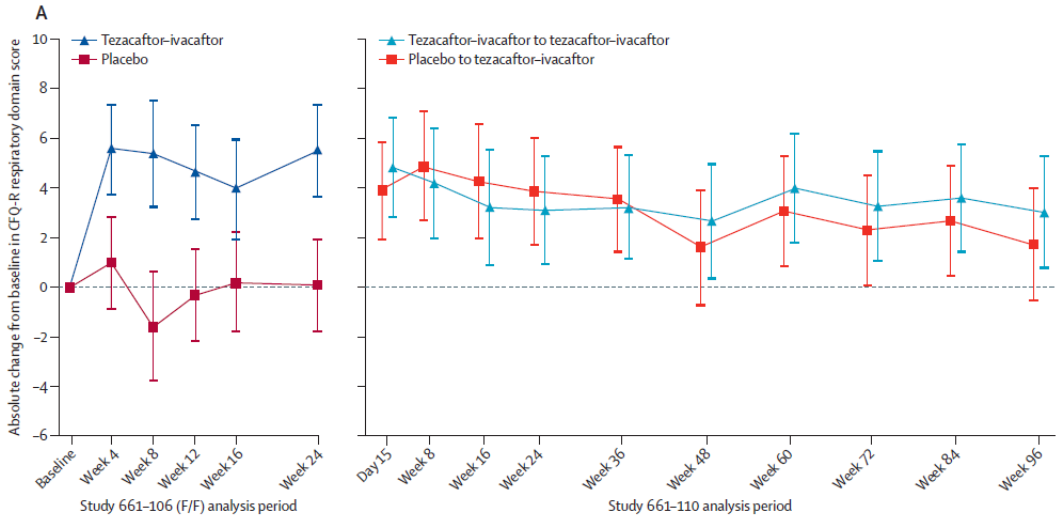


Note: Datapoints are least squares mean and error bars are 95% Cis; the dashed line indicates no change from baseline; data from the PBO and TEZ/IVA groups in the 661-106 (F/F) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

Patients who received PBO in study 661-106 and transitioned to TEZ/IVA in study 661-110 showed an improvement in CFQ-R RD with similar magnitude to the improvement observed in TEZ/IVA group in the parent study, with the LS mean absolute change from baseline in CFQ-R RD score at Week 96 of 1.7 (95% CI: −0.6 to 4.0). Improvements in CFQ-R RD scores

observed in TEZ/IVA group were generally maintained through Week 96 in study 661-110. The LS mean absolute change from baseline in CFQ-R RD score at Week 96 observed in this treatment group was 3.0 (95% CI: 0.7 to 5.3) (Figure 65) (222).

Figure 65. Absolute change from baseline in CFQ-R respiratory domain score – study 661-110 (F/F)

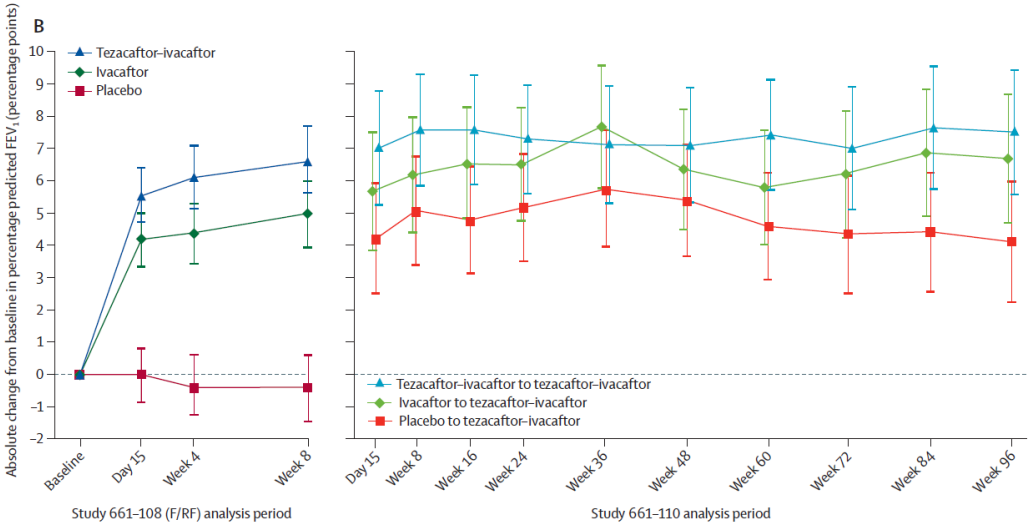


Note: Datapoints are least squares mean and error bars are 95% CIs; the dashed line indicates no change from baseline; data from the PBO and TEZ/IVA groups in the 661-106 (F/F) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Abbreviations: CFQ-R, cystic fibrosis questionnaire—revised.
Reference: Flume et al. (222)

Patients with F/RF genotype (enrolled from parent study 661-108, EXPAND)

In the 108/110 (F/RF) efficacy set, improvements in ppFEV$_1$ were maintained through Week 96 in patients who received IVA in study 661-108 and transitioned to TEZ/IVA and patients who continued TEZ/IVA from the parent study to study 661-110. The LS mean absolute change from baseline in ppFEV$_1$ at 96 weeks was 6.7% (95% CI: 4.7 to 8.7) and 7.5% (95% CI: 5.6 to 9.4) in the IVA to TEZ/IVA and TEZ/IVA to TEZ/IVA group, respectively. Patients in the PBO to TEZ/IVA group showed acute improvements in ppFEV$_1$ consistent with those observed in TEZ/IVA-treated patients in study 661-108, and improvements were generally maintained over the 96-week OLE: the LS mean absolute change from baseline at 96 weeks was 4.1% (95% CI: 2.2 to 6.0) (Figure 66) (222).

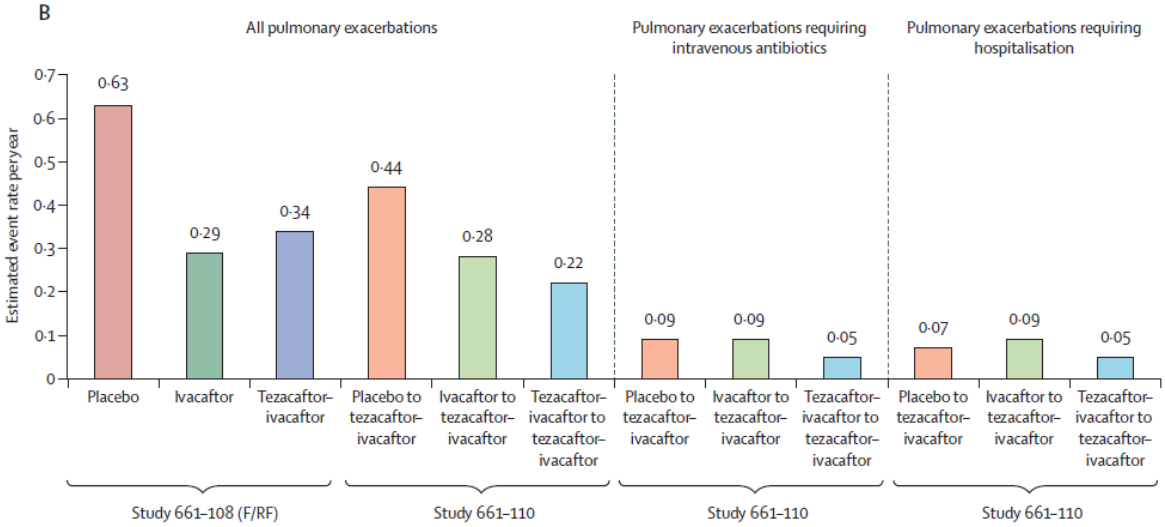
Figure 66. Absolute change from baseline in ppFEV$_1$ – study 661-110 (F/RF)



Note: Datapoints are least squares mean and error bars are 95% Cis; the dashed line indicates no change from baseline; ppFEV$_1$ calculated using Wang and Hankinson equations; data from the PBO, IVA, and TEZ/IVA groups in the 661-108 (F/RF) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

PEx rates in the TEZ/IVA groups in study 661-110 were numerically lower than the PBO group and comparable to those observed in the TEZ/IVA group in the parent study. In the 108/110 PEx analysis set (F/RF), the estimated annualised event rates were 0.44 (95% CI: 0.29 to 0.66) for all PEx, 0.09 (95% CI: 0.04 to 0.22) for PEx requiring IV antibiotics, and 0.07 (95% CI: 0.03 to 0.18) for PEx requiring hospital admission in the PBO to TEZ/IVA treatment group. In the IVA to TEZ/IVA group, the estimated annualised event rates for all PEx, PEx requiring antibiotics, and PEx requiring hospitalisation were 0.28 (95% CI: 0.18 to 0.44), 0.09 (95% CI: 0.04 to 0.22) and 0.09 (95% CI: 0.04 to 0.22), respectively, while patients in the TEZ/IVA to TEZ/IVA group, annually experienced 0.22 (95% CI: 0.14 to 0.35), 0.05 (95% CI: 0.02 to 0.13), and 0.05 (95% CI: 0.02 to 0.13) episodes of same PEx-related events (Figure 67) (222).

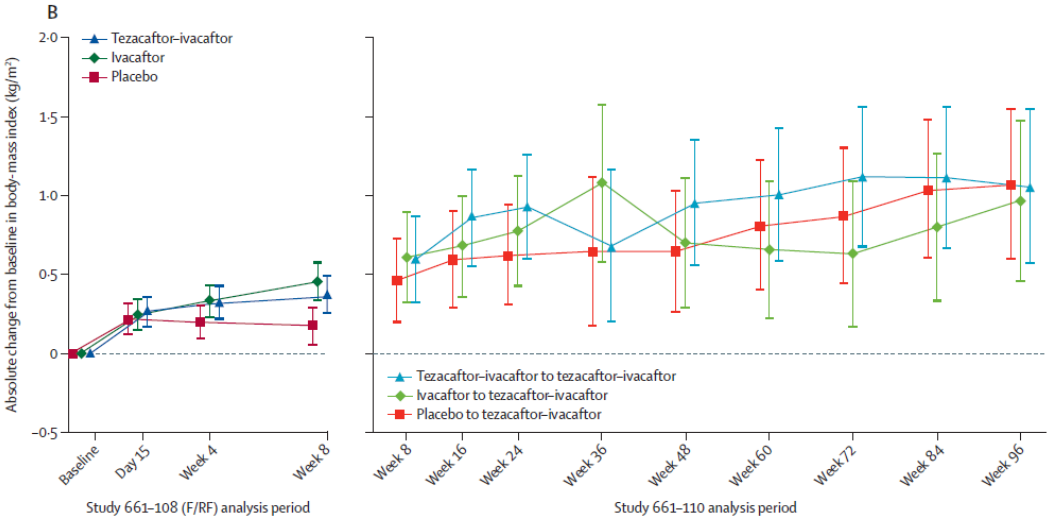
Figure 67. Pulmonary exacerbation rates – study 661-110 (F/RF)



Note: Annualised PEx rate was calculated based on 48 weeks in a year; PEx event rates in the PBO, IVA, and TEZ/IVA groups in the 661-108 (F/RF) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

Increases in BMI observed in the parent study were generally maintained during the treatment period, with observed LS means absolute changes from baseline at Week 96 of 0.96 (95% CI: 0.45 to 1.47), 1.05 (95% CI: 0.56 to 1.55), and 1.07 (95% CI: 0.59 to 1.55) in the IVA to TEZ/IVA, TEZ/IVA to TEZ/IVA and PBO to TEZ/IVA treatment groups, respectively (Figure 68) (222).

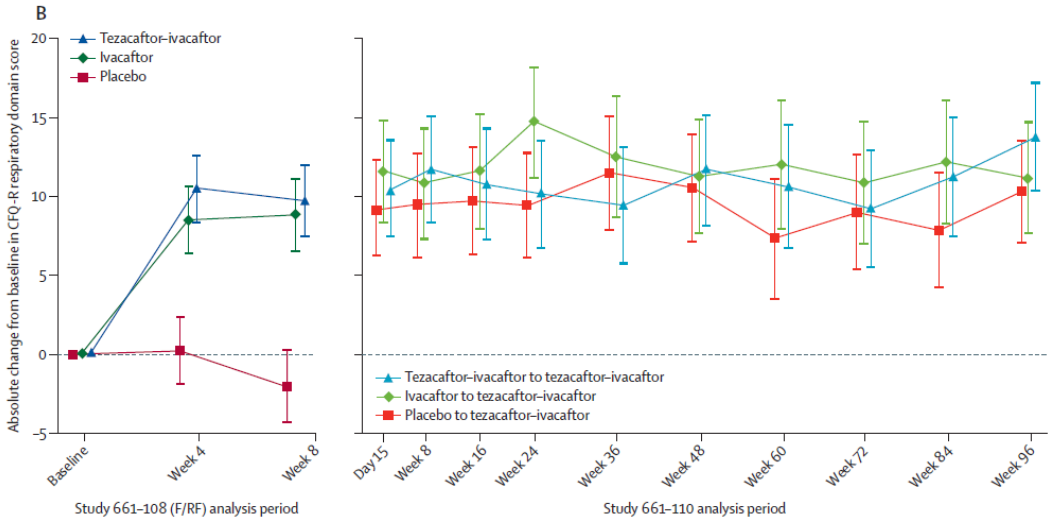
Figure 68. Absolute change from baseline in BMI – study 661-110 (F/RF)



Note: Datapoints are least squares mean and error bars are 95% CIs; the dashed line indicates no change from baseline; data from the PBO, IVA, and TEZ/IVA groups in the 661-108 (F/RF) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Reference: Flume et al. (222)

In the 108/110 (F/RF) efficacy set, patients who received PBO in study 661-108 showed an improvement in CFQ-R RD score consistent with those seen in the parent study. In the IVA to TEZ/IVA and TEZ/IVA to TEZ/IVA groups, improvements in CFQ-R RD at Week 96 were numerically higher than those observed at the end of study 661-108. The LS mean change from baseline in CFQ-R RD at Week 96 was 10.3 (95% CI: 7.0 to 13.6), 11.2 (95% CI: 7.7 to 14.7) and 13.8 (95% CI: 10.3 to 17.2) in the PBO to TEZ/IVA, IVA to TEZ/IVA and TEZ/IVA-TEZ/IVA groups, respectively (Figure 69) (222).

Figure 69. Absolute change from baseline in CFQ-R respiratory domain score – study 661-110 (F/RF)



Note: Datapoints are least squares mean and error bars are 95% CIs; the dashed line indicates no change from baseline; data from the PBO, IVA, and TEZ/IVA groups in the 661-108 (F/RF) parent study are shown only for visual comparison; statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.
Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised.
Reference: Flume et al. (222)

Summary of the results of efficacy outcomes of study 661-110 are shown in Table 46.

Table 46. Summary results of EXTEND OLE (study 661-110)

EXTEND OLE (study VX14-661-110, NCT02565914) (222)					
	106/110 F/F (parent study 661-106)		**108/110 F/RF (parent study 661-108)**		
	PBO to TEZ/IVA*	**TEZ/IVA to TEZ/IVA***	**PBO to TEZ/IVA***	**IVA to TEZ/IVA***	**TEZ/IVA to TEZ/IVA***
Primary outcome					
Safety and tolerability	Table 75				
Secondary outcomes[a]					
Absolute change in $ppFEV_1$ from baseline at Week 96 (95% CI)	2.1 (0.8 to 3.3) n=187	2.0 (0.7 to 3.2) n=194	4.1 (2.2 to 6.0) n=68	6.7 (4.7 to 8.7) n=61	7.5 (5.6 to 9.4) n=67
Relative change in $ppFEV_1$ from baseline at Week 96 (95% CI)	4.3 (2.1 to 6.5) n=187	4.2 (2.0 to 6.4) n=194	7.9 (4.7 to 11.1) n=68	11.6 (8.2 to 15.0) n=61	13.0 (9.7 to 16.2) n=67
Estimated annualised PEx event rate (95% CI)[b]	0.68 (0.55 to 0.83) n=231	0.76 (0.63 to 0.92) n=248	0.44 (0.29 to 0.66) n=81	0.28 (0.18 to 0.44) n=74	0.22 (0.14 to 0.35) n=78
Time to first PEx (Kaplan-Meier estimate of event-free probability) (95% CI)	0.470 (0.402 to 0.535) n=231	0.438 (0.374 to 0.501) n=248	0.497 (0.383 to 0.601) n=81	0.493 (0.372 to 0.603) n=74	0.639 (0.519 to 0.737) n=78
Absolute change in BMI from baseline at Week 96 (95% CI), kg/m^2	0.47 (0.30 to 0.65) n=195	0.38 (0.20 to 0.55) n=208	1.07 (0.59 to 1.55) n=75	0.96 (0.45 to 1.47) n=65	1.05 (0.56 to 1.55) n=68
Absolute change in CFQ-R RD score from baseline at Week 96 (95% CI)	1.7 (−0.6 to 4.0) n=196	3.0 (0.7 to 5.3) n=208	10.3 (7.0 to 13.6); n=74	11.2 (7.7 to 14.7) n=65	13.8 (10.3 to 17.2) n=68

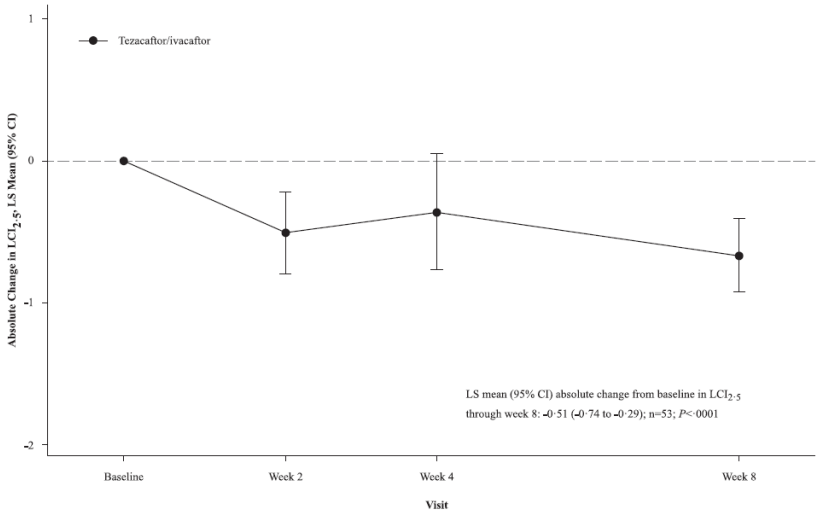
Note: Results are LS mean absolute change (95% CI), except as noted; *Calculated from parent study baseline; [a]**Study 661-106 (F/F)** was a PBO-controlled, parallel design study; study 661-110 was an open-label TEZ/IVA extension study in participants from study 661-106 (F/F) and others. For efficacy analyses of participants in the 106/110 Efficacy Set (F/F) who were randomised to PBO in study 661-106 (F/F), baseline was defined as the most recent non-missing measurement before the first dose of study drug in study 661-110; for participants randomised to TEZ/IVA in study 661-106 (F/F), baseline was defined as the most recent non-missing measurement before the first dose of study drug in study 661-106 (F/F); PEx and time-to-first PEx were analysed for the PEx Analysis Set (F/F). **Study 661-108 (F/RF)** was a PBO-controlled crossover design study; study 661-110 was an open-label TEZ/IVA extension study in participants in study 661-108 (F/RF) and others. For efficacy analyses of participants in the 108/110 Efficacy Set (F/RF), baseline was defined as the most recent non-missing measurement before the first dose of study drug in study 661-108 (F/RF). The number of participants in study 661-108 (F/RF) was approximately twice as large as the number who transitioned into study 661-110 due to the crossover design of study 661-108 (F/RF); PEx and time-to-first PEx were analysed for the PEx Analysis Set (F/F). [b]Annualised PEx rate was calculated based on 48 weeks in a year.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire–revised; CI, confidence interval; F/F, homozygous for the *F508del-CFTR* mutation; F/RF, heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein; IVA, ivacaftor; LS, least-squares; PBO, placebo; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted expiratory volume in 1 second; RD, respiratory domain; TEZ, tezacaftor.

B.2.5.3.2 CF patients aged 6 to 11 years

B.2.5.3.2.1 Study 661-115

A statistically significant improvement was observed in the primary efficacy endpoint of absolute change in $LCI_{2.5}$ from baseline through Week 8 in the CF patients aged 6 to 11 years with F/F or F/RF genotype randomised to TEZ/IVA group (within-group change from baseline LS mean −0.51 (95% CI: −0.74 to −0.29; P<0.001). Since the upper bound of the 95% CI (−0.29) was below the prespecified maximum PBO effect of −0.10, the primary endpoint met the predefined requirement for success (Figure 70) (165).

Figure 70. Absolute change from baseline in $LCI_{2.5}$ at each visit in the TEZ/IVA group – study 661-115

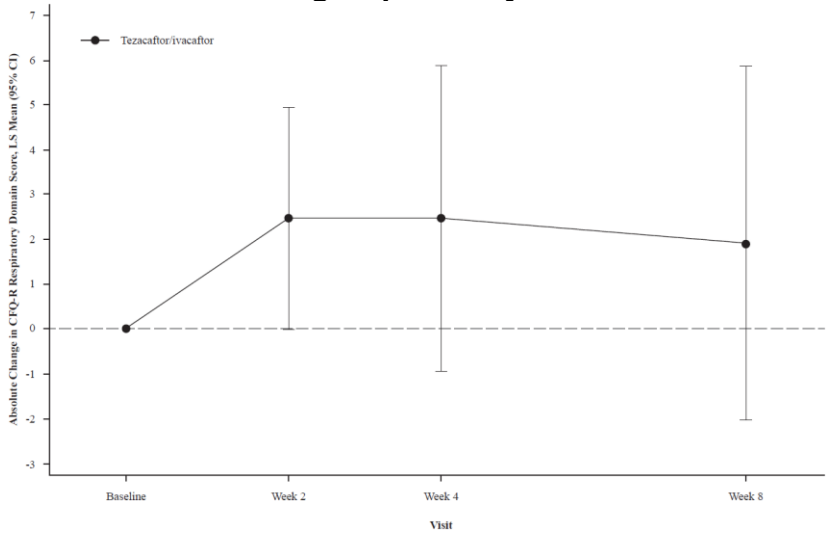


Note: The y-axis corresponds to the LS means from the MMRM model analysis with all measurements up to Week 8, including those for on-treatment and after-treatment discontinuation. Baseline is the most recent non-missing measurement before the first dose of the study drug. The MMRM included visit, baseline $LCI_{2.5}$, and genotype group (F/F vs F /RF) as covariates.
Abbreviations: CI, confidence interval; $LCI_{2.5}$, lung clearance index 2.5; LS, least-squares; MMRM, mixed model of repeated measures.
Reference: Davies et al. (165)

Secondary endpoints relevant for this submission consisted of absolute change in CFQ-R RD score and in $ppFEV_1$ from baseline through Week 8, and absolute change in BMI from baseline at Week 8.

Treatment with TEZ/IVA resulted in a numerical increase in the mean CFQ-R RD score from baseline through Week 8 (LS mean absolute change from baseline 2.3 points; 95% CI: -0.1 to 4.6], nominal P=0.0546) (Figure 71) (165).

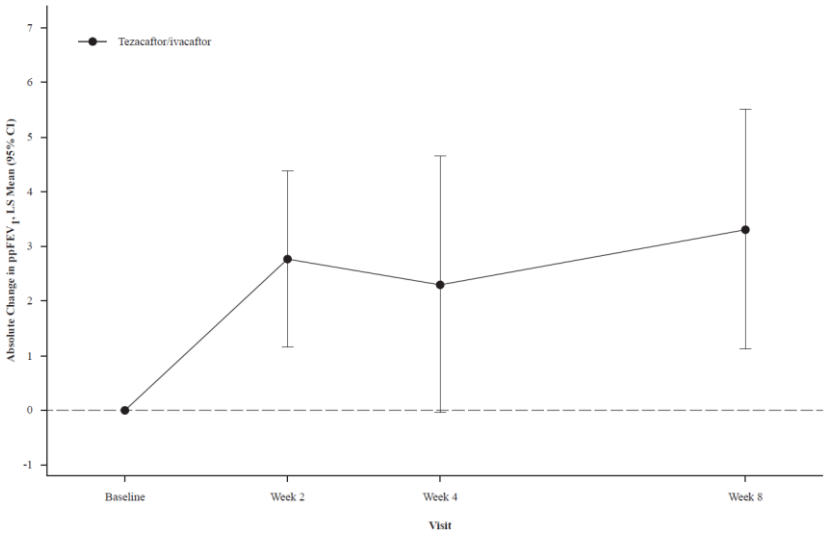
Figure 71. Absolute change from baseline in CFQ-R respiratory domain score (child's version) at each visit in the TEZ/IVA group – study 115



Note: The y-axis corresponds to the LS means from the MMRM model analysis with all measurements up to Week 8, including those for on-treatment and after-treatment discontinuation. Baseline is the most recent non-missing measurement before the first dose of the study drug. The MMRM included visit, baseline $LCI_{2.5}$, baseline CFQ-R respiratory score, and genotype group (F/F vs F/RF) as covariates.
Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; LS, least-squares; MMRM, mixed model of repeated measures.
Reference: Davies et al. (165)

Despite having a mean baseline $ppFEV_1$ within the normal range, children treated with TEZ/IVA experienced a 2.8% increase (95% CI: 1.0 to 4.6; nominal P=0.0024) in $ppFEV_1$ through 8 weeks of treatment (Figure 72) (165).

Figure 72. Absolute change from baseline in $ppFEV_1$ at each visit in the TEZ/IVA group – study 115



Note: The y-axis corresponds to the LS means from the MMRM model analysis with all measurements up to Week 8, including those for on-treatment and after-treatment discontinuation. Baseline is the most recent non-missing measurement before the first dose of the study drug. The MMRM included visit, baseline $LCI_{2.5}$, baseline $ppFEV_1$, and genotype group (F/F vs F/RF) as covariates.
Abbreviations: CI, confidence interval; LS, least-squares; MMRM, mixed model of repeated measures; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.
Reference: Davies et al. (165)

BMI remained stable over the 8 weeks of TEZ/IVA treatment. At Week 8, the mean absolute change from baseline was -0.04 kg/m^2 (SD, 0.43) (165).

Summary of the results of efficacy outcomes of study 661-115 are shown in Table 47.

Table 47. Summary results of EMBRACE (study 661-115)

EMBRACE (study VX16-661-115, NCT03559062)[a,b] (165)		
	TEZ/IVA n=54	**p value**
Primary outcome		
Absolute change in $LCI_{2.5}$ from baseline through Week 8 (95% CI)[e]	−0.51 (−0.74 to −0.29)[c]	<0.0001[d]
Key secondary outcomes		
Absolute change in CFQ-R RD (child's version) score from baseline through Week 8 (95% CI)[e]	2.3 (−0.1 to 4.6)[c]	0.0546
Additional secondary outcomes		
Absolute change in $LCI_{5.0}$ from baseline through Week 8 (95% CI)[e]	−0.30 (−0.39 to −0.20)[c]	<0.0001[d]
Absolute change in $ppFEV_1$ from baseline through Week 8 (95% CI)[e]	2.8 (1.0 to 4.6)[c]	0.0024[d]
Absolute change in BMI from baseline at Week 8 (SE), kg/m^2[f]	−0.04 (0.43)[d]	N/A
Note: Results are LS mean within-group change (95% CI) for endpoints presented with the MMRM approach and mean within-group change (SD) for endpoints presented with summary statistics; [a]Baseline was the most recent non-missing measurement before the first dose of the study drug; [b]P values for secondary and additional endpoints were considered nominal. There were no corrections for multiple hypothesis testing; [c]The LS mean and 95% CIs were obtained from an MMRM. This model included visit, baseline $LCI_{2.5}$ (or $LCI_{5.0}$ for the $LCI_{5.0}$ endpoint), and genotype group (F/F vs F/RF) as covariates. Models for CFQ-R RD score and $ppFEV_1$ also included baseline of each respective endpoint as a covariate; [d]Based on 53 participants; [e]Endpoints presented with the MMRM approach; [f]Endpoints presented with summary statistics. Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; $LCI_{5.0}$, lung clearance index 5.0; LS, least-squares; MMRM, mixed model of repeated measures; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; RD, respiratory domain; TEZ, tezacaftor.		

B.2.5.4 Real-world evidence

Outcomes of real-world studies that were either applied directly in the economic model or validated trial-based model inputs are described in this section.

B.2.5.4.1 Study VX20-CFD-004 (MAGNIFY)

Clinical manifestations of CF lead to impaired mental and physical HRQoL for pwCF, as well as their families and caregivers (115, 136-138). The Interim Part A and Part B, analyses of pwCF HRQoL include [redacted], respectively, whose CFQ-R scores are collected at baseline and in the post-baseline period. These data, however, are not used in the cost-effectiveness analysis due to lack of stratification by severity of lung disease and are therefore not discussed further.

Care-Related Quality of Life (CarerQoL) is a validated instrument for measuring care-related quality of life in informal caregivers which combines a questionnaire encompassing seven dimensions of burden related to a specific aspect of caregiving with a valuation component (a VAS scale for well-being) (248). In study VX20-CFD-004, CarerQoL-7D was used to measure and value the impact of providing informal care on caregivers of pwCF aged 6-11 years treated with LUM/IVA, TEZ/IVA or IVA/TEZ/ELX.

[redacted] (Table 48) (230).

[redacted] (Table 48) (230). [redacted] Summary of the results is shown in Table 48.

Table 48. Summary results of CarerQoL-7D from MAGNIFY (study VX20-CFD-004)

MAGNIFY (study VX20-CFD-004) (230)		
	Part A[a] LUM/IVA or TEZ/IVA [redacted]	**Part B[b] IVA/TEZ/ELX** [redacted]
Outcome		
Average CarerQoL-7D utility score, mean (SD)	[redacted]	[redacted]
Time frame	Through Part A Study Period	Through Part B Post-Baseline Period
Absolute change in CarerQoL-7D utility score from baseline, mean (SD)	NR	[redacted]
Notes: [redacted]		

Abbreviations: CarerQol, care-related quality of life instrument; ELX, elexacaftor; IA, interim analysis; IVA, ivacaftor; NR, not reported; SD, standard deviation; TEZ, tezacaftor.

B.2.5.4.2 Study VX20-CFD-005 (TRAJECTORY)

[redacted] (Table 49) (231, 249).

Table 49. Summary results of CFQ-R from TRAJECTORY (study VX-20-CFD-005)

Efficacy results	TRAJECTORY (VX20-CFD-005) (231, 249)			
Age group	[redacted]			
Genotype	[redacted]			
Disease severity	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
CFQ-R Respiratory Domain Score at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
CFQ-R Respiratory Domain Score absolute change from baseline, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) CFQ-R-8D utility score at baseline	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFQ-R-8D, Cystic Fibrosis Questionnaire – Revised 8 dimensions; CFQ-R, Cystic Fibrosis Questionnaire – Revised; CI, confidence interval; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation.

B.2.5.4.3 UKCFR Study

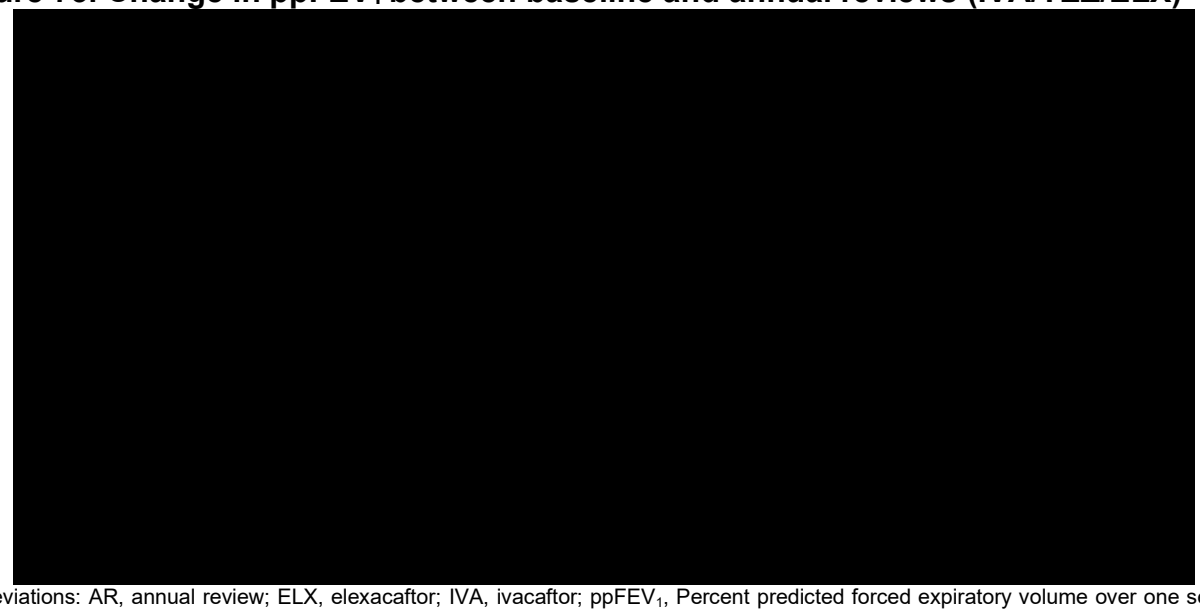
Primary objective 2: Progression in $ppFEV_1$

[redacted] (Table 50)[redacted].

Primary objective 1: Rate of change in $ppFEV_1$ over time

[redacted] Error! Reference source not found. [redacted] Error! Reference source not found.(8).

Figure 73. Change in ppFEV$_1$ between baseline and annual reviews (IVA/TEZ/ELX)



Abbreviations: AR, annual review; ELX, elexacaftor; IVA, ivacaftor; ppFEV$_1$, Percent predicted forced expiratory volume over one second; TEZ, tezacaftor.
Reference: Vertex, Data on File (8)

Figure 74. Change in ppFEV$_1$ between baseline and annual reviews (H-CFTRm-naïve)

Abbreviations: H-CFTRm-naïve, historic cystic fibrosis transmembrane regulator modulator naïve cohort; ppFEV$_1$, Percent predicted forced expiratory volume over one second; TEZ, tezacaftor.
Reference: Vertex, Data on File (8)

[redacted]

Figure 75. Mixed effects linear regression before and after IVA/TEZ/ELX treatment initiation

Reference: Vertex, Data on File (8)

Primary objective 4: annualised PEx rate

[redacted] (Table 50) (8, 250).

Primary objective 5: discontinuation rates

[redacted] Table 50 [redacted]

[redacted]

Exploratory objective 14: change in CFQ-R domain scores from baseline

[redacted]Figure 76) (8).

Figure 76. Change from baseline in CFQ-R scores per domain in IVA/TEZ/ELX patients

[redacted]

Reference: Vertex, data on file (8)

Exploratory objective 11: Prevalence of lung infections

Prevalence of lung infections at baseline and annual reviews 1, 2 and 3 post-index are shown in Figure 77, Figure 78 and Figure 79. A[redacted]

Figure 77. IVA/TEZ/ELX lung infection prevalence

Reference: Vertex, Data on File (8)

Figure 78. LUM/IVA lung infection prevalence

Reference: Vertex, Data on File (8)

Figure 79. TEZ/IVA lung infection prevalence

Reference: Vertex, Data on File (8)

Table 50. Summary results of the UKCFR study

UKCFR Study (8)					
			IVA/TEZ/ELX	LUM/IVA	TEZ/IVA
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]		[redacted]	[redacted]	[redacted]

UKCFR Study (8)			
	IVA/TEZ/ELX	LUM/IVA	TEZ/IVA
[redacted]	[redacted]	[redacted]	[redacted]

B.2.5.4.4 Data Collection Agreement compliance rate report

Objective: real-world CFTRm compliance rates

The real-world compliance rate of CFTRm was collected as part of the DCA. [redacted]

B.2.6 Subgroup analysis

The clinical effectiveness inputs in the cost-effectiveness analyses of CFTRms in CF patients were derived from FAS (full analysis set) populations of the relevant studies comprising all patients that received at least one dose of drug under study. This was the most statistically robust approach since none of the studies were powered to evaluate the treatment effect in subgroups. With many subgroup analyses carried out without adjusting the overall significance level of the trial, any p values associated with treatment effects in subgroups are considered nominal and may represent spurious findings. Given that the efficacy endpoint results for the subgroups were generally consistent with the FAS analyses, only the FAS population of each trial was considered in the economic analysis.

B.2.6.1 IVA/TEZ/ELX

Details of subgroup analyses carried out in the relevant IVA/TEZ/ELX studies as well as details of the statistical tests used, are described in Table 51 and Table 52. Results of these subgroup analyses are further described in Appendix E.

Subgroup analyses were conducted to explore clinical heterogeneity in the efficacy of the treatment with IVA/TEZ/ELX with respect *CFTR* genotype and known effect modifiers in both age groups: patients aged ≥12 years (study 445-102, study 445-103, study 445-105 IA4, study 445-104), and in patients aged 6 to 11 years (study 445-106 Part B, study 445-107, study 445-116) (Table 51 and Table 52).

B.2.6.1.1 CF patients ≥12 years of age

Table 51. Summary of subgroup analyses carried out in IVA/TEZ/ELX studies, ≥12 years

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 194, 252)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 253)	AURORA OLE (study 445-105) (188)	AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168, 254)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (191)
Pre-planned or post-hoc	Pre-planned, ad-hoc	Pre-planned, post-hoc	[redacted]	Pre-planned, post-hoc	[redacted]
Subgroup analysis	Pre-specified subgroup analyses were conducted for the primary efficacy endpoint [redacted] (absolute change in $ppFEV_1$ from	Prespecified subgroup analyses were performed for the primary efficacy endpoint (absolute change in $ppFEV_1$ from baseline at Week 4). An additional post-	[redacted]	Pre-planned subgroup analyses were conducted for the primary endpoint (absolute change in $ppFEV_1$ from baseline through Week 8 for the IVA/TEZ/ELX	[redacted]

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 194, 252)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 253)	AURORA OLE (study 445-105) (188)	AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168, 254)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (191)
	baseline through Week 4 and Week 24, respectively). Additional ad-hoc analyses for the primary efficacy endpoint [redacted], by genotype subgroup and in patients with $ppFEV_1$ <40% at baseline were conducted	hoc subgroup analysis was conducted for SwCl	[redacted]	group). Additional post-hoc subgroup analyses were performed for between group comparison of $ppFEV_1$, within and between group comparison of SwCl and CFQ-R RD score, according to genotype subgroup (F/RF vs F/G) using a similar MMRM	[redacted]
Analysed subgroups	**Pre-specified analyses:** • Age at screening (≥12 to <18 years, ≥18 years) • $ppFEV_1$ at baseline (<70%, ≥70%) • Sex (male, female) • Geographic region (North America, Europe/Australia) • Prior use of inhaled antibiotic (yes, no) • Prior use of dornase alfa (yes, no) • Prior use of inhaled bronchodilator (yes, no) • Prior use of inhaled hypertonic saline (yes, no) • Prior use of inhaled corticosteroids (yes, no) • Prior use of azithromycin (yes, no) • Infection with *Pseudomonas aeruginosa* within 2 years before screening (positive, negative) **Ad-hoc analyses:** • Genotype (class I, missense and in-frame deletions) • $ppFEV_1$ <40% at baseline	**Pre-specified analyses:** • Age at the Screening Visit (<18, ≥18 years) • $ppFEV_1$ at baseline (<70, ≥70) • Sex (male, female) • Geographic region (North America, Europe) • Prior use of inhaled antibiotic before the first dose of study drug in the Treatment Period (Yes, No) • Prior use of dornase alfa before the first dose of study drug in the Treatment Period (Yes, No) • Prior use of inhaled bronchodilator before the first dose of study drug in the Treatment Period (Yes, No) • Prior use of inhaled hypertonic saline before the first dose of study drug in the Treatment Period (Yes, No) • Prior use of inhaled corticosteroids before the first dose of study drug in the Treatment Period (Yes, No) • Prior use of azithromycin before the first dose of study drug in the Treatment Period (Yes, No) • Infection with Pseudomonas aeruginosa within 2 years prior to screening (Positive, Negative) **Post-hoc analysis:** • Age at the Screening Visit (<18, ≥18 years) • $ppFEV_1$ at baseline (<70, ≥70) • Sex (male, female) • Prior use of CFTR modulator	[redacted]	**Pre-planned analyses:** • Age at screening (<18, ≥18 years) • $ppFEV_1$ at baseline (<70, ≥70) • Comparator cohort (TEZ/IVA, IVA) • Sex (male, female) • Geographic region (North America, Europe) **Post-hoc analyses:** • F/Gating and F/RF genotype subgroups (comparator cohorts)	[redacted]

Study	AURORA F/MF (study VX17-445-102, NCT03525444) (7, 194, 252)	AURORA F/F (study VX17-445-103, NCT03525548) (170, 253)	AURORA OLE (study 445-105) (188)	AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168, 254)	AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (191)
		(Yes, No)			
Appropriateness to the decision problem	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above, as well as the *CFTR* genotype	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above, as well as the *CFTR* genotype	
Statistical tests	A model similar to that of the primary analysis was used in pre-specified subgroup analysis. The primary result obtained was treatment effect at Week 4. The MMRM was applied to each category of the subgroup. For the subgroup analysis based on age and sex, the covariate of age at screening (<18 vs ≥18 years of age) and sex (male vs female) was removed from the MMRM, respectively. Adjusted means with 2-sided 95% CI were provided, and the estimated treatment difference at Week 4 in different categories within a subgroup were presented in a forest plot (Appendix E). Results from the subgroup analysis should be interpreted with caution in cases where sample sizes were small. Ad-hoc analyses conducted for $ppFEV_1$ by genotype subgroup and in patients with $ppFEV_1$ <40% at baseline were also based on a MMRM, [redacted]	A model similar to that of the primary analysis was used in subgroup analysis. The primary result obtained was treatment effect at Week 4. The MMRM was applied to each category of the subgroup. For the subgroup analysis based on age, the covariate of age at screening (<18 vs ≥18 years of age) was removed from the MMRM. Adjusted means with 2-sided 95% CI were provided, and the estimated treatment difference at Week 4 in different categories within a subgroup were presented in a forest plot (Appendix E). Results from the subgroup analysis should be interpreted with caution in cases where sample sizes were small	[redacted]	A model similar to that of the primary analysis was used in subgroup analysis. The primary result obtained was estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the IVA/TEZ/ELX group. The MMRM was applied to each category of the subgroup. For the subgroup analysis based on comparator group, the covariate of comparator group (TEZ/IVA vs IVA) was removed from the MMRM. Adjusted means with 2-sided 95% CI were provided, and the estimated within-treatment difference through Week 8 for the IVA/TEZ/ELX group in different categories within a subgroup were presented in a forest plot (Appendix E). Results from the subgroup analysis, especially the comparison between two comparator groups, should be interpreted with caution due to potential small sample size. The purpose of subgroup analysis was to assess trend consistency; no hypothesis testing with sufficient power was performed. Regarding post-hoc subgroup analyses, a similar MMRM method as for the primary analysis was applied to each subgroup category	A MMRM similar to that of the parent study analysis was used for $ppFEV_1$. For the parent study period, MMRM was the same as parent study analysis. For the OL efficacy period, [redacted]

Abbreviations: CI, confidence interval; CFQ-R, cystic fibrosis questionnaire-revised; IVA, ivacaftor; MMRM, mixed effects model for repeated measures; $ppFEV_1$, percent predicted forced expiratory volume over one second; N/A, not applicable; RD, respiratory domain; SwCl, sweat chloride; TEZ, tezacaftor.

B.2.6.1.2 CF patients aged 6 to 11 years

Table 52. Summary of subgroup analyses carried out in IVA/TEZ/ELX studies, 6-11 years

Study	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174, 199)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (202, 206)	GALILEO (study VX19-445-116, NCT04353817) (204)
Pre-planned or post-hoc	Post-hoc	[redacted]	Ad-hoc
Subgroup analysis	Subgroup analyses were performed using an MMRM model similar to the main efficacy analysis for $ppFEV_1$, SwCl, CFQ-R RD score, and $LCI_{2.5}$	[redacted]	A subgroup analysis was performed for $LCI_{2.5}$
Analysed subgroups	F/F and F/MF genotype subgroups	[redacted]	• $LCI_{2.5}$ at screening (<10, ≥10)
Appropriateness to the decision problem	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to *CFTR* genotype	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to *CFTR* genotype	Subgroup analysis was conducted to explore clinical heterogeneity in the treatment efficacy with respect to $LCI_{2.5}$ at baseline
Statistical tests	A similar MMRM to that of the primary analysis was used in the subgroup analysis for $ppFEV_1$, SwCl, CFQ-R RD and $LCI_{2.5}$, [redacted] LS means with 2-sided 95% CI were provided (Appendix E).	[redacted] (Appendix E)	LS means with 2-sided 95% CI were provided (Appendix E)
Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised; $LCI_{2.5}$, lung clearance index 2.5; MMRM, mixed effects model for repeated measures; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SE, standard error; SwCl, sweat chloride.			

B.2.6.2 LUM/IVA

B.2.6.2.1 CF patients ≥12 years of age

Subgroup analyses were conducted to explore clinical heterogeneity in the efficacy of treatment with LUM/IVA with respect to known effect modifiers in patients aged ≥12 years (study 809-103, study 809-104 and study 809-105) (see Table 53).

B.2.6.2.2 CF patients 6-11 years of age

Subgroup analyses were conducted to explore clinical heterogeneity in the efficacy of treatment with LUM/IVA with respect to known effect modifiers in patients aged 6 to 11 years (study 809-109 and study 809-110) (see Table 54).

B.2.6.2.3 CF patients 2-5 years of age

There were no subgroup analyses in the studies investigating LUM/IVA treatment in CF patients aged 2-5 (study 809-115B and study 809-116). The study 809-115B CSR states 'no subgroups were specified apart from the 2 weight-based treatment groups already described'.

Table 53. Summary of subgroup analyses carried out on the primary endpoint in LUM/IVA studies, ≥12 years

Study	TRAFFIC & TRANSPORT (study VX12-809-103 and study VX12-809-104, NCT01807923 & NCT01807949) (158, 242, 243)	PROGRESS (study VX12-809-105, NCT01931839) (241)
Pre-planned or post-hoc	Pre-planned	Pre-planned
Subgroup analysis	Pre-specified subgroup analyses were conducted for the primary efficacy endpoint (Absolute Change in $ppFEV_1$ From Baseline at Week 24)	Pre-specified subgroup analyses were conducted for the primary efficacy endpoint (safety)
Analysed subgroups	• Age (<18, ≥18 years old) • $ppFEV_1$ severity at screening (<70, ≥70) • Sex (female, male) • Region (North America, Europe, and Australia), • Prior use of inhaled treatments (antibiotics, bronchodilators, hypertonic saline, or corticosteroids) • Prior use of inhaled bronchodilator • *Pseudomonas aeruginosa* status at baseline.	[redacted]
Appropriateness to the decision problem	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above	[redacted]
Statistical tests (for the primary endpoint)	Subgroup analyses of the primary endpoint were performed in a similar manner as the primary analysis. The primary result obtained from the model was the average treatment effect at Week 16 and at Week 24. The MMRM model for the age subgroups utilised the same model as for the primary analysis but excluded age as a covariate. The MMRM model for the $ppFEV_1$ severity at screening subgroups was the main MMRM model but excluded the term for $ppFEV_1$ severity at Screening. The MMRM model for sex subgroups was the main MMRM model but excluded the term for sex. The MMRM model for the other subgroups was the same as the main model	[redacted]
Abbreviations: IVA, ivacaftor; LUM, lumacaftor; MMRM, mixed effects model for repeated measures; $ppFEV_1$, percent predicted forced expiratory volume over one second; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse events.		

Table 54. Summary of subgroup analyses carried out on the primary endpoint in LUM/IVA studies, 6-11 years

Study	Study VX-14-809-109 (NCT02514473) (244)	Study VX15-809-110 (NCT02544451) (215)
Pre-planned or post-hoc	[redacted]	[redacted]
Subgroup analysis	[redacted]	[redacted]

Study	Study VX-14-809-109 (NCT02514473) (244)	Study VX15-809-110 (NCT02544451) (215)
Analysed subgroups (for the primary endpoint)	[redacted]	[redacted]
Appropriateness to the decision problem	[redacted]	[redacted]
Statistical tests (for the primary endpoint)	[redacted]	[redacted]

Abbreviations: AE, adverse event; AESI, adverse events of special interest; IVA, ivacaftor; kg, kilograms; $LCI_{2.5}$, lung clearance index 2.5; LUM, lumacaftor; $ppFEV_1$, percent predicted forced expiratory volume over one second.

B.2.6.3 TEZ/IVA

Details of subgroup analyses carried out in the relevant TEZ/IVA studies as well as details of the statistical tests used, are described in Table 55 (patients aged ≥12 years) and Table 56 (patients aged 6 to 11 years). Results of these subgroup analyses are further described in Appendix E.

B.2.6.3.1 CF patients ≥12 years of age

Table 55. Summary of subgroup analyses carried out in TEZ/IVA studies, ≥12 years

Study	EVOLVE (study VX14-661-106, NCT02347657) (157, 246, 255)	EXPAND (study VX14-661-108, NCT02392234) (164, 225)	EXTEND OLE (study VX14-661-110, NCT02565914) (222)
Pre-planned or post-hoc	Pre-planned	Pre-planned	No subgroup analyses were conducted
Subgroup analysis	Pre-specified subgroup analyses were conducted for the primary efficacy endpoint (absolute change in $ppFEV_1$ through Week 24) using a MMRM model similar to that of the primary analysis. Pre-specified subgroup analyses of adverse events were also carried out	Pre-specified subgroup analyses were conducted for the primary efficacy endpoint (absolute change in $ppFEV_1$ from study baseline to the average of the Week 4 and Week 8 measurements in each treatment period) using a model similar to that for the primary analysis. Pre-specified subgroup analyses of adverse events were also carried out	N/A
Analysed subgroups	**Pre-specified efficacy analyses:** • Age (<18 years, ≥18 years) • $ppFEV_1$ at baseline (<40%, ≥40 to <70%, ≥70%) • Sex (male, female) • Region (North America, Europe) • Prior use of inhaled antibiotic (yes, no) • Prior use of inhaled bronchodilator (yes, no) • Prior use of inhaled hypertonic saline (yes, no) • Prior use of inhaled corticosteroids (yes, no) • Prior use of azithromycin (yes, no) • *Pseudomonas aeruginosa* infection status (positive/negative) **Pre-specified safety analyses:** • Age (<18 years, ≥18 years) • $ppFEV_1$ at baseline (<40%, ≥40 to <70%, ≥70%) • Sex (male, female) • Region (North America, Europe)	**Pre-specified efficacy analyses:** • Age (<18 years, ≥18 years) • $ppFEV_1$ at baseline (<40%, ≥40 to <70%, ≥70%) • Residual function mutation type (CFTR class V noncanonical splice vs CFTR classes II to IV residual function) • Sex (male, female) • Region (North America, Europe [including Israel and Australia]) • Use of inhaled antibiotic (yes, no) • Use of inhaled bronchodilator (yes, no) • Use of inhaled hypertonic saline (yes, no) • Use of inhaled corticosteroids (yes, no) • Use of azithromycin (yes, no) • Colonization of *Pseudomonas aeruginosa* (positive/negative) **Pre-specified safety analyses:** • Age (<18 years, ≥18 years) • $ppFEV_1$ at baseline (<40%, ≥40 to <70%, ≥70%) • Sex (male, female) • Residual function mutation type (CFTR class V noncanonical splice vs CFTR classes II to IV residual function) • Region (North America, Europe)	N/A
Appropriateness to the decision problem	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to the effect modifiers listed above	N/A
Statistical tests	A model similar to that of the primary analysis was used in pre-specified subgroup analysis with additional covariates: subgroup and subgroup by treatment interaction, where appropriate. [redacted]. The estimated	A model similar to that of the primary analysis was used in pre-specified subgroup analysis with an additional covariate for the relevant grouping factor as well as a term for interaction with treatment. The primary result obtained from the model was the estimated difference between the treatment groups.	N/A

Study	EVOLVE (study VX14-661-106, NCT02347657) (157, 246, 255)	EXPAND (study VX14-661-108, NCT02392234) (164, 225)	EXTEND OLE (study VX14-661-110, NCT02565914) (222)
	treatment differences in different subgroup categories were presented in a forest plot (Appendix E)	The estimated mean of the primary endpoint and between-group treatment differences with the corresponding 95% CIs and 2-sided P values were presented for each subgroup. The estimated between-group treatment differences in different subgroup categories were presented in a forest plot (Appendix E)	
Abbreviations: CI, confidence interval; CFTR cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; MMRM, mixed effects model for repeated measures; $ppFEV_1$, percent predicted forced expiratory volume over one second; N/A, not applicable; TEAE, treatment-emergent adverse events; TEZ, tezacaftor.			

B.2.6.3.2 CF patients aged 6 to 11 years

Table 56. Summary of subgroup analyses carried out in TEZ/IVA studies, 6-11 years

Study	EMBRACE (study 115) (165)
Pre-planned or post-hoc	Post-hoc
Subgroup analysis	Subgroup analyses were performed for $LCI_{2.5}$, SwCl, CFQ-R RD, $LCI_{5.0}$, $ppFEV_1$, BMI, BMI z-score, weight, weight z-score, height, height z-score
Analysed subgroups	F/F and F/RF genotype subgroups
Appropriateness to the decision problem	Subgroup analyses were conducted to explore clinical heterogeneity in the treatment efficacy with respect to *CFTR* genotype
Statistical tests	Mean estimates with SD were provided (Appendix E)
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire-revised; $LCI_{2.5}$, lung clearance index 2.5; $LCI_{5.0}$, lung clearance index 5.0; $ppFEV_1$, percent predicted forced expiratory volume over one second; RD, respiratory domain; SD, standard deviation; SwCl, sweat chloride.	

B.2.7 Meta-analysis

N/A

B.2.8 Indirect and mixed treatment comparisons

B.2.8.1 Overview

B.2.8.1.1 Objective and treatments of interest

In the absence of head-to-head data from RCTs for all relevant treatment comparisons within the scope of this appraisal, estimates of relative efficacy and safety for relevant treatment options in each CF subpopulation were derived from ITCs. The three CFTRms in the scope of this appraisal are each indicated for the treatment of CF patients of a particular age and genotype as shown in Table 57. In all subpopulations, the relevant comparator for the approved CFTRms is the established clinical management comprising components of ECM as explained in Section B.1.1. The only exception is the heterozygous F/Gating population aged 6 years or older, in which ivacaftor monotherapy as an add-on to standard care comprises established clinical practice within NHSE.

Table 57. Available treatment options for CF patients, by age and genotype*

Genotype	F/MF	F/F	F/Gating	F/RF
Age group, years				
<1			IVA	
1-2			IVA	
2-5		LUM/IVA, ECM	IVA	
6-11	IVA/TEZ/ELX, ECM	LUM/IVA, TEZ/IVA, IVA/TEZ/ELX, ECM	IVA, IVA/TEZ/ELX, ECM	TEZ/IVA, IVA/TEZ/ELX, ECM
12+	IVA/TEZ/ELX, ECM	LUM/IVA, TEZ/IVA, IVA/TEZ/ELX	IVA, IVA/TEZ/ELX, ECM	TEZ/IVA, IVA/TEZ/ELX, ECM

*Therapies and populations within the scope of this appraisal are presented within the borders. IVA monotherapy is not within the scope of appraisal.
Abbreviations: ECM, established clinical management; ELX, elexacaftor; 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 IVA, ivacaftor; LUM, lumacaftor; TEZ, tezacaftor.

B.2.8.1.2 Populations included

Within each subpopulation, the evidence was reviewed to determine whether an ITC was required, this review is detailed below. A summary of the relevant comparators and analyses conducted is provided in Table 58.

CF patients aged 2-5 years with F/F genotype

Established clinical management without LUM/IVA in this subpopulation is represented by components of the ECM. Study 121 (VX16-809-121, NCT03625466) provides head-to-head comparison of LUM/IVA as an add-on to ECM vs PBO plus ECM, and therefore ITC is not required for treatments relevant in this population (Table 58).

CF patients aged 6-11 with F/MF genotype

Similarly, GALILEO trial (VX19-445-116, NCT04353817) provides direct evidence for relative efficacy and safety of IVA/TEZ/ELX as an add-on to ECM vs PBO plus ECM. Since these are the only licenced treatments in this population, ITC is not required (Table 58).

CF patients aged 6-11 years with F/F genotype

IVA/TEZ/ELX, LUM/IVA, TEZ/IVA and ECM are currently indicated in this subpopulation of pwCF. Direct estimate of relative efficacy of LUM/IVA+ECM vs PBO+ECM in this population is available from study VX14-809-109. However, no head-to-head RCTs of IVA/TEZ/ELX or TEZ/IVA vs PBO have been identified in the SLR. Since only single arm evidence for IVA/TEZ/ELX (study VX18-445-106 Part B) and TEZ/IVA (VX15-661-113) is available in this population, an ITC is required to provide adjusted relative effect estimates of IVA/TEZ/ELX and TEZ/IVA vs PBO.

CF patients aged 6-11 with F/Gating and F/RF genotype

In addition to ECM, IVA/TEZ/ELX fixed dose combination and IVA monotherapy are licensed treatments for CF patients who are 6-11 years of age and are heterozygous for the *F508del-CFTR* mutation and a gating mutation. In the absence of randomised or non-randomised evidence on IVA/TEZ/ELX in this subpopulation, ITC analysis to derive estimates of relative efficacy vs ECM or IVA monotherapy cannot be performed. Likewise, ITC is not possible for the subgroup of patients heterozygous for *F508del-CFTR* and a RF mutation due to paucity of trial evidence for IVA/TEZ/ELX, but direct evidence for the comparison of TEZ/IVA with ECM in this subpopulation exists [EMBRACE trial (VX16-661-115)].

CF patients aged 12+ with F/MF genotype

The relative efficacy of the two treatment options in this population, IVA/TEZ/ELX as an add on to ECM, and ECM, has been evaluated in the 24-week phase 3 trial study 445-102. There is therefore no need for an ITC in this subpopulation (Table 58).

CF patients aged 12+ years with F/F genotype

IVA/TEZ/ELX, LUM/IVA and TEZ/IVA are all currently indicated in this subpopulation of CF patients. The 4-week pivotal trial of IVA/TEZ/ELX in this population (study 445-103), as well as the 24-week phase 3b IVA/TEZ/ELX trial [KEPLER (VX18-445-109)] were active-controlled studies that evaluated the clinical benefit of IVA/TEZ/ELX beyond that provided by TEZ/IVA alone. Thus, analyses are required in this population to provide indirect evidence of relevant treatment options, including IVA/TEZ/ELX compared to LUM/IVA and PBO (ECM).

CF patients aged 12+ years with F/Gating and F/RF genotypes

In addition to IVA/TEZ/ELX, IVA is indicated for CF patients with a gating (including *R117H*) mutation and TEZ/IVA is indicated for the treatment of CF in patients who are *F508del-CFTR* heterozygous with a residual function mutation (F/RF). Since IVA and TEZ/IVA were available for these populations, study 445-104, the 8-week trial designed to evaluate the safety and efficacy of IVA/TEZ/ELX in patients heterozygous for *F508del-CFTR* with a gating (F/Gating) or F/RF mutation, was an active-controlled study which evaluated the benefit of IVA/TEZ/ELX beyond that provided by the currently indicated CFTRm treatments for these patients (i.e., IVA and TEZ/IVA). Thus, analyses are required in this population to provide indirect evidence of relevant treatment options, including IVA/TEZ/ELX compared to PBO+ECM.

Table 58. Overview of the analyses conducted for the populations in scope of this appraisal – by age and genotype

Age	F/MF		F/F		F/Gating		F/RF	
	Treatments in scope	**Analysis conducted**	**Treatments in scope**	**Analysis conducted**	**Treatments in scope**	**Analysis conducted**	**Treatments in scope**	**Analysis conducted**
2-5	None	N/A	• LUM/IVA • ECM	× (direct trial evidence from 809-121)	None	N/A	None	N/A
6-11	• IVA/TEZ/ELX • ECM	× (direct trial evidence from 445-116)	• IVA/TEZ/ELX • LUM/IVA • TEZ/IVA • ECM	✓	• IVA/TEZ/ELX • IVA • ECM	× (no trial evidence for IVA/TEZ/ELX)	• IVA/TEZ/ELX • TEZ/IVA • ECM	× (no trial evidence for IVA/TEZ/ELX)
12+	• IVA/TEZ/ELX • ECM	× (direct trial evidence from 445-102)	• IVA/TEZ/ELX • LUM/IVA • TEZ/IVA • ECM	✓	• IVA/TEZ/ELX • IVA • ECM	✓	• IVA/TEZ/ELX • TEZ/IVA • ECM	✓

Abbreviations: ECM, established clinical management; ELX, elexacaftor; 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 IVA, ivacaftor; LUM, lumacaftor; N/A, not applicable; TEZ, tezacaftor.

B.2.8.1.3 Selection of studies for the ITC

Studies included in the ITC were identified from a SLR of clinical studies, which was conducted in line with the NICE scope to identify relevant evidence of CFTRms compared with ECM in the treatment of CF. Details on search strategy and results of the SLR are provided in Appendix D.

A total of 289 unique studies were identified. To further refine the results of the SLR to produce relevant networks in accordance with the decision problem, a detailed feasibility assessment was conducted, which included the studies based on the following criteria:

- Clinical trials investigating currently licenced CFTRm treatments in any of the populations of interest for the ITC (as described in Section B.2.8.1.2)
- Studies reporting the outcomes of interest (as described in Section B.2.8.1.4)

Furthermore, clinical studies with the longest available follow-up were chosen for each population. RCTs with outcomes for up to 24 weeks are available for the F/F populations (aged 6-11 and 12+), while RCTs reporting outcomes for up to 8 weeks are available for the F/RF and F/Gating populations.

In all trials included in the analysis, both intervention and comparator were administered as add-ons to components of ECM. It was therefore assumed that the PBO arm from the CTFR modulator trials sufficiently captures the efficacy of ECM. Standard of care (SoC) is heterogenous and varies by individual patients, and while ECM aims to alleviate the symptoms of CF, CFTRms are the first class of disease-modifying treatments representing a major advancement in CF management. Additionally, studies of ECM were not generally marked out by genotype.

The results of the ITCs and an overview of the studies included in each analysis are provided in Sections B.2.8.2 through B.2.8.5. The full feasibility assessment and list of studies excluded from the ITC is detailed in Appendix D.

B.2.8.1.4 Outcomes of interest

The efficacy endpoints of interest were endpoints commonly evaluated in clinical trials, and are widely accepted and generally recognised as valid patient-relevant markers of CF disease progression.

Measures of lung function are critical for the assessment and management of pwCF. The FEV_1 is the most frequently used outcome to measure severity and treatment success.

Consequently, most of the trials considered for the ITC had $ppFEV_1$ as a primary endpoint. Frequency of PEx and time between PEx episodes are associated with lung function decline and survival in CF, making them valuable endpoints in clinical trials (64, 65, 88). Nutritional parameters and CFQ-R endpoints are also widely accepted as reliable, accurate, and relevant to the study of individuals with CF and treatment targets linked to nutritional status are recognised in Europe (256, 257).

The following outcomes were included in the ITC feasibility assessment:

- Lung function
    - $ppFEV_1$
    - $LCI_{2.5}$ (for the 6-11 population only)
- Nutritional parameters
    - Weight
    - BMI
- HRQoL
    - CFQ-R RD scores
    - CFQ-R non-RD scores
- PEx

Due to the exclusion of studies of treatments other than CFTRms from the ITC, only trials conducted by Vertex were included in the analysis. Therefore, outcomes reported generally applied a consistent definition across trials. An overview of the outcomes and trial definitions is provided below.

Lung function

The most commonly used outcome to measure CF lung disease severity and treatment effects is the FEV1, and ppFEV1 was the primary endpoint in the majority of studies in the ITC. Across all studies, FEV1 was assessed by spirometry according to American Thoracic Society/European Respiratory Society guidelines (258). However, the reference equations to calculate ppFEV1 vary; in recent years, the Global Lung Function Initiative equations have become the gold standard for normalising FEV1 (259), while older trials use the Wang-Hankinson reference (260, 261). As explained in Appendix D, ppFEV1 outcomes were re-calculated using the GLI method for comparability.

Additionally, in trials of patients younger than 12 years of age, the LCI2.5 was used to assess lung function. Young children may have relatively well-preserved lung function as measured by ppFEV1, but most have abnormal LCI reflective of lung damage that has occurred in the

small airways. Therefore, LCI2.5 was included as an outcome in the ITC conducted for the F/F population 6-11 years of age, represented as the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. Measurements across all studies were performed using spirometry according to the American Thoracic Society guideline (258).

Nutritional parameters

Weight and BMI were measured consistently across trials, and weight-for-age and BMI-for-age z-scores were calculated using Centers for Disease Control and Prevention (CDC) growth charts (262).

Health-related quality of life

CFQ-R scores, both RD and non-RD were measured consistently across trials using the CFQ-R questionnaire (263). For patients <14 years of age, patients completed the CFQ-Child version and parents/caregiver completed the CFQ-Parent version. Patients 14 years or older complete the CFQ-adult/adolescent version.

Pulmonary exacerbations

The feasibility of including PEx events in the ITC was also explored (see Appendix D). However, while usually reported in studies, it varied whether PEx was considered as an efficacy outcome or a safety outcome. As a result of inconsistent PEx definition applied across trials in each population, this outcome was excluded from the ITC following the feasibility assessment.

B.2.8.2 Indirect treatment comparison for the F/F population aged 6-11

An ITC was conducted to derive relative efficacy of treatments relevant to the decision problem. The relevant comparisons in this population are:

- IVA/TEZ/ELX+ECM vs PBO+ECM
- LUM/IVA+ECM vs PBO+ECM
- TEZ/IVA+ECM vs PBO+ECM

Since all treatments (CFTRms as well as PBO) were investigated as add-ons to ECM, in the subsequent sections, they are referred to simply either by the name of the CFTRm in question or as PBO. Direct trial evidence is available for LUM/IVA vs PBO at 24 weeks from study 809-109 (VX14-809-109), and for TEZ/IVA vs PBO at 8 weeks from the EMBRACE trial (study

VX14-661-106). The analysis conducted additionally provides estimates for IVA/TEZ/ELX vs PBO and TEZ/IVA vs PBO at 24 weeks.

All studies identified in the SLR reporting outcomes in this population were considered for inclusion in the analysis. A summary of the studies included is presented in Table 59 and the resulting network diagram is shown in Figure 80. Full details of the study selection criteria, studies excluded, and a detailed feasibility assessment, are provided in Appendix D.

Table 59. Studies included in the ITC (F/F 6-11 population)

Reference of trial	PBO/ECM	LUM/IVA	TEZ/IVA	IVA/TEZ/ELX
Study 809-109 (VX14-809-109)	✓	✓		
ENTRUST (VX15-661-113)			✓	
AURORA 6-11 (study 445-106B) (VX18-445-106)				✓
Study 809-011 Part B (VX13-809-011)		✓		
EMBRACE (VX16-661-115) *Included in supporting analysis only*	✓		✓	
Abbreviations: ECM, established clinical management; ELX, elexacaftor; IVA, ivacaftor; LUM, lumacaftor; PBO, placebo; TEZ, tezacaftor.				

Figure 80. Analysis network diagram (F/F 6-11 population)

Abbreviations: ELX, elexacaftor; F/F, homozygous for the *F508del-CFTR* mutation; IVA, ivacaftor; LUM, lumacaftor; TEZ, tezacaftor.

The following outcomes were commonly reported across the included RCTs and thus considered in the ITC analysis:

- Absolute change from baseline in ppFEV$_1$ through 24 weeks of treatment
- Absolute change from baseline in LCI$_{2.5}$ through 24 weeks of treatment
- Absolute change from baseline in BMI-for-age z-score at Week 24 of treatment
- Absolute change from baseline in weight-for-age z-score at Week 24 of treatment
- Absolute change from baseline in CFQ-R RD scores through 24 weeks of treatment

As noted above, PBO-controlled data directly comparing LUM/IVA to PBO is available from Study 809-109 for up to 24 weeks. Other studies available for the analysis at 24 weeks are single arm trials. However, for TEZ/IVA there is an additional RCT that reports outcomes for up to 8 weeks (EMBRACE). Therefore, to support the findings from the base case analysis conducted at 24 weeks, an additional analysis pooling data for TEZ/IVA was conducted to provide a comparison against PBO at 8 weeks.

The analysis was conducted using a mixed-effects model for repeated measures (MMRM) using individual patient data from each trial and adjusted for a number of covariates. Full details of the ITC methodology are provided in Appendix D.

The results of the analysis are presented in Table 60 below.

Results of IVA/TEZ/ELX vs ECM comparison

[redacted]

Results of LUM/IVA vs ECM comparison

[redacted]

[redacted]

Results of TEZ/IVA vs ECM comparison

[redacted]

Table 60. Mean change from baseline in endpoints evaluated at 24 weeks for ECM vs IVA/TEZ/ELX, LUM/IVA and TEZ/IVA – results from MMRM analysis (F/F 6-11 population)

Endpoint	IVA/TEZ/ELX 445-106B (N=29)	LUM/IVA 809-109 & 809-011B (N=160)	TEZ/IVA 661-113B (N=61)	PBO/ECM 809-109 (N=101)
Absolute change in $ppFEV_1$ from baseline through 24 weeks				
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (comparator - PBO) *P value*	[redacted]	[redacted]	[redacted]	
Absolute change in $LCI_{2.5}$ from baseline through 24 weeks				
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (comparator - PBO) *P value*	[redacted]	[redacted]	[redacted]	
Absolute change in weight-for-age z-score from baseline at 24 weeks				
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (comparator - PBO) *P value*	[redacted]	[redacted]	[redacted]	
Absolute change in BMI-for-age z-score (kg/m^2) from baseline at 24 weeks				
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (comparator - PBO) *P value*	[redacted]	[redacted]	[redacted]	
Absolute change from baseline through 24 weeks in CFQ-R RD score				
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (comparator - PBO) *P value*	[redacted]	[redacted]	[redacted]	

Endpoint	IVA/TEZ/ELX 445-106B (N=29)	LUM/IVA 809-109 & 809-011B (N=160)	TEZ/IVA 661-113B (N=61)	PBO/ECM 809-109 (N=101)
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ECM, established clinical management; ELX, elexacaftor: IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; LS, least squares; LUM, lumacaftor; MMRM, mixed-effects model for repeated measures; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume over 1 second; TEZ, tezacaftor.				

Supporting analysis: Results of TEZ/IVA vs ECM comparison at Week 8

Results from the [redacted] are presented in Table 61 [redacted]

Table 61. Supporting analysis: Mean change from baseline in endpoints evaluated at 8 weeks for ECM vs TEZ/IVA – results from MMRM analysis (F/F 6-11 population)

Endpoint	TEZ/IVA 661-113B & 661-115 (N=103)	PBO/ECM 809-109 (N=101)
Absolute change in $ppFEV_1$ from baseline through 8 weeks		
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (TEZ/IVA vs PBO) *P value*	[redacted]	
Absolute change in $LCI_{2.5}$ from baseline at 4 weeks		
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (TEZ/IVA vs PBO) *P value*	[redacted]	
Absolute change in weight-for-age z-score from baseline at 8 weeks		
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (TEZ/IVA vs PBO) *P value*	[redacted]	
Absolute change in BMI-for-age z-score (kg/m^2) from baseline at 8 weeks		
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (TEZ/IVA vs PBO) *P value*	[redacted]	
Absolute change from baseline through 8 weeks in CFQ-R RD score:		
LS mean within-group (95% CI) *P value*	[redacted]	[redacted]
LS mean PBO adjusted difference (95% CI) (TEZ/IVA vs PBO) *P value*	[redacted]	
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ECM, established clinical management; ELX, elexacaftor; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; LS, least squares; LUM, lumacaftor; MMRM, mixed-effects model for repeated measures; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume over 1 second; TEZ, tezacaftor.		

B.2.8.3 Indirect treatment comparison for the F/F population aged 12+

An ITC was conducted to derive relative efficacy of treatments relevant to the decision problem. The relevant comparisons in this population are:

- IVA/TEZ/ELX+ECM vs PBO+ECM
- LUM/IVA+ECM vs PBO+ECM
- TEZ/IVA+ECM vs PBO+ECM

Direct trial evidence is available for LUM/IVA vs PBO from the TRAFFIC/TRANSPORT trials (studies VX12-809-103/104), and for TEZ/IVA vs PBO from the EVOLVE trial (study VX14-661-106). The ITC conducted provides estimates for IVA/TEZ/ELX vs PBO.

All studies identified in the SLR reporting outcomes in this population were considered for inclusion in the ITC. A summary of the studies included is presented in Table 62 and the resulting network diagram is shown in Figure 81. Full details of the study selection criteria, studies excluded, and a detailed ITC feasibility assessment, are provided in Appendix D.

Table 62. Studies included in the ITC (F/F 12+ population)

Reference of trial	PBO/ECM	LUM/IVA	TEZ/IVA	IVA/TEZ/ELX
TRAFFIC (VX12-809-103)	✓	✓		
TRANSPORT (VX12-809-103)	✓	✓		
EVOLVE (VX14-661-106)	✓		✓	
KEPLER (VX18-445-109)			✓	✓
Abbreviations: ECM, established clinical management; ELX, elexacaftor; IVA, ivacaftor; LUM, lumacaftor; PBO, placebo; TEZ, tezacaftor.				

Figure 81. ITC network diagram (F/F 12+ population)

Abbreviations: ELX, elexacaftor; IVA, ivacaftor; LUM, lumacaftor; TEZ, tezacaftor.

The following outcomes were commonly reported across the included RCTs and thus considered in the ITC analysis:

- Absolute change from baseline in ppFEV$_1$ through 24 weeks of treatment
- Absolute change from baseline in BMI at Week 24 of treatment
- Absolute change from baseline in weight-for-age z-score at Week 24 of treatment

- Absolute change from baseline in CFQ-R RD and non-RD scores through 24 weeks of treatment

[redacted] Full details of the ITC methodology are provided in Appendix D.

Results of IVA/TEZ/ELX vs ECM comparison

The results of the ITC are presented in Table 63. [redacted] are also presented in Table 63, although these are not applied in the [redacted].

Table 63. Mean change from baseline in endpoints evaluated at 24 weeks in IVA/TEZ/ELX vs ECM indirect treatment comparison (F/F 12+ population)

Endpoint	**Study 109[a] IVA/TEZ/ELX vs TEZ/IVA (N = 175)** LS mean between-group difference (95% CI), *P value*	**EVOLVE[a] TEZ/IVA vs PBO/ECM (N = 504)** LS mean between-group difference (95% CI), *P value*	**TRAFFIC/ TRANSPORT[a] LUM/IVA vs PBO/ECM (N = 740)** LS mean between-group difference (95% CI), *P value*	**IVA/TEZ/ELX vs PBO/ECM** Bucher's mean between-group difference (95% CI), *P value*
Absolute change in **ppFEV$_1$** from baseline through 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in **BMI** (kg/m^2) from baseline at 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in **weight-for-age z-score**[b] from baseline at 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change from baseline through 24 weeks in **CFQ-R domain score**:				
Respiratory symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Body image	[redacted]	[redacted]	[redacted]	[redacted]
Eating problems	[redacted]	[redacted]	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]	[redacted]	[redacted]
Health perceptions	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]
Digestive symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]

[a] Note: Results may differ from those presented in the clinical study reports due to methods used in ITC to provide consistency across the included studies (e.g., covariates included in MMRM, GLI method used to normalize ppFEV$_1$); [b] Weight-for-age z-score evaluated for all patients; assuming growth statistics of 20-year-olds for all patients aged >20 years.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; GLI, Global Lung Initiative; LS, least squares; LUM, lumacaftor; MMRM, mixed-effects model for repeated measures; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume over 1 second; TEZ, tezacaftor.

B.2.8.4 Indirect treatment comparison for the F/RF population aged 12+

An ITC was conducted to derive relative efficacy of treatments relevant to the decision problem. The relevant comparisons in this population are:

- IVA/TEZ/ELX+ECM vs PBO+ECM
- TEZ/IVA+ECM vs PBO+ECM

Direct trial evidence is available for TEZ/IVA vs PBO from the EXPAND trial (study VX14-661-108), and the ITC conducted provides estimates for IVA/TEZ/ELX vs PBO.

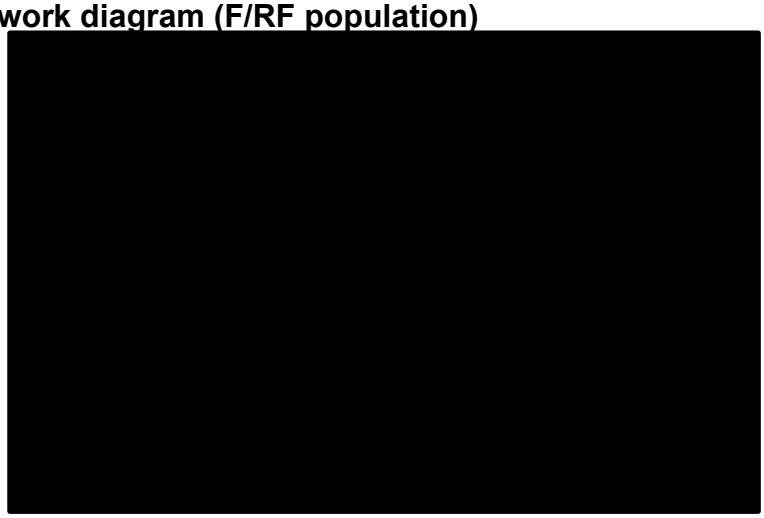
All studies identified in the SLR reporting outcomes in this population were considered for inclusion in the ITC. A summary of the studies included is presented in Table 64 and the resulting network diagram is shown in Figure 82. Full details of the study selection criteria, studies excluded, and a detailed ITC feasibility assessment, are provided in Appendix D.

Table 64. Studies included in the ITC (F/RF population)

Reference of trial	PBO/ECM	TEZ/IVA	IVA/TEZ/ELX
Study 445-104		✓	✓
Study 661-108	✓	✓	

Abbreviations: ECM, established clinical management; ELX, elexacaftor; IVA, ivacaftor; PBO, placebo; TEZ, tezacaftor.

Figure 82. ITC network diagram (F/RF population)



Abbreviations: ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor.

The following outcomes were commonly reported across the included RCTs and thus considered in the ITC analysis:

- Absolute change from baseline in ppFEV$_1$ through 8 weeks of treatment
- Absolute change from baseline in BMI at Week 8 of treatment
- Absolute change from baseline in weight-for-age z-score at Week 8 of treatment
- Absolute change from baseline in CFQ-R RD and non-RD scores through 8 weeks of treatment

Full details of the ITC methodology are provided in Appendix D.

Results of IVA/TEZ/ELX vs ECM comparison

The results of the ITC are presented in Table 65.

[redacted]

Table 65. Mean change from baseline in endpoints evaluated at 8 weeks in IVA/TEZ/ELX vs ECM indirect treatment comparison (F/RF population)

Endpoint	**AURORA F/RF F/G**[a] **IVA/TEZ/ELX vs TEZ/IVA** LS mean between-group difference (95% CI), *P value*	**EXPAND**[a] **TEZ/IVA vs PBO/ECM** LS mean between-group difference (95% CI), *P value*	**IVA/TEZ/ELX vs PBO/ECM** Bucher's mean between-group difference (95% CI), *P value*
Absolute change in **ppFEV$_1$** from baseline through 8 weeks	[redacted]	[redacted]	[redacted]
Absolute change in **BMI** (kg/m^2) from baseline at 8 weeks	[redacted]	[redacted]	[redacted]
Absolute change in **weight-for-age z-score**[b] from baseline at 8 weeks	[redacted]	[redacted]	[redacted]
Absolute change from baseline through 8 weeks in **CFQ-R domain score**:			
Respiratory symptoms	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]
Body image	[redacted]	[redacted]	[redacted]
Eating problems	[redacted]	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]	[redacted]
Health perceptions	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]
Digestive symptoms	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]

[a]Note: Results may differ from those presented in the clinical study report due to methods used in ITC to provide consistency across the included studies (e.g., covariates included in MMRM, GLI method used to normalize ppFEV1, see Appendix D for details on the methodology); [b]Weight-for-age z-score evaluated for all patients; assuming growth statistics of 20-year-olds for all patients aged >20 years.
Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; GLI, Global Lung Initiative; LS, least squares; MMRM, mixed-effects model for repeated measures; PBO, placebo; ppFEV1, percent predicted forced expiratory volume over 1 second; TEZ/IVA, tezacaftor.

B.2.8.5 Indirect treatment comparison for the F/Gating population aged 12+

An ITC was conducted to derive relative efficacy of treatments relevant to the decision problem. The relevant comparisons in this population are:

- IVA/TEZ/ELX+ECM vs PBO+ECM

- IVA/TEZ/ELX+ECM vs IVA+ECM

Direct trial evidence is available for IVA/TEZ/ELX vs IVA from the study 445-104, and the ITC conducted provides estimates for IVA/TEZ/ELX vs PBO.

All studies identified in the SLR reporting outcomes in this population were considered for inclusion in the ITC. A summary of the studies included is presented in Table 66 and the resulting network diagram is shown in Figure 83. Full details of the study selection criteria, studies excluded, and a detailed ITC feasibility assessment, are provided in Appendix D.

Table 66. Studies included in the ITC (F/Gating population)

Reference of trial	PBO/ECM	IVA	IVA/TEZ/ELX
AURORA F/RF F/G (study 445-104)		✓	✓
STRIVE (study 770-102)	✓	✓	
KONNECTION (study 770-111)	✓	✓	
KONDUCT (study 770-110)	✓	✓	
Abbreviations: ECM, established clinical management; ELX, elexacaftor; IVA, ivacaftor; PBO, placebo; TEZ, tezacaftor.			

Figure 83. ITC network diagram (F/Gating population)

Abbreviations: ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor.

The following outcomes were commonly reported across the included RCTs and thus considered in the ITC analysis:

- Absolute change from baseline in ppFEV$_1$ through 8 weeks of treatment
- Absolute change from baseline in BMI at Week 8 of treatment
- Absolute change from baseline in weight-for-age z-score at Week 8 of treatment
- Absolute change from baseline in CFQ-R RD and non-RD scores through 8 weeks

[redacted] Full details of the ITC methodology are provided in Appendix D.

As detailed in Appendix D, consistent with the definition of $ppFEV_1$ and CFQ-R domain scores in study 445-104, the primary result obtained from the model was the estimated treatment difference through Week 8 (i.e., including earlier endpoints). For AURORA F/RF F/G, KONNECTION, and KONDUCT, these endpoints were estimated as the average of the absolute change at Week 4 and Week 8 assessments, respectively. Since STRIVE did not include a clinic visit at Week 4, only the Week 8 measurements contributed to the treatment difference estimation. A sensitivity analysis was therefore conducted in which a consistent definition of endpoints was used for all included studies (excluding the Week 4 measurements for study 104, KONNECTION, and KONDUCT).

Results of IVA/TEZ/ELX vs ECM comparison

The results of the ITC are presented in Table 67 (effect estimates from each individual IVA RCT are also summarised in Table 68). [redacted]

Table 67. Mean change from baseline in endpoints evaluated at 8 weeks in IVA/TEZ/ELX vs ECM indirect treatment comparison (F/Gating population)

Endpoint	Study 104[a] **IVA/TEZ/ELX vs IVA** LS mean between-group difference (95% CI), *P value*	Pooled[b] **IVA vs PBO** LS mean between-group difference (95% CI), *P value*	**IVA/TEZ/ELX vs PBO/ECM** Bucher's mean between-group difference (95% CI), *P value*
Absolute change in **ppFEV$_1$** from baseline through 8 weeks[c]	[redacted]	[redacted]	[redacted]
Absolute change in **BMI** (kg/m^2) from baseline at 8 weeks	[redacted]	[redacted]	[redacted]
Absolute change in **weight-for-age z-score**[d] from baseline at 8 weeks	[redacted]	[redacted]	[redacted]
Absolute change from baseline through 8 weeks[c] in **CFQ-R domain score:**			
Respiratory symptoms	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]
Body image	[redacted]	[redacted]	[redacted]
Eating problems	[redacted]	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]	[redacted]
Health perceptions	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]
Digestive symptoms	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]

[a] Note: Results may differ from those presented in the clinical study report due to methods used in ITC to provide consistency across the included studies (e.g., [redacted]); [b] Estimate of overall efficacy for IVA vs PBO was derived using [redacted] See table below; [c] For study 104, KONNECTION, and KONDUCT, the treatment effect estimate was calculated as the average of the absolute change at Week 4 and Week 8 assessments, respectively. Since STRIVE did not include a clinic visit at Week 4, only the Week 8 measurements contributed to the treatment difference estimation; [d] Weight-for-age z-score evaluated for all patients; assuming growth statistics of 20-year-olds for all patients aged >20 years.

Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume over 1 second; TEZ, tezacaftor.

Table 68. Study treatment effect estimates from each phase 3 IVA RCT contributing to the overall IVA vs PBO effect used in the ITC conducted in F/Gating (including F/R117H) patients

Endpoint	IVA vs PBO LS mean between-group difference (95% CI), *P value*			
	STRIVE **Subset of F/G551D patients**	**KONNECTION** **Subset of F/non-G551D gating patients**	**KONDUCT** **Subset of F/R117H patients**	**Pooled[a]**
Absolute change in **ppFEV$_1$** from baseline through 8 weeks[b]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in **sweat chloride** from baseline through 8 weeks[b]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in **BMI** (kg/m^2) from baseline at 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in **weight-for-age z-score**[c] from baseline at 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change from baseline through 8 weeks[b] in **CFQ-R domain score:**				
Respiratory symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Body image	[redacted]	[redacted]	[redacted]	[redacted]
Eating problems	[redacted]	[redacted]	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]	[redacted]	[redacted]
Health perceptions	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]
Digestive symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]

[a] Estimate of overall efficacy for IVA vs PBO was derived using a [redacted]; [b] For KONNECTION and KONDUCT, the treatment effect estimate was calculated as the average of the absolute change at Week 4 and Week 8 assessments, respectively. Since STRIVE did not include a clinic visit at Week 4, only the Week 8 measurements contributed to the treatment difference estimation; [c] Weight-for-age z-score evaluated for all patients; assuming growth statistics of 20-year-olds for all patients aged >20 years.

Abbreviations: BMI, body mass index; CFQ-R, cystic fibrosis questionnaire - revised; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; LS, least squares; PBO, placebo; ppFEV$_1$, percent predicted forced expiratory volume over 1 second; RCT, randomised controlled trial.

[redacted]

B.2.8.6 Uncertainties in the indirect and mixed treatment comparisons

In the absence of head-to-head clinical data for all comparisons relevant to the decision problem, several analyses were conducted to produce relative treatment effect estimates. These analyses rely on a number of assumptions, and therefore, results should be interpreted accordingly. [redacted]. A detailed ITC feasibility assessment was conducted to assess the similarity of trials (Appendix D). Although studies were considered sufficiently similar, a key limitation which applies to all analyses is that IVA/TEZ/ELX trials included an active run-in period, i.e., patients were treated with CFTRms prior to study baseline. As a result, patients in IVA/TEZ/ELX studies may have already experienced disease-modifying effects at study baseline, and this difference in study design leads to uncertainties in any comparisons to studies assessing patients without prior CFTR-modulator use. However, the results of the ITC derived for IVA/TEZ/ELX vs PBO in the absence of head-to-head data is in line with the significant improvements observed for IVA/TEZ/ELX in clinical trials.

The estimates derived for the F/F population aged 6-11 relied on single arm trials due to lack of RCTs available in this population, i.e., comparisons using common comparators as per the Bucher method cannot be applied. As detailed in Appendix D, the trials were considered sufficiently similar for comparison, and as Vertex has access to patient-level data from all trials, heterogeneity was accounted for using analyses methods allowing for covariate adjustments across trials.

B.2.8.7 Conclusions

Consistent with clinical trial evidence, all analyses conducted [redacted]

[redacted]. No PBO-adjusted evidence for IVA/TEZ/ELX treatment of F/F patients aged 6-11 is available from clinical trials, [redacted].

The results of the analysis also suggested [redacted]. [redacted] (235). [redacted] Supplementary analyses conducted for the F/Gating and F/F 6-11 populations also supported the findings from the base case analyses.

These results further demonstrate the [redacted]. CFTRms are expected to provide significant and clinically meaningful improvements in lung function, nutritional parameters, and multiple aspects of health-related quality-of-life.

B.2.9 Adverse reactions

B.2.9.1 IVA/TEZ/ELX

B.2.9.1.1 CF patients ≥12 years of age

Study 445-102

IVA/TEZ/ELX was generally well tolerated with an acceptable side-effect profile throughout 24 weeks of treatment, and the percentage of patients with at least one AE was similar in the IVA/TEZ/ELX and PBO groups (93.1% and 96.0%, respectively) (7).

Serious AEs were reported in 28 patients (13.9%) in the IVA/TEZ/ELX group and in 42 patients (20.9%) in the PBO group. Two patients (1.0%) in the IVA/TEZ/ELX group discontinued the trial regimen due to AEs: rash in one patient and portal hypertension in one patient with pre-existing cirrhosis. No patients in the PBO group discontinued the trial regimen because of an AE. No deaths due to AEs occurred in either trial group (7).

Study 445-103

IVA/TEZ/ELX regimen was generally safe and well-tolerated throughout the 4-week treatment period. AEs occurred in 32 patients (58%) in the IVA/TEZ/ELX group and in 33 patients (63%) in the TEZ/IVA group, with the majority of AEs resolving during the study period (170).

Serious AEs occurred in two patients (4%) in the IVA/TEZ/ELX group (rash in one participant and PEx in another) and in one patient (2%) in the TEZ/IVA group (PEx). There were no AEs that led to the trial regiment discontinuation or death in either group. The safety profile showed to be consistent among subgroups (age, baseline ppFEV$_1$, sex, and geographical region) (170).

Study 445-105 IA4

Overall, IVA/TEZ/ELX showed a favourable safety profile and was well tolerated for up to 144 weeks of treatment. Results from the Week 144 IA4 were generally consistent with the safety data from parent studies (study 445-102, study 445-103). No new safety concerns were identified in a longer IVA/TEZ/ELX treatment period (188).

Serious AEs occurred in 154 (30.4%) patients in this study. [redacted] there was 1 (0.2%) death due to oxycodone toxicity that was assessed as not related to study drug. Fourteen (2.8%) subjects discontinued IVA/TEZ/ELX treatment due to AEs (188).

Study 445-104

IVA/TEZ/ELX was well tolerated during the treatment period. Overall, 66.7% (n=88) of patients in the IVA/TEZ/ELX group and 65.9% (n=83) of patients in the active control group had one or more AEs, which were mostly mild or moderate in terms of severity and resolved during the trial (168).

Serious AEs occurred in 5 patients (3.8%) in the IVA/TEZ/ELX group and in 11 patients (8.7%) in the active control group, with the difference being attributable to a higher incidence of PEx in the active control group. AEs led to discontinuation of treatment in 1 patient in the IVA/TEZ/ELX group (elevated aminotransferase level) and in 2 patients in the active control group (anxiety or depression in 1 patient and PEx in 1 patient), and no AEs leading to death were reported (168).

Study 445-110

Treatment with IVA/TEZ/ELX was generally safe and well tolerated for up to 96 weeks, consistently with the known safety profile of IVA/TEZ/ELX. The proportion of subjects with at least 1 AE was 96.0%, with the majority of AEs classified as mild or moderate in severity (190, 191).

Serious AEs were reported in 38 (15.1%) patients, and 13 (5.2%) patients discontinued treatment due to AEs. Events leading to treatment discontinuation in ≥2 subjects were liver-related events, anxiety and insomnia. There was 1 (0.4%) AE of colon cancer leading to death that was assessed as unlikely related to study drug (190, 191).

Table 69 summarises the safety results of relevant IVA/TEZ/ELX studies identified in Section B.2.2 which are considered most relevant for the decision problem. There are no additional studies that report additional adverse reactions to those reported in the studies in Section B.2.2. Additional adverse reactions reported in the relevant studies are further described in Appendix F.

Table 69. Summary of safety results of IVA/TEZ/ELX studies, ≥12 years

Safety results	AURORA F/MF (study VX17-445-102, NCT03525444) (7)		AURORA F/F (study VX17-445-103, NCT03525548) (170)		AURORA OLE (study VX17-445-105 IA4, NCT03525574) (188)	AURORA F/RF F/G (study VX18-445-104, NCT04058353) (168)		AURORA F/RF F/G OLE (study VX18-445-110, NCT04058366) (190, 191)
n (%)	IVA/TEZ/ELX (N=202)	PBO (N=201)	IVA/TEZ/ELX N=55	TEZ/IVA N=52	IVA/TEZ/ELX (N=506)	IVA/TEZ/ELX (N=132)	Control (IVA or TEZ/IVA) (N=126)	IVA/TEZ/ELX (N=251)
Any AE	188 (93.1)	193 (96.0)	32 (58)	33 (63)	500 (98.8)	88 (66.7)	83 (65.9)	241 (96.0)
SAEs	28 (13.9)	42 (20.9)	2 (4)	1 (2)	154 (30.4)	5 (3.8)	11 (8.7)	38 (15.1)
AEs leading to discontinuation	2 (1.0)	0	0	0	14 (2.8)	1 (0.8)	2 (1.6)	13 (5.2)
AEs leading to death	0	0	0	0	1 (0.2)	0	0	1 (0.4)
TEAEs	–	–	12 (22)*	9 (17)*	–	–	–	–
Serious TEAEs	–	–	1 (2)*	0*	–	–	–	–

*Adverse events related to trial drug. Relatedness to trial drug was determined by the investigators. When summarising the number of participants with adverse events or serious adverse events related to the trial drug, adverse events with relationship of related, possibly related, and missing were counted.
Abbreviations: AE, adverse event; ELX, elexacaftor; IVA, ivacaftor; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse events; TEZ, tezacaftor.

B.2.9.1.2 CF patients aged 6 to 11 years

Study 445-106 Part B

Overall, IVA/TEZ/ELX was well tolerated throughout the treatment period of study 445-106 Part B, with an acceptable safety profile and no new safety concerns identified. AEs were reported in 65 patients (98.5%), which were mostly mild (54.5%) or moderate (42.4%) and generally consistent with CF manifestations or common childhood infections (174).

Serious AEs occurred in one patient (1.5%), and these were concurrent events of rhinovirus infection, metapneumovirus infection, and pneumonia (resolved with IV antibiotics). One patient (1.5%) discontinued the treatment due to an AE (rash), and no deaths occurred during safety follow-up (174).

Study 445-107 Part A

Safety results from study 445-107 Part A showed that IVA/TEZ/ELX was generally safe and well tolerated with no new safety concerns identified in the extended treatment period. The majority of reported AEs were mild or moderate in severity. Serious AEs occurred in four patients, one subject had an AE of aggression that led to treatment discontinuation and no deaths occurred (201, 202).

Study 445-116

Overall, IVA/TEZ/ELX was safe and well tolerated over the 24-week treatment period. Safety results were consistent with the established safety profile, and the incidence of AEs was similar in both groups (IVA/TEZ/ELX and PBO, 80.0% and 93.4%, respectively) (204).

Serious AEs occurred in 4 patients (6.7%) in the IVA/TEZ/ELX group and 9 patients (14.8%) in the PBO group. Seven patients (11.7%) in the IVA/TEZ/ELX group had AEs that led to study drug interruption, and one patient (1.7%) in the IVA/TEZ/ELX group discontinued treatment due to rash (204).

Table 70 summarises the safety results of relevant IVA/TEZ/ELX studies. There are no additional studies that report additional adverse reactions to those reported in the studies in Section B.2.2. Additional adverse reactions reported in the relevant studies are further described in Appendix F.

Table 70. Summary of safety results of IVA/TEZ/ELX studies, 6-11 years

Safety results	AURORA 6-11 (study VX18-445-106 Part B, NCT03691779) (174)	AURORA 6-11 OLE (study VX19-445-107 Part A, NCT04183790) (201, 202)	GALILEO (study VX19-445-116, NCT04353817) (204)	
n (%)	IVA/TEZ/ELX (N=66)	IVA/TEZ/ELX (N=64)	IVA/TEZ/ELX (N=60)	PBO (N=61)
Any AE	65 (98.5)	–	48 (80.0)	57 (93.4)
SAEs	1 (1.5)	–	4 (6.7)	9 (14.8)
AEs leading to discontinuation	1 (1.5)	–	1 (1.7)	0 (0)
AEs leading to death	0 (0)	–	0 (0)	0 (0)
TEAEs	–	63 (98.4)	–	–
Serious TEAEs	–	4 (6.3)	–	–
TEAEs leading to discontinuation	–	1 (1.6)	–	–
TEAEs leading to death	–	0	–	–

Abbreviations: AE, adverse event; ELX, elexacaftor; IVA, ivacaftor; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse events; TEZ, tezacaftor.

B.2.9.2 LUM/IVA

B.2.9.2.1 CF patients aged ≥ 12 years

The safety profile for LUM/IVA has been well characterised by the clinical development programme. LUM/IVA is generally well tolerated by patients (241-243). Respiratory events (e.g. chest discomfort, dyspnoea, and respiration abnormal) were more common during initiation of LUM/IVA therapy. Serious respiratory events were seen more frequently in patients with $ppFEV_1$ <40 (3).

The majority of AEs were mild to moderate in intensity (158). No deaths were reported in either study 809-103 or study 809-104 (158).

Table 71. Study 809-103, study 809-104 and study 809-105 summary of AEs

Safety results	TRAFFIC (study VX12-809-103, NCT01807923) (243)		TRANSPORT (study VX12-809-104, NCT01807949) (242)		PROGRESS (study VX12-809-105, NCT01931839) (241)*	
n (%)	PBO (N=184) (%)	LUM 400/IVA (n = 182), N (%)	PBO (N=186) (%)	LUM 400/IVA (n = 187), N (%)	PBO transitioned to- LUM 400/IVA (N=176), N (%)	LUM 400/IVA (N= 40) N (%)
Subjects with any AEs	174 (94.6)	174 (95.6)	181 (97.3)	177 (94.7)	176 (100.0)	333 (97.9)
Subjects with AEs leading to treatment discontinuation	4 (2.2)	6 (3.3)	2 (1.1)	9 (4.8)	[redacted]	[redacted]
Subjects with SAEs	49 (26.6)	33 (18.1)	57 (30.6)	31 (16.6)	89 (50.6)	143 (42.1)
Subjects with related SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

*the majority of subjects received ≥72 to 96 weeks of treatment
Abbreviations: AE, adverse event; IVA, ivacaftor; LUM, lumacaftor; n, size of subsample; N, number of subjects; PBO, placebo; q12h, every 12 hours; qd, daily; SAE, serious adverse event

B.2.9.2.2 CF patients aged 6 to 11 years

LUM/IVA was generally well tolerated, as observed in study 809-109, with the proportion of patients reporting TEAEs being similar to the PBO group ([redacted]) (Table 72). Most AEs were mild or moderate in intensity. Three patients in the LUM/IVA group discontinued because of AEs (elevated ALT/AST and abnormal respiration) (159). No deaths due to AEs occurred in the study. In the extension study it was observed that LUM/IVA was generally safe and well tolerated for up to 120 weeks of treatment (156). AEs were generally consistent with manifestations of the underlying CF disease and the previously established safety profile of LUM/IVA; no new safety concerns were identified. The rates of TEAEs were generally consistent with those observed in the 24-week parent studies (159, 214). While most patients experienced at least one TEAE, the majority of TEAEs were classified as mild or moderate in severity and were considered not related or unlikely related to treatment. No deaths due to AEs occurred in either trial group (Table 73).

Table 72. Study 809-109 summary of AEs

Safety results	**Study VX14-809-109 (NCT02514473)(244)**	
n (%)	**PBO N = 101**	**LUM200/IVA N = 103**
Number of AEs (total)	[redacted]	[redacted]
Subjects with any AEs	98 (97.0)	98 (95.1)
Subjects with any TEAE	98 (97)	98 (95)
Subjects with AEs leading to treatment discontinuation	2 (2.0)	3 (2.9)
Subjects with serious AEs	11 (10.9)	13 (12.6)
Subjects with related serious TEAEs	3 (3)	2 (2)
Subjects with AEs leading to death	0	0
Abbreviations: AE, adverse event; IVA, ivacaftor; LUM, lumacaftor; n, size of subsample; N, number of subjects; PBO, placebo; q12h, every 12 hours; qd, daily; SAE, serious adverse event		

Table 73. Study 809-110 summary of AEs

Safety results	**StudyVX15-809-110 (NCT02544451) (215)**	
n (%)	**Treatment-to treatment group**	**PBO-to treatment group**
Number of TEAEs (total)	[redacted]	[redacted]
Subjects with any TEAEs	[redacted]	[redacted]
Subjects with TEAEs leading to treatment discontinuation	2 (1.4)	7 (7.3)
Subjects with serious TEAEs	[redacted]	[redacted]
Subjects with related serious TEAEs	[redacted]	[redacted]
Subjects with TEAEs leading to death	0	0
Abbreviations: IVA, ivacaftor; LUM, lumacaftor; n, size of subsample; N, number of subjects; PBO, placebo; q12h, every 12 hours; qd, daily; SAE, serious adverse event; TEAE, treatment emergent adverse event.		

B.2.9.2.3 CF patients aged 2 to 5 years

In study 809-115B in patients aged 2 to 5 years, LUM/IVA was generally well tolerated for up to 24 weeks of treatment. The results were consistent with the background profile in pwCF of similar age and the established safety profile of LUM/IVA; no new safety concerns were observed (162).

Nearly all of the 60 patients (98%) experienced at least one AE (Table 74). Cough was the most common AE reported in 38 patients (63%), which is consistent with the characteristic symptoms of CF (162). The majority of AEs were mild or moderate in severity; 7% experienced an SAE (N=4), of which 2 were due to infective PEx of CF, 1 was viral gastroenteritis, and 1 was due to constipation (162). Except for constipation, the 3 other SAEs were considered unrelated to LUM/IVA.

In study 809-116 nearly all patients experienced at least 1 AE (98.2%). The majority were mild (33.3%) or moderate (50.9%) in severity and 68.4% were considered not related or unlikely to be related to LUM/IVA. AEs leading to treatment discontinuation were reported in 5.3% of patients and no AEs were life-threatening or lead to death. SAEs were reported in 26.3% of patients (161, 175).

Table 74. AE summary in LUM/IVA studies, 2-5 years

Safety results	Study VX15-809-115 (NCT02797132) (245)	Study VX16-809-116 (NCT03125395) (161)	
n (%)	Number of events per 100 participant years (N=60)*	Participants (N=57)**	Number of events per 100 participant years (N=57)*
Any adverse event	[redacted]	[redacted]	[redacted]
Adverse events leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]	[redacted]
Treatment-related serious adverse events	[redacted]	[redacted]	[redacted]
Adverse events leading to death	[redacted]	[redacted]	[redacted]

Data are N (%), unless otherwise specified
*Number of events per 100 participant-years was calculated by the number of events divided by the total treatment-emergent period in 100 participant-years; a participant with a total treatment-emergent period of 48 weeks was considered as 1 participant-year. The number of events per 100 participant-years uses all events in the corresponding category, regardless of the maximum relationship or maximum severity
** A participant with multiple events within a category was counted only once in that category.

B.2.9.3 TEZ/IVA

B.2.9.3.1 CF patients ≥12 years of age

Study 661-106

Overall, TEZ/IVA was safe and well tolerated for up to 24 weeks of treatment, with the incidence of AEs being similar in both TEZ/IVA and PBO treatment groups. No new safety signals were seen (157).

Serious AEs were reported in 31 patients (12.4%) in the TEZ/IVA group and in 47 (18.2%) in the PBO group, and no deaths occurred during the trial. 7 patients (2.8%) in the TEZ/IVA group and 8 (3.1%) in the PBO group discontinued the trial regimen due AE (157).

Study 661-108

Overall, treatment with TEZ/IVA over an 8-week treatment period was safe and well tolerated, with no treatment discontinuations and no new risks attributable to the treatment intervention (164).

The incidence of AEs was similar for all three treatment groups. Serious AEs were reported in 8 (4.9%) patients in the TEZ/IVA group, 10 (6.4%) in the IVA group and 14 (8.6%) in the PBO group. No deaths occurred during this trial (164).

Study 661-110

Treatment with TEZ/IVA showed to be generally safe and well tolerated up to 120 weeks, with a safety profile consistent with that observed in the parent studies (222).

Serious TEAEs were reported by 351 (34%) participants, with the most frequently reported serious TEAEs (occurring in ≥1% of participants) being infective PEx of CF, haemoptysis and distal intestinal obstruction syndrome. 22 patients (2%) had TEAEs leading to treatment discontinuation. No deaths occurred during the TE period and 2 deaths occurred after the TE period. The investigators deemed the events leading to death as not related to the study drug (222).

Table 75 summarises the safety results of relevant TEZ/IVA studies identified in Section B.2.2 which are considered most relevant for the decision problem. There are no additional studies that report additional adverse reactions to those reported in the studies in Section B.2.2. Additional adverse reactions reported in the relevant studies are further described in Appendix F.

Table 75. Summary of safety results of TEZ/IVA studies, ≥12 years

Safety results	EVOLVE (study VX14-661-106, NCT02347657) (157)	EXPAND (study VX14-661-108, NCT02392234) (164)	EXTEND OLE (study VX14-661-110,

						NCT02565914) (222)
n (%)	TEZ/IVA (N=251)	PBO (N=258)	TEZ/IVA (N=162)	IVA (N=157)	PBO (N=162)	TEZ/IVA (N=1042)
Any AE	227 (90.4)	245 (95.0)	117 (72.2)	114 (72.6)	126 (77.8)	–
SAEs	31 (12.4)	47 (18.2)	8 (4.9)	10 (6.4)	14 (8.6)	–
AEs leading to discontinuation	7 (2.8)	8 (3.1)	0	2 (1.3)[a]	1 (0.6)[a]	–
AEs leading to death	0	0	0	0	0	–
TEAEs	–	–	–	–	–	995 (95.5)
Serious TEAEs	–	–	–	–	–	351 (33.7)
TEAEs leading to discontinuation	–	–	–	–	–	22 (2.1)
TEAEs leading to death	–	–	–	–	–	0

[a]One patient discontinued PBO for AEs of fatigue, oropharyngeal pain, productive cough, and respiration abnormal. One patient discontinued treatment and/or the study during or following IVA treatment for increased CPK. One patient had the AE after the last dose but the action taken was treatment discontinuation.
Abbreviations: AE, adverse event; IVA, ivacaftor; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse events; TEZ, tezacaftor.

B.2.9.3.2 CF patients aged 6 to 11 years

Study 661-115

Overall, TEZ/IVA treatment was safe and well tolerated in CF patients aged 6 to 11 years, with no new safety concerns identified for TEZ/IVA (165).

41 (75.9%) patients in the TEZ/IVA group had at least 1 TEAE, with most of them being mild or moderate in severity. There were no serious AEs or deaths, and no TEAE led to study drug discontinuation (165).

Table 76 summarises the safety results of relevant TEZ/IVA studies identified in Section B.2.2 which are considered most relevant for the decision problem. There are no additional studies that report additional adverse reactions to those reported in the studies in Section B.2.2. Additional adverse reactions reported in the relevant studies are further described in Appendix F.

Table 76. Summary of safety results of TEZ/IVA studies, 6-11 years

Safety results	EMBRACE (study VX16-661-115, NCT03559062) (165)
n (%)	TEZ/IVA (N=54)
TEAEs	41 (75.9)
Serious TEAEs	0
TEAEs leading to discontinuation	0
TEAEs leading to death	0
Abbreviations: AE, adverse event; IVA, ivacaftor; TEAE, treatment-emergent adverse events; TEZ, tezacaftor.	

B.2.9.4 Real-world evidence

B.2.9.4.1 Study VX20-CFD-004 (MAGNIFY)

[redacted]

[redacted]

B.2.9.4.2 Study VX20-CFD-005 (TRAJECTORY)

[redacted]

B.2.9.4.3 UKCFR study

Safety data were not collected in UKCFR.

B.2.10 Ongoing studies

B.2.10.1 IVA/TEZ/ELX

There are seven on-going studies of IVA/TEZ/ELX. These are described below and summarised in Table 77. The majority of these are OLE studies.

Study 445-107 is a 2-part phase 3 192-week OLE study (Part A 96 weeks + Part B 96 weeks) (201) (173, 202) to evaluate the long-term safety, tolerability, efficacy, and pharmacodynamics of IVA/TEZ/ELX treatment in pwCF aged 6 years or older, who are homozygous for the *F508del-CFTR* mutation (F/F), or heterozygous for *F508del* with a minimal function mutation (F/MF) (173). Patients were required to have completed study visits in study 445-106 Part B to be eligible for enrolment in study 445-107 (173). The estimated completion date for this study is April 2024 (203). Part A results have been published and have been included in the previous section.

Study 445-119 is a phase 3b OLE study that is being conducted to evaluate the long-term safety and tolerability of IVA/TEZ/ELX treatment in patients ≥6 years of age with an F/MF genotype (264). Patients are required to have completed study drug treatment in the parent study 445-116 or to have had study drug interruption(s) in the parent study but completed study visits up to the last scheduled visit of the treatment period in the parent study. The estimated completion date of this ongoing study is April 2023 (264).

Study 445-105 is a 196-week, phase 3, OLE study designed to evaluate the long-term safety and efficacy of treatment with IVA/TEZ/ELX, in patients aged ≥12 years with F/MF and F/F genotypes who completed the treatment period visits in study 445-102 or study 445-103, respectively (187). Patients who had been randomised to the comparator arm in the parent study started receiving IVA/TEZ/ELX in study 445-105, while those receiving IVA/TEZ/ELX in the parent studies remained on this treatment. Results of this trial are expected in January 2023 (187). Interim results of this trial which have been published have been detailed in the previous sections.

KEPLER OLE (study 115) is a phase 3b OLE study that is being conducted to evaluate the long-term safety and tolerability of IVA/TEZ/ELX treatment in patients ≥12 years of age with an F/F genotype (265). Patients were required either to have completed study drug treatment in the parent study KEPLER (study 109), or to have had study drug interruption(s) in the parent study but completed study visits up to the last scheduled visit of the treatment period in the parent study. The estimated completion date for this study is June 2023 (265).

Table 77. On-going studies for IVA/TEZ/ELX

Study name	Study identifier	Genotype	Age	Parent study (if an OLE)	Expected study completion date
AURORA 6-11 OLE (study 445-107) (173)	VX19-445-107 (NCT04183790; EudraCT 2019-001827-11)	F/F and F/MF	6+	Study VX18-445-106 Part B	April 2024
GALILEO OLE (study 445-119) (264)	VX20-445-119 (NCT04545515)	F/MF	6+	VX19-445-116	April 2023
AURORA OLE (study 445-105) (187)	VX17-445-105 (NCT03525574)	F/F or F/MF	12+	VX17-445-102 or study VX17-445-103	January 2023
SHUTTLE (study 445-113) (266)	VX18-445-113 (NCT04043806)	F/F or F/MF	12+	VX17-659-105	July 2023
KEPLER OLE (study 445-115) (265)	VX19-445-115 (NCT04362761; EudraCT2019-003455-11)	F/F	12+	VX18-445-109	June 2023

Abbreviations: CEM, cost effectiveness model; F/F, homozygous for the *F508del-CFTR* mutation; F/RF F/Gating; 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 activity ('residual function'); ITC, indirect treatment comparison; N/A, not applicable; OLE, open-label extension.

B.2.10.2 LUM/IVA

There is one on-going study of LUM/IVA (Table 78).

A single arm study by Lee et al. compared impulse oscillometry with spirometry in evaluating the effectiveness of LUM/IVA treatment in subjects with CF homozygous for *F508del* is in progress (267). At the time of the publication in 2020 only 14 of the

recruited participants had completed the 6-month trial. It is unclear from the available data when this trial will be completed.

Table 78. On-going studies LUM/IVA

Study name	Study identifier	Genotype	Age	Interventions	Status	Expected completion date
Lee, Morton, et al. 2020	N/A	F/F	12+	LUM/IVA	On-going/unclear	Not available
Abbreviations: F/F, homozygous for *F508del*; IVA, ivacaftor; LUM, lumacaftor; N/A, not applicable; PBO, placebo.						

B.2.10.3 TEZ/IVA

The two on-going studies of TEZ/IVA are described below and summarised in Table 79.

Study 661-110 (NCT02565914) is a phase 3, 96-week OLE study to evaluate the long-term safety and efficacy of TEZ/IVA in pwCF aged 12 years or older who are homozygous or heterozygous for the *F508del-CFTR* mutation and who completed one of six parent studies: 661-103, 661-106, 661-107, 661-108, 661-109, and 661-111. The estimated study completion date is March 2023 (222, 228).

Study 661-116 is a phase 3, 96-week OLE rollover study to evaluate the safety and efficacy of long-term treatment with TEZ/IVA in subjects with CF aged 6 years or older, homozygous or heterozygous for the *F508del-CFTR* mutation. Patients are required to have completed the Week 24 visit in studies ENTRUST (study 661-113) and EMBRACE (study 661-115). The estimated study completion date is September 2022 (268, 269).

Table 79. On-going studies for TEZ/IVA

Study name	Study identifier	Genotype	Age	Parent study (if an OLE)	Expected study completion date
EXTEND OLE (study 661-110) (222)	VX14-661-110 (NCT02565914)	F/F or F/RF	12+	EVOLVE (study 661-106) EXPAND (study 661-108)	March 2023 (actual primary completion date: May 2019)
Study 661-116 (268)	VX17-661-116 (NCT03537651)	F/F or F/RF	6+	ENTRUST (study 661-113) EMBRACE (study 115)	September 2022 (actual primary completion date: October 2020)
Abbreviations: F/F, homozygous for the *F508del-CFTR* mutation; F/RF, heterozygous for the *F508del* mutation with a mutation associated with residual CFTR protein; OLE, open-label extension.					

B.2.11 Interpretation of clinical efficacy, clinical effectiveness and safety evidence

CF is a chronically progressive, life-limiting condition, whose key manifestations and drivers of morbidity and mortality include:

Inevitable decline in lung function, as measured by $ppFEV_1$ in adolescents and adults, and $LCI_{2.5}$ in paediatric patients; each 1% reduction in $ppFEV_1$ increasing the risk of death over 5 years by 4% (64)

Number of PEx per year; PEx are associated with a faster rate of lung function decline and an increased mortality risk: compared with having no exacerbations in a year, one to two exacerbations per year increase the risk of death threefold (P<0.0001) while three or more exacerbations per year increase the risk of death 4.5 fold (p<0.001) (65)

Poor nutritional status (low BMI) (65)

The goal of the treatment is therefore to delay the decline in lung function for as long as possible, and prevent PExs and other complications of the disease.

B.2.11.1 IVA/TEZ/ELX

B.2.11.1.1 Clinical efficacy

IVA/TEZ/ELX is a breakthrough therapy that treats the underlying cause of CF. It represents a step change in the treatment of CF as it is the only disease-modifying therapy with the potential to treat up to 90% of pwCF:

By expanding the treatment to patients ≥6 years of age who currently do not any have CFTRm as approved treatment options (F/MF genotype) (7, 174, 204)

By enhancing the clinical benefit for patients that are currently eligible for treatment with one of the previously licensed CFTRms (F/F, F/Gating and F/RF genotypes) (168, 170, 172).

Efficacy of IVA/TEZ/ELX in combination with ECM has been proven in patients 12 years or older in three phase 3 RCTs and the two corresponding OLE studies; improvements were observed in multiple outcome measures across CFTR genotypes with a single *F508del-CFTR* allele (7, 168, 170, 190, 236). Efficacy has also been assessed in the 6-11 age group in one phase 3 RCT as a primary endpoint, as well as through several secondary endpoints in a phase 3 single arm trial and an OLE. Results from trials conducted in pwCF 6-11 years of age were consistent with efficacy and safety findings in pwCF 12 years or older, demonstrating substantial benefits of IVA/TEZ/ELX treatment on respiratory function and symptoms, rate of severe exacerbations and nutritional parameters (174, 201).

Statistically significant improvements in absolute change in $ppFEV_1$ both within and between treatment groups were noted in Studies 445-102, 445-103, 445-104, and 445-106 with IVA/TEZ/ELX treatment (7, 168, 170, 174). Extension studies demonstrate that continuous treatment with IVA/TEZ/ELX leads to sustained $ppFEV_1$ improvement, which is strongly associated with decreased CF mortality (188, 190, 201). Although there is no standard definition of a minimal clinically important difference for $ppFEV_1$, a validated survival model by Liou *et al.* indicates that every percentage point increase in FEV_1 leads to a 4% reduction in 5-year risk of death on average, assuming all other factors equal (270). A previous EMA workshop on endpoints for CF clinical trials noted that any significant difference between PBO and active treatment could be clinically relevant, since declines in $ppFEV_1$ are associated with increased mortality (233).

In patients 12 years or older IVA/TEZ/ELX has shown an improvement in $ppFEV_1$ of 13.8 points vs PBO in study 445-102 (patients with F/MF) (7) and improvements of 10.0 points vs TEZ/IVA in study 445-103 (homozygous population) (170). These findings were corroborated by the IA4 from study 445-105, where improvements were sustained or increased for up to a total of 144 weeks of treatment (188, 236). IVA/TEZ/ELX has also shown a mean between group improvement in $ppFEV_1$ of 3.5 points (95%CI: 2.2 to 4.7) vs IVA or TEZ/IVA in study 445-104 (patients with F/RF or F/G) (168). Furthermore, findings from a post-hoc analysis of study 445-105 indicate that pwCF treated with IVA/TEZ/ELX experience no loss of lung function over the long-term (144 weeks) (236). In contrast, pwCF treated with ECM experience, on average, an annual rate of decline in $ppFEV_1$ of 1 to 3 percentage points (234).

In patients aged 6 to 11 years of age, safety and efficacy of IVA/TEZ/ELX were consistent with those reported in adults and adolescents with CF (174, 201, 204). The magnitude of the treatment effect on absolute change in $ppFEV_1$ from baseline vs PBO was very similar in studies 445-116 (F/MF 6-11), 445-102 (F/MF 12+) and 445-103 (F/F 12+) (treatment difference 14.3 [12.7 to 15.8], 10.0 [7.4 to 12.6], and 11.0 [6.9 to 15.1], respectively) (175, 186, 194). The within-group absolute changes from baseline in $ppFEV_1$ observed in studies 445-116 and 445-106 (F/MF or F/F 6-11) of 9.5 (6.6 to 12.4) and 10.2 (7.9 to 12.6) percentage points, respectively, were also consistent with within-group changes in 445-102 and 445-103 (within-group difference from baseline

13.6 [12.4 to 14.8] and 10.4 [8.6 to 12.2] percentage points, respectively) (174, 204). Rollover study 445-107 found that the improvement in $ppFEV_1$ noted in 445-106 was sustained through additional 96 weeks of treatment (absolute change from baseline at Week 96 of 11.2 points [8.3 to 14.2]) (201, 202). The LCI, a primary outcome in 445-116 and a secondary outcome in 445-106 and 445-107, is considered a more sensitive measure of early lung disease than $ppFEV_1$ in younger pwCF since a substantial proportion of paediatric patients have well-preserved lung function with $ppFEV_1$ values in the normal range (270). Within-group absolute mean change in $LCI_{2.5}$ through Week 24 of -2.29 (-2.6 to -1.97) and -1.71 (-2.11 to -13) units was observed in 445-116 and 445-106, respectively (174, 204). This reduction in $LCI_{2.5}$ (i.e., improvement in lung disease) was maintained over a prolonged treatment period of study 445-107 and was further reduced to an absolute change of -2.00 (-2.45 to -1.55) units from baseline of 445-106 at extended Week 96 of 445-107 (201, 202).

Results of the UKCFR study, an observational study of CFTRm users in the UK Cystic Fibrosis Registry initiated to establish long-term effectiveness of CFTRms under real-world conditions of use, [redacted] (8).

Treatment with IVA/TEZ/ELX in 445-102 (F/MF) resulted in a lower rate of PEx from baseline in pwCF aged 12 years or older, including severe events leading to hospitalisation or treatment with IV antibiotics, compared to PBO (7). Study 445-105 proved these results were durable since estimated PEx event rates per 48 weeks (all PEx) were consistent with the low PEx rate observed in IVA/TEZ/ELX group of parent study 445-102 (188). The pwCF with F/MF genotype aged 6-11 who received IVA/TEZ/ELX experienced an even lower annualised rate of PEx than IVA/TEZ/ELX-treated adolescents and adults, consistent with their well-preserved lung function at baseline(174). This treatment effect was maintained for additional 96 weeks of

treatment, with an annualised event rate of 0.04 observed in study 445-107 (201, 202). PEx have an acute negative effect on patient health and QoL, as well as several long-term consequences, including irreversible and accelerated lung function decline (88), an increased risk of future exacerbations and hospitalisation (90), a higher likelihood of lung transplantation (93) and an increased mortality risk (64, 65, 88). The findings were [redacted] (8).

CFQ-R RD was an endpoint in all the studies. The MCID, which corresponds to the smallest clinically relevant change a patient can detect, is defined as a 4-point within-group change in CFQ-R RD scores (235). In all studies across the 6-11 and 12+ years age groups (445-102, 445-103, 445-104, 445-105, 445-110, 445-106 and 445-107), the within-group absolute mean change from baseline was greater than 4 points (7, 168, 170, 174, 190, 201, 236), [redacted] (8).

Since malnutrition and malabsorption represent complications of CF (105, 106), BMI was a common outcome measured in the trials. In pwCF aged 12 years or older treated with IVA/TEZ/ELX in studies 445-102 (F/MF population) and 445-103 (F/F population), a significantly greater absolute change from baseline in BMI vs PBO group was observed, with between-group differences of 1.04 kg/m^2 at Week 24 and 0.6 kg/m^2 at Week 4, respectively (7, 170). This increase was maintained in rollover study 445-105 where an absolute increase in BMI of 1.61 kg/m^2 and 1.74 kg/m^2 was observed from the baseline of each parent study to Week 144 of the extension study in patients who continued with IVA/TEZ/ELX treatment from parent study 445-102 or 445-103, respectively (188). Increases in BMI were also observed in pwCF aged 6-11 years, which is of particular relevance since younger children with CF struggle to achieve normal nutritional status leading to a low BMI and failure to thrive (105, 106). Study 445-106 reported an absolute change from baseline to Week 24 of 1.02 kg/m^2 in patients with F/MF receiving IVA/TEZ/ELX (174). [redacted]

[redacted] (8).

Overall, evidence from clinical trials and real-world studies demonstrates that IVA/TEZ/ELX improves upon the clinical benefits demonstrated by available CFTRms, further enhancing and expanding the benefits to the wider CF population (271). Unlike previous CFTRms, triple combination therapy strongly modulates CFTR in pwCF with F/MF genotypes. The ability to effectively modulate F508del-CFTR protein from a single allele was evident in the 78% of pwCF enrolled in 445-102 who had minimal-function mutations associated with an absence of CFTR protein production, but nevertheless had a pronounced and lasting response to IVA/TEZ/ELX that could occur only through modulation of F508del-CFTR (7, 188, 194). Available trial and real-world data support the conclusion that the presence of a single *F508del-CFTR* allele is sufficient to impart long-term benefit of triple therapy independent of the minimal-function mutation. Accordingly, it is expected that any pwCF with ≥1 *F508del-CFTR* allele aged 6 years or older would experience a significant treatment benefit that could be maintained long-term with continuous IVA/TEZ/ELX therapy regardless of the mutation on the second allele and whether it produces any CFTR protein (188, 190, 201, 236). The impact of IVA/TEZ/ELX treatment on $LCI_{2.5}$ and $ppFEV_1$ outcomes suggests that early initiation of IVA/TEZ/ELX is likely to minimize disease progression, providing an effective treatment option at an early stage of disease when serious long-term complications may be averted (174, 239, 272).

B.2.11.1.2 Safety

IVA/TEZ/ELX was generally well tolerated. Very few patients discontinued treatment in studies 445-102, 445-103 and 445-104 due to AEs (1%, 0% and 1%, respectively) (7, 168, 170). Results from IA4 of safety data from study 445-105 were consistent with safety findings from Studies 102 and 103 (188, 236, 273).

Studies 445-106 and 445-107 found that the safety profile of IVA/TEZ/ELX in the 6-11 age group was generally consistent with that observed in older patients (174, 201). Similarly, the number of patients who discontinued treatment due to AEs was low (1.5% and 1.6% in 445-106 and 445-107, respectively) (174, 201).

B.2.11.1.3 Strengths and weaknesses, the validity of the study results

Strengths

The evidence base for pwCF aged 12 years or older is derived from three phase 3 RCTs and two phase 3 OLE. In patients aged 6-11 years, the evidence base comprises one phase 3 RCT, one phase 3 single arm trial and a phase 3 OLE. The studies evaluated clinically relevant endpoints associated with lung function including ppFEV$_1$, PEx, CFQ-R RD, nutritional status (BMI, weight, BMI-and weight-for-age z scores), and biomarkers of CFTR modulation (sweat chloride levels). The FEV$_1$ is a measure of lung function which is strongly correlated with CF morbidity and mortality (64). An episode of PEx has a detrimental impact on QoL, may require IV antibiotic therapy and/or hospitalisation (90, 92, 113) and leads to irreversible acute decline in lung function (88, 91). The impact of treatment on respiratory symptoms was also captured in the IVA/TEZ/ELX trial programme by means of CFQ-R RD scores. The selected trial endpoints provide crucial insights into survival and QoL of pwCF relevant to real-world practice and clinical decision making.

Limitations

Study 445-103 had the treatment duration of 4 weeks, which was considered acceptable given a sustained benefit has been observed from Day 15 through Week 24 in clinical studies of other CFTRms. In addition, extension study 445-105, which enrolled patients from both 445-102 and 445-103, provided long term efficacy and safety data for eligible patients from 445-103 parent study.

Study 445-106 did not enrol patients with F/Gating or F/RF genotypes. Since the underlying aetiology of CF is consistent between younger or older patients, it is considered acceptable and appropriate to extrapolate available efficacy results to younger populations provided sufficient evidence that PK and safety profiles are consistent across age groups (274-276), as demonstrated in 445-106 (174). Therefore, the robust evidence package consisting of Phase 3 studies in pwCF 12 years or older across F/MF, F/F, F/RF and F/Gating genotypes, and the PK, safety and efficacy findings from studies conducted in pwCF aged 6 to 11 years, supports the conclusion that IVA/TEZ/ELX effectively modulates the function of F508del CFTR protein from a single *F508del* allele.

Validity of study results

A quality assessment revealed no concerns regarding the risk of bias in RCTs or study quality in single-arm trials (Appendix D). Study 445-106 conducted in pwCF aged 6-11 did not include a control group; by virtue of its single-arm design, its findings are at inherently higher risk of bias compared to an RCT. Recent completion of study 445-116, an RCT of pwCF with F/MF genotype aged 6-11, whose results are generally consistent with those of 445-106, provides a reasonable external reference and lends further credibility to the efficacy and safety findings of 445-106 (175, 199).

B.2.11.2 LUM/IVA

B.2.11.2.1 Clinical efficacy

LUM/IVA is the only approved medicine that targets the underlying protein defect in patients as young as 2 years of age with CF homozygous for the *F508del-CFTR* mutation.

Three phase 3 RCTs as well as two extension studies investigated the efficacy of LUM/IVA treatment across multiple outcome measures including $ppFEV_1$, $LCI_{2.5}$, BMI, CFQ-R-RD and PEx event rate.

LUM/IVA modifies the course of disease by slowing the rate of lung function decline in patients aged 12 years or older (155). This was evident from statistically significant improvements in lung function in all three RCTs in this age group (TRAFFIC. TRANSPORT and PROGRESS). Pooled data from studies 809-103 and 809-104 showed a rapid and consistent 2.8 percentage point absolute increase in $ppFEV_1$ from baseline at Week 24 ($P<0.001$), with a 4.8% relative improvement compared to PBO ($P<0.0001$) which was sustained for up to 120 weeks of treatment (155). Treatment with LUM/IVA was also associated with statistically significant improvements in lung function vs PBO in patients homozygous for *F508del* aged 6 to 11 years (159): in study 809-109, the LS mean differences in $LCI_{2.5}$ and $ppFEV_1$ compared with PBO through Week 24 of -1.1 (95% CI: -1.4 to -0.8; $P<0.0001$) and 2.4 percentage points (95% CI: 0.4 to 4.4; $P=0.0182$), respectively, were observed (159). These improvements were sustained for a further 96 weeks with continued LUM/IVA treatment (156). Real-world data from the cohort of pwCF [redacted]

[redacted]

(8).

LUM/IVA also significantly reduces the risk of PEx in patients aged 12 years or older (158, 277). The RRs showed a treatment effect that favoured LUM/IVA vs PBO for both study 809-103 (RR: 0.66, P=0.02) and study 809-104 (RR: 0.57, P<0.001) (158). The annualised PEx rate through extension Week 96 of study 809-105 remained lower in the LUM/IVA group (0.65 [95% CI: 0.56 to 0.75]) than the event the rate observed in the PBO group during study 809-103 or study 809-104 (1.19 [95% CI: 1.00 to 1.40]). (155, 158, 277). There was also evidence to suggest that LUM/IVA may have a significant and meaningful impact on the rate of PEx in patients who do not experience an increase in $ppFEV_1$ with LUM/IVA treatment (P=0.04) (278). Compared with subjects 12 years of age or older, the subjects aged 6-11 [redacted] (215, 244).

Statistically significant benefits in BMI were consistently observed across all three RCTs in patients aged 6 years or older from baseline at Week 24. The longevity of the effect was confirmed by the findings from studies 809-105 and 809-110, where BMI continued to increase over the extended 96-week period of treatment (215, 241). Real world data from UKCFR study [redacted] (8). Improvements in nutritional status are of clinical relevance since a low BMI is associated with reduced lung function, and poor nutritional status is an independent predictor of survival (279).

LUM/IVA positively impacts patients' QoL. The pooled analysis of study 809-103 and study 809-104 in those aged 12 years or older found a statistically significant increase from baseline at Week 24 in CFQ-RD score 4.1 (P<0.001). Similarly, in study 809-105 a statistically significant change was observed at extension week-96 of 3.5 (95% CI: 1.3 to 5.8; P=0.0018), however, for those that transitioned from PBO to LUM/IVA an improvement was observed but it was not statistically significant. [redacted] (242, 243). However, it is difficult to assess the HRQoL of pwCF, particularly when using generic measures of HRQoL, such as EQ-5D (see Section B.3.4). EQ-5D-3L was not included as an outcome in study 809-105.

In study 809-109 the LS mean increase in CFQ-R RD score from baseline through Week 24 was 5.5 points (95% CI: 3.4 to 7.6; P<0.0001) for the LUM/IVA group indicating a clinically meaningful improvement was achieved (235) (159). These improvements were maintained over a further 96 weeks in study 809-110 (215).

LUM/IVA therefore addresses the primary goals of CF treatment in patients aged 6 years or older by improving lung function and nutritional status while simultaneously reducing the rate of PEx, all of which are independent key drivers of morbidity and mortality in CF (64, 65).

Statistically significant improvements in key outcomes were also observed in the 2-5 years age group in a phase 3 single arm trial and its corresponding 96-week extension study. These included BMI, BMI for age z-score, weight and weight for age z-score. The risk of bias in these single arm studies was estimated by directly comparing their results to the results of RCTs conducted in older age groups. Given the consistency in results observed across the age groups a low risk of bias was estimated.

Statistically significant increases in BMI and BMI for age z-scores from baseline were observed at Week 24 in study 809-115B of 0.27 kg/m² (95% CI: 0.07 to 0.47; P=0.0091) and 0.29 (95% CI: 0.14 to 0.45; P=0.0003) respectively. These findings were corroborated by the extension study, study 809-116, where improvements were sustained over 96 weeks of treatment with increases from baseline of study 809-115B at Week 96 of study 809-116 in BMI of 0.30 kg/m² (95% CI: –0.06 to 0.65) and in BMI z-score of 0.27 (95% CI: 0.05 to 0.48). The annualised rates of PEx and CF-related hospital admissions were low over the course of study 809-115B and study 809-116. In the 96-week extension study, an improvement in both $ppFEV_1$ and $LCI_{2.5}$ was observed. However, these results were not statistically significant. Study 809-121, a phase 2 RCT demonstrated that treatment with LUM/IVA led to improvement in chest magnetic resonance imaging score and $LCI_{2.5}$ through 96 weeks of treatment in patients aged 2-5 years (280). Collectively, trial and real-world data demonstrate the potential long-term impact of LUM/IVA on disease progression with early CFTR targeted treatment in 2-5 age group.

B.2.11.2.2 Safety

In patients aged 6 years or older LUM/IVA was generally well tolerated (241-243). Very few patients discontinued treatment in studies 809-103, 809-104, 809-105, 809-109 or 809-110 due to AEs (3.3%, 4.7%, 7%, 2.9% and 3.8% respectively). Of the 7% that discontinued treatment in study 809-105 about [redacted] (241). [redacted]

Similarly, in children aged 2 to 5 years, LUM/IVA was well tolerated and had a safety profile consistent with the established safety profile of LUM/IVA in patients aged 6 to 11 years. Very few patients discontinued treatment in studies 809-115B and 809-116 due to AEs (5% in both studies) (161).

B.2.11.2.3 Strengths and weaknesses, the validity of the study results

Strengths

In patients 6 years or older the evidence is based on three RCTs and two corresponding extension studies. Data from these studies capture evidence on many clinically relevant outcomes in this multisystemic disease including lung function ($ppFEV_1$, $LCI_{2.5}$ and PEx) nutritional status (weight, BMI and their z scores) and HRQoL. The selected trial endpoints provide important insights that are relevant to real-world practice and clinical decision making.

Limitations

A potential limitation of study 809-115B is that there is no direct comparator group. However, the rapid reversal of improvements in outcomes such as $LCI_{2.5}$ to baseline levels after a 2-week LUM/IVA washout period strongly suggest that the improvements noted in this open-label study were related to LUM/IVA treatment (162). In study 809-105 a potential limitation is that there was an increase in discontinuations between extension weeks 72 and 96 of study 809-105, which was because LUM/IVA became commercially available and consequently subjects transitioned from the study drug to the commercially available supply of LUM/IVA (155). Therefore, the main efficacy analyses were limited to data up to extension Week 72. Sensitivity analyses that also

include data from extension week 84 and 96 visits should be interpreted with caution. Finally, in patients aged 2-5 years of age the clinical evidence base described is based on a single arm study and its corresponding extension study. However, historical data from untreated patients and data from CFTRm trials provide perspective on drug exposures, safety, and tolerability (281, 282). Furthermore the rapid reversal of improvements in SwCl, faecal elastase-1, and IRT concentrations and return of $LCI_{2.5}$ to baseline levels after a 2-week LUM/IVA washout at the end of study 809-115, followed by improvements in those endpoints when LUM/IVA was re-initiated in study 809-116, strongly suggest that the improvements noted in these single arm studies were associated with LUM/IVA treatment (161, 162).

Validity of study results

A quality assessment was conducted, the results revealed no concerns regarding potential sources of bias (Appendix D). The trials were designed and conducted appropriately with regard to the randomisation and treatment allocation. All groups were similar at the outset and there were no imbalances or unexpected drop-outs between the treatment groups.

B.2.11.3 TEZ/IVA

B.2.11.3.1 Clinical efficacy

Clinical effectiveness of TEZ/IVA has been evaluated in CF patients aged 12 years or older with F/F and F/RF genotypes: two phase 3 RCTs and an OLE study (157, 164, 222), while one phase 3 RCT comprises the evidence base in patients aged 6 to 11 years (165).

Improvements in lung function in patients 12 years or older were assessed through absolute change in $ppFEV_1$ from baseline, with increases ranging from 2.0 to 7.5 percentage points generally maintained through a longer 96-week treatment period (157, 164, 222). Moreover, TEZ/IVA has demonstrated the ability to modify the course of CF disease by slowing the rate of lung function decline by 61.5% compared to matched controls not treated with a CFTRm (222). In this age group, treatment with TEZ/IVA also resulted in the reduction in PEx in studies 661-106 (annualised PEx event rate of 0.64 [TEZ/IVA] vs 0.99 [PBO]) and 661-108 (annualised PEx event rate of 0.34 [TEZ/IVA] vs 0.29 [IVA] and 0.63 [PBO]), which were sustained over a 96-week

treatment period in study 661-110 (157, 164, 222). In patients aged 6 to 11 years, significant improvements were seen in lung function in patients treated with TEZ/IVA over 8 weeks, measured with both $LCI_{2.5}$ (−0.51 units) and $ppFEV_1$ (+2.8 percentage points) (165). Initiation of TEZ/IVA [redacted] (8). [redacted] (8).

The impact of treatment with TEZ/IVA on HRQoL was assessed in all the studies using the CFQ-R RD endpoint. TEZ/IVA improved CF-related symptoms and quality of life, with increases in CFQ-R RD scores consistently observed across all studies in both age groups treated with TEZ/IVA, ranging from 2.3 to 13.8 points. The increase in CFQ-R RD scores endured with continuing TEZ/IVA treatment up to 96 weeks (157, 164, 165, 222).

Moreover, TEZ/IVA represents a valuable treatment option particularly for patients with F/F genotype aged 12 years or older who are not able to tolerate LUM/IVA due to respiratory AEs, as it was demonstrated in study 661-114. This phase 3b TEZ/IVA study was conducted in CF patients with the F/F genotype aged 12 years or older who discontinued LUM/IVA due to treatment-related respiratory symptoms, especially those with more severe lung disease ($ppFEV_1$ <40%). Since the observed respiratory AE profile may limit the use of LUM/IVA in these patients, an alternative treatment regimen with TEZ/IVA was assessed in study 661-114. In this randomised, double-blind, PBO-controlled study, treatment with TEZ/IVA did not lead to an increased incidence of respiratory AEs compared to PBO. Most of the respiratory AEs of special interest were not considered treatment-related and there were no serious AEs or AEs leading to treatment interruption or discontinuation. Moreover, patients treated with TEZ/IVA experienced improvements in lung function compared with PBO (mean difference with TEZ/IVA vs PBO in the absolute change from baseline to the average value of days 28 and 56 of 2.7%). Therefore, results of study 661-114 support the use

of TEZ/IVA as a safe, well-tolerated and efficacious treatment option in CF patients who were unable to tolerate LUM/IVA due to respiratory AEs (283).

Overall, available trial and real-world evidence demonstrates TEZ/IVA's ability to address the key primary goals of CF treatment for F/F and F/RF patients by improving lung function, reducing PExs, enhancing nutritional status, and improving quality of life, with clinical benefits generally maintained over an additional 96 weeks of treatment in OLE studies and consistent clinical effectiveness profile in the real-world setting (157, 164, 165, 222). Additionally, TEZ/IVA offers an alternative therapeutic option for CF patients with F/F genotype aged 12 years or older, particularly those who are not able to tolerate LUM/IVA due to AEs (283).

B.2.11.3.2 Safety

Overall, treatment with TEZ/IVA was safe and well tolerated and no new safety concerns were identified. There were no AEs leading to study drug discontinuation in studies study 661-115 and study 661-108, and only 2.8% and 2.1% of patients discontinued TEZ/IVA treatment in study 661-106 and study 661-110, respectively. In patients aged 6 to 11 years, TEZ/IVA also demonstrated a favourable safety and tolerability profile, consistent with the established safety profile in patients aged 12 years or older (157, 164, 165, 222).

B.2.11.3.3 Strengths and weaknesses, the validity of the study results

Strengths

The clinical evidence base described in patients aged 6 to 11 years is derived from one phase 3 RCT, while the evidence base in patients 12 years or older is derived from two phase 3 RCTs and one phase 3 OLE. Data from these studies assessed clinically relevant outcomes in the treatment of CF, namely ppFEV$_1$, LCI$_{2.5}$, PEx, CFQ-R RD and BMI. The selected trial endpoints provide important insights relevant to assess TEZ/IVA's impact on the disease course of CF and on patient's qualify of life.

Limitations

Possible limitations of study 661-115 include the relatively short duration of 8 weeks of treatment (165). However, an OLE study 661-116 provides long-term data on both efficacy and safety for the enrolled patients (268).

A potential limitation of study 661-110 is its open-label design, which might be associated with potential biases, including biases in symptom reporting by study participants, assessment of the severity and relatedness of AEs to the study drug, as well as patient-reported outcomes (PROs), including the CFQ-R RD score. Other potential limitation includes the fact that participants with all eligible F/RF genotypes were assessed combined because of the rare prevalence of the RF mutations. Due to small sample sizes, it was not possible to present efficacy data for TEZ/IVA on individual F/RF genotypes. Nevertheless, study results indicate that treatment with TEZ/IVA led to improvements in efficacy endpoints over the longer term in CF patients with F/RF genotypes (222).

Validity of study results

A quality assessment was conducted, and the results revealed no concerns regarding potential sources of bias (Appendix D). The trials were designed and conducted appropriately with regards to the randomisation and treatment allocation. All groups were similar at the outset and there were no imbalances or unexpected drop-outs between treatment groups.

B.2.11.4 Real-world evidence

B.2.11.4.1 Clinical effectiveness

The real-world evidence on the use of CFTRms in the UK is still accruing. Emerging evidence from three real-world studies conducted in the UK, whose interim analyses were published at the time of preparing this dossier, [redacted].

The largest UK registry-based cohort study to date, the UKCFR study, has been conducted to satisfy commitments of the DCA and further understand the long-term effectiveness of CFTRms under real-world conditions of use in the UK (8). Due to the rapid uptake of IVA/TEZ/ELX in the UK, a large cohort of pwCF aged 6 years or older with data before and after treatment initiation was available for analyses. [redacted]

[redacted] (8).

Patients treated with IVA/TEZ/ELX or TEZ/IVA [redacted]

One of the objectives of CFD-004 (MAGNIFY), CDF-005 (TRAJECTORY) and UKCFR was to address the data gap on the impact of CFTRms, especially IVA/TEZ/ELX, on QoL of UK patients and their caregivers across all levels of disease severity. Results of the IA of MAGNIFY [redacted]

[redacted]

(231).

B.2.11.4.2 Safety

[redacted]

B.2.11.4.3 Strengths and limitations

[redacted]

[redacted]

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify economic evaluations associated with management of pwCF. The SLR was carried out in June 2022. It identified 30 unique economic evaluation studies described in 32 publications (Table 80). The full search methodology is provided in Appendix G. Eleven of the 30 economic evaluations have been conducted from the perspective of the UK healthcare payer, but the model structure of all identified studies could be considered relevant and generalisable to the UK setting.

Table 80. Summary list of published cost-effectiveness studies

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
1	Christopher 1999 (284)	CF patients, aged ≥5 years, with mild to moderate lung disease	**Model type:** Cohort model based on association between $ppFEV_1$ and lung function **Health states:** Model tracks mean FEV_1 as a function of age and treatment **Time horizon:** Lifetime **Cycle length:** NR **Perspective:** UK NHS perspective **Cost year/ currency:** 1996-1997/GBP (£) **Discount rate:** Costs: 6.0%, outcomes: 0.0%	rhDNase	NR	rhDNase was associated with 2 discounted incremental LYs	NR	£26,275	£52,550/ LY gained
				BSC without rhDNase	NR		NR		
2	Suri 2002 (285) and Grieve 2003 (286)	Children with CF aged 5 to 18 years	**Model type:** Cost-consequence **Health states:** NR	HS	NA	NA	£4,285	NA	NA
				Daily rhDNase	NA	**Incremental effectiveness in $ppFEV_1$:**	£5,694	Daily rhDNase vs HS: £1409 Daily vs alternate day rhDNase: £464	Daily rhDNase vs HS: £110 per 1% gain in FEV_1

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Time horizon: 12 weeks **Cycle length:** NR **Perspective:** UK NHS perspective **Cost year/currency:** 1999-2000/GBP (£) **Discount rate:** NR			Daily rhDNase vs HS: 14 Daily vs alternate day rhDNase: 2			Daily vs alternate day rhDNase: £214 per 1% gain in FEV_1
				Alternate day rhDNase	NA	**Incremental effectiveness in ppFEV$_1$:** Alternate day rhDNase vs HS: 12	£5,230	Alternate day rhDNase vs HS: £945	Alternate day rhDNase vs HS: £89 per 1% gain in FEV_1
3	Iles 2003 (287)	CF patients	**Model type:** Model based on a retrospective cohort during one-year period before TNS treatment and one-year period on treatment, matched to a cohort of patients on usual care **Health States:** NR **Time horizon:** 2 years **Cycle length:** NR **Perspective:** UK NHS perspective **Cost year/currency:** 2001/GBP (£) **Discount rate:** NR	TNS	NA	FEV_1% predicted change in 1-year pre-TNS and 1-year post-TNS: -1.26	1-year pre-TNS: £28,394 1-year post-TNS: £28,394	Change (post minus pre): £6,292	NA
4	Groen 2004 (288)	CF patients in lung transplantation program	**Model type:** Microsimulation **Health states:** Flow of patients through the phases of the Dutch lung transplantation program **Time horizon:** Lifetime **Cycle length:** NR **Perspective:** Societal perspective in Netherlands	Lung transplantation	1,177	526	$81.36 million	$43.62 million	CUR: $83,200 CER: $101,700
				No lung transplantation	652		$37.74 million		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Cost year/currency: 2000/USD ($) **Discount rate:** 5% for both costs and effects						
5	Thornton 2005 (289)	Adult CF patients	**Model type:** Cost-consequence **Health states:** NR **Time horizon:** 1 year **Cycle length:** NR **Perspective:** UK NHS perspective **Cost year/currency:** 2002/GBP (£) **Discount rate:** NR	Home-based IV antibiotic treatment	Proportion of patients with decline in ppFEV$_1$ ≤0%: 42.6	NA (reference)	£13,528	NA (reference)	NA (reference)
				Hospital-based IV antibiotic treatment	Proportion of patients with decline in ppFEV$_1$ ≤0%: 58.8	**Hospital vs both:** 8.8% increase in proportion of patients with a decline >0% **Hospital vs home:** 16.2% increase in proportion of patients with a decline >0%	£22,609	**Hospital vs both:** £2,682 **Hospital vs home:** £9,081	**Hospital vs both:** £10,923 **Hospital vs home:** £46,098
				Both home- and hospital-based antibiotic treatment	Proportion of patients with decline in ppFEV$_1$ ≤0%: 50	**Both vs home:** 7.4% increase in proportion of patients with a decline >0%	£19,927	**Both vs home:** £6,339	**Both vs home:** £71,710
6	Woodward 2010 (290)	CF patients aged ≥6 years with chronic *Pseudomonas aeruginosa* infection	**Model type:** Population-based budget impact model in Microsoft Excel **Health States:** NR **Time horizon:** 4 years **Cycle length:** NR **Perspective:** US managed-care perspective **Cost year/currency:** 2018/USD ($) **Discount rate:** NR	TIS + BSC	NA	NA	**Total budget impact**: - Current utilisation: $2,923,103 - Year 1: $3,154,353 - Year 2: $3,385,604 - Year 3: $3,616,854 - Year 4: $3,848,105	NA	NA
7	NICE TA266 2012 (291)	CF patients, aged ≥18 years	**Model type:** Patient-level simulation Markov model	Mannitol DPI	10.52	0.77	£211,923	£31,735	£41,074
				BSC	9.75		£180,188		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Health states: • CF • Improved respiratory symptoms • Lung transplant • Death due to CF • Death due to unrelated cause **Time horizon:** Lifetime **Cycle length:** • Cycle 1: 6 weeks • Cycle 2: 8 weeks; • Cycle 3+: 12 weeks **Perspective:** UK NHS and PSS perspective **Cost year/currency:** 2009/GBP (£) **Discount rate:** 3.5% for both costs and effects	Mannitol DPI + rhDNase	10.52	0.77	£285,858	£36,386	£47,095
				BSC + rhDNase	9.75		£249,472		
8	Tappenden 2013 (292)	CF patients with chronic *Pseudomonas aeruginosa* infection	**Model type:** Markov model **Health states:** • FEV_1 70-99% • FEV_1 40-69% • FEV_1 <40% • Post transplant • Death **Time horizon:** Lifetime **Cycle length:** 24 weeks **Perspective:** UK NHS perspective **Cost year/currency:** 2011-2012/GBP (£) **Discount rate:** 3.5% for both costs and effects	Colistimethate sodium DPI	**Colistimethate sodium DPI price:** £9.11: 9.48 £10.60: 9.48 £15.98: 9.48 £19.64: 9.48 £21.20: 9.48 £39.29: 9.48	**Colistimethate sodium DPI price:** £9.11: -0.13 £10.60: -0.13 £15.98: -0.13 £19.64: -0.13 £21.20: -0.13 £39.29: -0.13	**Colistimethate sodium DPI price:** £9.11: £93,916 £10.60: £107,391 £15.98: £156,045 £19.64: £189,145 £21.20: £203,253 £39.29: £366,852	**Colistimethate sodium DPI price:** £9.11: -£16,603.1 £10.60: -£3,128.1 £15.98: £45,526.7 £19.64: £78,626.4 £21.20: £92,734.5 £39.29: £256,333.8	**Colistimethate sodium DPI price:** £9.11: £126,259 £10.60: £23,788 £15.98: Dominated £19.64: Dominated £21.20: Dominated £39.29: Dominated
				Nebulised tobramycin	**Colistimethate sodium DPI price:** £9.11: 9.61 £10.60: 9.61 £15.98: 9.61 £19.64: 9.61 £21.20: 9.61 £39.29: 9.61		**Colistimethate sodium DPI price:** £9.11: £110,519 £10.60: £110,519 £15.98: £110,519 £19.64: £110,519 £21.20: £110,519 £39.29: £110,519		
	Tappenden 2014 (293)			Colistimethate sodium DPI	**Pricing scenario:** List price: 9.48 PAS price: 9.48	**Pricing scenario:** List price: -0.13 PAS price: -0.13	**Pricing scenario:** List price: £167,983 PAS price: £72,572.6	**Pricing scenario:** List price: £57,464.3 PAS price: -£37,946.1	**Pricing scenario:** List price: Dominated PAS price: £288,563
				Nebulised tobramycin	**Pricing scenario:** List price: 9.61 PAS price: 9.61		**Pricing scenario:** List price: £110,518.7 PAS price: £110,518.7		
				Tobramycin DPI	**Pricing scenario:**	**Pricing scenario:**	**Pricing scenario:**	**Pricing scenario:**	**Pricing scenario:**

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
					List price:8.73 PAS price: 8.73	List price: 0.34 PAS price: 0.34	List price: £136,965.0 PAS price: £75,237.2	List price: £42,453.2 PAS price: £19,274.6	List price: £123,563 PAS price: Dominated
				Nebulised tobramycin	**Pricing scenario:** List price: 8.38 PAS price: 8.38		**Pricing scenario:** List price: £94,511.8 PAS price: £94,511.8		
9	Sole 2014 (294)	CF patients and chronic pulmonary infection by *Pseudomonas aeruginosa*	**Model type:** Annual cost analysis model **Health states:** NR **Time horizon:** NR **Cycle length:** NR **Perspective:** Spanish National Healthcare System perspective **Cost year/currency:** 2014 /Euro (€) **Discount rate:** Ex-factory prices considering local mandatory discounts	Inhaled antibiotic treatment switched to AZLI	NA	NA	**Cost savings related to switch from current treatment to AZLI:** I. Switching from colistimethate sodium (Promixin®) continuous - 4 units: €2,398 savings II. Switching from tobramycin (Bramitob®) continuous: €1,649 savings III. Switching from tobramycin (TOBI®) continuous: €1,649 savings IV. Switching from TOBI® alternated with Promixin® - 4 units: €2,024	NA	NA
10	Whiting 2014 (128)	CF patients, aged ≥6 years who have at least one *G551D* mutation in the *CFTR* gene	**Model type:** Deterministic patient-level simulation **Health states:** Model simulates disease progression of CF patients included in two trials beyond the trial duration based on decline in ppFEV$_1$. At each time step patient characteristics are updated and fed back into the model **Time horizon:** Lifetime **Cycle length:** NR **Perspective:** UK NHS perspective **Cost year/currency:** 2011/ GBP (£)	IVA + BSC	**Scenario:#** Conservative: 9.87 Intermediate: 10.76 Optimistic: 13.86	**Scenario:#** Conservative:1.27 Intermediate: 2.16 Optimistic: 5.26	**Scenario:#** Conservative: £1,882,254 Intermediate: £1,930,690 Optimistic: £2,029,969	**Scenario:#** Conservative: £1,614,861 Intermediate:£1,663,297 Optimistic: £1,762,567	**Scenario:#** Conservative: £1,273,805 Intermediate: £771,297 Optimistic: £334,775
				BSC	**Scenario:#** Conservative: 8.60 Intermediate: 8.60 Optimistic: 8.60		**Scenario:#** Conservative: £267,393 Intermediate: £267,393 Optimistic: £267,393		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Discount rate: 3.5% for both costs and effects						
11	Schechter 2015 (295)	CF patients, aged ≥6 years *Pseudomonas aeruginosa* - positive sputum culture within the previous three months, and FEV_1 less than or equal to 75% predicted at screening	**Model type:** Markov state transition model **Health States:** • $ppFEV_1$ severity • Transplant status • Death **Time horizon:** 3 years **Cycle length:** 28 days **Perspective:** US third party payer perspective **Cost year/currency:** 2013-2014/USD ($) **Discount rate:** 3% for both costs and effects	AZLI	1.916	0.029	$226,352	$41,947	AZLI is dominant
				TIS	1.887		$268,298		
12	Schultz 2015 (296)	CF patients, aged ≥8 years with indicated mutation	**Model type:** Patient-level Markov model **Health States:** • Mild disease • Moderate disease • Severe disease • Lung transplant • Post-lung transplant • Death **Time horizon:** 65 years **Cycle length:** NR **Perspective:** US third party payer perspective **Cost year/currency:** NR/USD ($) **Discount rate:** 3% for both costs and effects	IVA + BSC	**Scenario:** I. Unchanged effectiveness: 15.8 II. Moderate decline in effectiveness: 15.4 III. Rapid decline in effectiveness: 15.2	**Scenario:** I. Unchanged effectiveness: 0.8 II. Moderate decline in effectiveness: 0.3 III. Rapid decline in effectiveness: 0.3	$4.7 million	$3.3 million	Ranged between $4.7 million to $29 million
				BSC	**Scenario:** I. Unchanged effectiveness: 15.0 II. Moderate decline in effectiveness: 15.1 III. Rapid decline in effectiveness: 15.1		$1.4 million		
13	Schwenkglenks 2015 (297)	Adult CF patients	**Model type:** Microsimulation **Health States:** NR **Time horizon:** Lifetime	Mannitol dry powder + BSC	NR	0.54	NR	€18,370	€33,772
				BSC	NR		NR		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Cycle length: NR **Perspective:** Publicly funded HSE perspective in Ireland **Cost year/currency:** NR/EUR (€) **Discount rate:** NR						
14	Dilokthornsakul 2016 (298)	CF patients with *G551D* mutation	**Model type:** Markov state transition model **Health States**: • FEV_1 70% and above • FEV_1 40-69% • FEV_1 <40% • Lung transplant • Death **Time horizon:** Lifetime **Cycle length:** 1 year **Perspective:** US payer **Cost year/currency:** 2013/USD ($) **Discount rate:** Costs: 3.0%, effects: 0.0%	IVA + usual care Usual care	57.18 42.15	15.03	$4,504,768 $1,130,184	$3,374,584	NR
15	Medic 2016a (299)	CF patients with chronic *Pseudomonas aeruginosa* lung infection	**Model type:** Markov model **Health states:** • CF disease states based on $ppFEV_1$ levels • Lung transplant • Death **Time horizon:** 3 years and 5 years **Cycle length:** 24 weeks **Perspective:** Belgian	LIS AZLI	3-year: 2.0 5-year: 2.9 3-year: 1.9 5-year: 2.7	3-year: 0.1 5-year: 0.2	3-year: €84,920 5-year: €124,426 3-year: €85,435 5-year: €125,377	3-year: -€515 5-year: -€952	3-year: LIS dominates 5-year: LIS dominates

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			healthcare payer perspective **Cost year/currency:** NR/EUR (€) **Discount rate:** NR						
16	Medic 2016b (300)	CF patients with chronic *Pseudomonas aeruginosa* lung infection	**Model type:** Markov model **Health states:** The model simulated CF disease progression based on ppFEV$_1$ levels as well as lung transplantation and death **Time horizon:** 3 years, 5 years, and lifetime **Cycle length:** 24 weeks **Perspective:** Swedish healthcare payer perspective **Cost year/currency:** 2016/ Swedish Kronar (SEK≈0.11 Euro) **Discount rate:** NR	LIS	3-year: 1.9 5-year: 2.9 Lifetime: 6.9	3-year: 0.2 5-year: 0.3 Lifetime: 0.9	3-year: SEK 1,033,727 5-year: SEK 1,513,528 Lifetime: SEK 3,558,076	3-year: SEK 584 5-year: SEK 2,273 Lifetime: SEK 177,808	3-year: SEK 3,477 5-year: SEK 7,516 Lifetime: SEK 190,316
				TIP	3-year: 1.8 5-year: 2.6 Lifetime: 5.9		3-year: SEK 1,033,143 5-year: SEK 1,511,254 Lifetime: SEK 3,380,269		
				LIS	3-year: 1.9 5-year: 2.9 Lifetime: 6.9	3-year: 0.1 5-year: 0.2 Lifetime: 0.7	3-year: SEK 1,033,727 5-year: SEK 1,513,528 Lifetime: SEK 3,558,076	3-year: SEK 35,444 5-year: SEK 52,348 Lifetime: SEK 253,955	3-year: SEK 309,547 5-year: SEK 243,603 Lifetime: SEK 348,375
				AZLI	3-year: 1.8 5-year: 2.6 Lifetime: 6.1		3-year: SEK 998,283 5-year: SEK 1,461,180 Lifetime: SEK 3,304,121		
17	NICE TA398 2016 (301)	CF patients aged ≥12 homozygous for the *F508del* mutation	**Model type:** Patient-level microsimulation **Health states:** The model simulated patients disease progression, clinical outcomes and associated health outcomes and costs beyond the trial duration, including ppFEV$_1$, weight-for-age z-score, risk of pulmonary exacerbations, age, probability of lung	LUM/IVA + BSC	12.38	3.45	£1,131,202	£753,570	£218,248
				BSC	8.92		£377,632		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			transplantation, probability of adverse events, diabetes status and probability of treatment discontinuation **Time horizon:** Lifetime **Cycle length**: 4-week cycle for the first 2 years and yearly thereafter **Perspective:** UK NHS and PSS perspective **Cost year/currency:** 2014/GBP (£) **Discount rate:** 3.5% for both costs and effects						
18	AWMSG 2017 (302)	CF patients aged ≥18 years who have an *R117H* mutation in the *CFTR* gene	**Model type:** Patient-level microsimulation **Health states:** The model simulated disease progression according to each patient's characteristics and medical history. Individual characteristics were captured as covariates in a Cox proportional hazards model, which was used to simulate the survival of each patient based on individual ppFEV$_1$, pulmonary exacerbations, weight-for-age z-score, diabetes status, certain respiratory infections, pancreatic sufficiency,	IVA + BSC	13.86	4.37	NR	NR	NR
				BSC	9.49		NR		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			patient age, and gender. **Time horizon:** Lifetime **Cycle length:** 4-week cycle for the first 2 years and yearly thereafter **Perspective:** UK NHS perspective **Cost year/currency:** NR/GBP (£) **Discount rate**: 3.5% for both costs and effects						
19	Dilokthornsakul 2017 (303)	CF patients homozygous for *F508del* mutation	**Model type**: Markov model **Health states:** • Mild lung disease • Moderate lung disease • Severe lung disease • Lung transplantation death **Time horizon:** Lifetime **Cycle length:** 1-year cycle **Perspective**: US payer perspective **Cost year/currency**: 2016/USD ($) **Discount rate:** 3% for both costs and effects	LUM/IVA + usual care	39.13	2.42	$3,904,539	$2,632,249	NR
				Usual care	36.71		$1,272,290		
20	Graz 2017 (304)	CF patients with *Pseudomonas aeruginosa* infection	**Model type**: Markov state transition model **Health states:** • FEV_1 70-99% • FEV_1 40-69% • FEV_1 <40% • Post-transplant	New technology was defined as an adjunct to BSC (i.e., inhaled aminoglycosides)	9.50	0.019	£103,974	£536.47	£27,833
				Tobramycin	9.49		£103,438		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			• Death **Time horizon**: Lifetime **Cycle length:** NR **Perspective**: UK NHS perspective **Cost year/ currency:** NR/GBP (£) **Discount rate**: NR						
21	Panguluri 2017 (305)	CF patients with chronic *Pseudomonas aeruginosa* infection	**Model type:** Patient-level simulation **Health States:** Parameters considered in this model included decline in ppFEV$_1$, frequency of pulmonary exacerbations, and overall survival **Time horizon:** 10 years **Cycle length:** 6 months **Perspective:** US healthcare payer perspective **Cost year/currency:** 2016/USD ($) **Discount rate:** 3% for both costs and effects	TIP	NR	0.27	NR	-$36,168	$134,000
				TIS	NR		NR		
22	Sharma 2018 (306)	CF patients, aged ≥12 years homozygous for *F508del-CFTR* mutation	**Model type:** Markov state transition model **Health States:** • Mild disease (FEV$_1$ 70% and above) • Moderate disease (FEV$_1$ 40-69%) • Severe disease (FEV$_1$ <40%)	LUM/IVA	2-year: 2.3 4-year: 3.7 6-year: 5.0 8-year: 6.2 10 year: 7.3	2-year: 0.1 4-year: 0.2 6-year: 0.2 8-year: 0.3 10 year: 0.5	2-year: $562,075 4-year: $904,313 6-year: $1,221,224 8-year: $1,512,761 10 year: $1,778,921	2-year: $531,306 4-year: $852,463 6-year: $1,148,863 8-year: $1,418,488 10 year: $1,662,765	2-year: $7,311,801 4-year: $5,835,535 6-year: $4,869,328 8-year: $4,173,169 10 year: $3,655,352
				Usual care	2-year: 2.2 4-year: 3.6 6-year: 4.8 8-year: 5.9 10 year: 6.8		2-year: $30,469 4-year: $51,850 6-year: $72,361 8-year: $94,274 10 year: $116,156		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			• Post-transplantation • Death **Time horizon:** 2 years, 4 years, 6 years, 8 years, 10 years (base case) **Cycle length:** 1 year **Perspective:** US healthcare payer perspective **Cost year/currency:** 2016/USD ($) **Discount rate:** 3% for both costs and effects						
23	Vadagam 2018 (307)	CF patients, aged ≥12 years homozygous for *F508del* mutation of the *CFTR* gene	**Model type:** Static decision model, cost-effectiveness analysis **Health States:** Based on $ppFEV_1$ from the clinical trial **Time horizon:** 1 year **Cycle length:** NR **Perspective:** US third party payer perspective **Cost year/currency:** 2016/USD ($) **Discount rate:** NR	LUM/IVA Placebo	NA NA	NA	$379,780 $113,735	$266,045	$95,016 per additional 1-unit $ppFEV_1$ per patient
24	Lopez 2019 (308)	CF patients, aged 2 years with an indicated *CFTR* gating mutation	**Model type:** Patient-level simulation **Health States:** NR **Time horizon:** Lifetime	IVA BSC	NR NR	NR	NR NR	NR	Base case: $1,165,595 Alternate scenario: $130,317

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Cycle length: NR **Perspective:** US third party payer perspective **Cost year/currency:** NR/USD ($) **Discount rate:** • Base-case: 3% for both costs and effects • Alternate scenario: 3% costs, 1.5% effects						
25	Rezaei 2019 (309)	CF patients	**Model type:** Patient-level simulation Markov model **Health States:** defined by ppFEV$_1$ levels **Time horizon:** 10 years **Cycle length:** NR **Perspective:** Iranian NHS perspective **Cost year/currency:** 2018/USD $ **Discount rate:** 5% for both costs and effects	Nebulized dornase alfa	5.6	0.2	$118,617	$615	$2,673
				Inhaled tobramycin	5.4		$118,002		
26	Warren 2019 (310)	CF patients, aged ≥6 years with severe baseline lung disease	**Model type:** Probabilistic patient-level simulation Markov model **Health States:** • No event • Pulmonary exacerbation • Lung transplant • Death	Inhaled mannitol + BSC	12.2	0.6	AU$308,027	AU$23,084	AU$39,165
				BSC	11.6		AU$284,943		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Time horizon: Lifetime **Cycle length:** • Cycle 1: 12 weeks • Cycle 2: 2 weeks • Cycle 3+: 12 weeks **Perspective:** Australian national healthcare system perspective **Cost year/currency:** 2017/AUD ($) **Discount rate:** 5% for both costs and effects						
27	Wherry 2020 (311)	CF patients with the *G551D* mutation	**Model type:** Patient-level simulation **Health States:** NR **Time horizon:** Lifetime **Cycle length:** 1 year **Perspective:** US payer perspective **Cost year/currency:** 2018/USD ($) **Discount rate:** 3% for both costs and effects	IVA + BSC	22.9	6.8	$8,797,840	$6,461,474	$950,217
				BSC	16.1		$2,336,366		
28	Langton Hewer 2021 (312)	CF patients aged over 28 days with a positive isolation of *Pseudomonas aeruginosa*	**Model type:** Linear regression models **Health States:** NR **Time horizon:** 15 months from randomisation **Cycle length:** NR	Oral antibiotic therapy (12 weeks of oral ciprofloxacin)	1.114	0.063	£3,565.4	£954.9	Oral IV antibiotic therapy dominates
				IV antibiotic therapy (2 weeks of IV ceftazidime and tobramycin)	1.050		£2,610.5		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
			Perspective: UK NHS and PSS perspective **Cost year/currency:** 2016-2017/GBP (£) **Discount rate:** NR						
29	Yang 2021 (313)	CF patients aged ≥6 years heterozygous for *F508del* and a minimal function mutation	**Model type:** Patient-level simulation, cost-consequence analysis **Health States:** NR **Time horizon:** 5 years **Cycle length:** NR **Perspective:** NR **Cost year/currency:** NR **Discount rate:** NR	ELX /TEZ/IVA + BSC	NA	NA	NA	ELX /TEZ/IVA + BSC was associated with an average cost savings of $358,985 over the 5-year time horizon	-
				BSC	NA		NA		
30	Rubin 2022 (314)	CF patients, aged ≥12 years with *F508del*/minimal function genotypes	**Model type:** Patient-level simulation **Health States:** NR Lifetime **Time horizon:** Lifetime **Cycle length:** 4-week cycles for the first 2 years of the model horizon, and 1-year cycles thereafter **Perspective:** NR **Cost year/currency:** 2019/USD ($) **Discount rate:** Costs: 3%, effects: 1.5%	ELX/TEZ/IVA + BSC	19.9	9.2	$6,609,000	$4,416,000	$482,000
				BSC	10.8		$2,193,000		

No.	Author year	Patient population	Summary of model	Intervention	QALYs	Incremental QALYs	Costs	Incremental costs	ICER
[#] In the conservative scenario, the percentage predicted FEV_1 of ivacaftor-treated patients stays stable for 96 weeks, after which it declines by the same rate as in the standard care population. In the optimistic scenario, the percentage predicted FEV_1 of ivacaftor-treated patients stays stable over lifetime, while in standard care patients the percentage predicted FEV_1 declines over time. The intermediate scenario lies between the conservative and optimistic scenarios, with the percentage predicted FEV_1 of ivacaftor-treated patients declining after 96 weeks at a rate of 66% of that of standard care patients. Abbreviations: AUD, Australian dollars; AZLI, aztreonam lysine for inhalation solution; BSC: best supportive care CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CER, cost-effectiveness ratio; CUR, cost-utility ratio; DPI, dry powder for inhalation; ELZ/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; EUR, Euro; GBP, Great British Pound; HS, hypertonic saline; HSE, health service executive ICER, incremental cost-effectiveness ratio; IV, intravenous; IVA, ivacaftor; LIS, levofloxacin inhalation solution; LUM/IVA, lumacaftor/ivacaftor; LY, life year; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; PSS, personal social services; QALY, quality-adjusted life year; rhDNase, recombinant human deoxyribonuclease; SEK, Swedish Krona; ECM, best supportive care; TIP; tobramycin inhalation powder; TIS, tobramycin inhalation solution; TNS, tobramycin nebuliser solution; vs, versus; UK, United Kingdom; US, United States; USD, US Dollar; FEV_1, Forced expiratory volume in 1 second.									

B.3.2 Economic analysis

A patient-level state-transition simulation model was developed to evaluate the cost-effectiveness of CFTRms in combination with ECM for the treatment of CF in patients with at least one *F508del* mutation in the *CFTR* gene from a UK NHS and Personal Social Services (PSS) perspective.

The decision analytic framework and the underlying survival model are consistent with those described in the single technology appraisal of LUM/IVA (TA398) (301). The latter is also consistent with several published survival analyses for CF patients in the UK and US treated with IVA/TEZ/ELX (315-319), LUM/IVA (320) and TEZ/IVA (321-323). Slight modifications to these published models have been made to improve efficiency and external validity, and to reflect the most recent cost and prevalence data.

Based on this patient-level simulation, three cost-effectiveness analyses have been conducted to independently evaluate IVA/TEZ/ELX, LUM/IVA and TEZ/IVA in combination with ECM for the treatment of CF in the indicated populations for each CFTRm. Detailed description of patient populations and comparators considered in the economic analyses is provided below.

B.3.2.1 Patient population

B.3.2.1.1 IVA/TEZ/ELX

The economic analysis for IVA/TEZ/ELX evaluates IVA/TEZ/ELX used in combination with ECM for the treatment of pwCF aged 6 years and older with at least one *F508del* mutation in the *CFTR* gene. The IVA/TEZ/ELX model considers four genotype subgroups, namely patients who are homozygous for *F508del* mutation (F/F) or who are heterozygous for the *F508del* mutation and have either a MF, or a RF, or a gating mutation in the *CFTR* gene. CF patients who are heterozygous for *F508del-CFTR* with a second allele that is unknown and/or has not yet been characterised as MF, RF, or gating, were included in the F/MF subgroup, since it is expected that any CF patient with at least one *F508del-CFTR* mutation would experience a similar or greater treatment benefit based on the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele, regardless of the mutation on the second allele.

B.3.2.1.2 LUM/IVA

The economic analysis for LUM/IVA evaluates LUM/IVA used in combination with ECM for the treatment of pwCF aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

B.3.2.1.3 TEZ/IVA

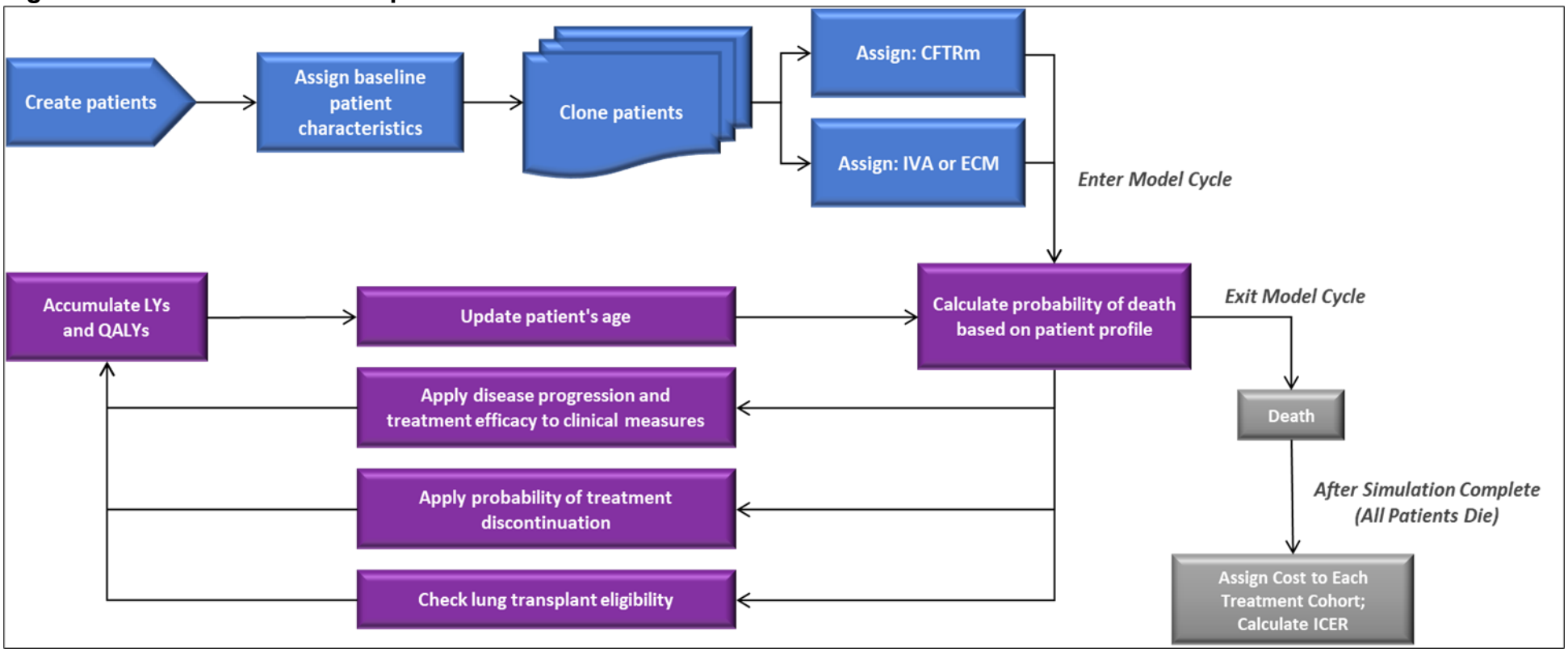
The economic analysis for TEZ/IVA evaluates TEZ/IVA used in combination with ECM for the treatment of pwCF aged 6 years and older who are homozygous for *F508del mutation* or who are heterozygous for the *F508del* mutation and have a RF mutation in the *CFTR* gene.

B.3.2.2 Model structure

The model was constructed as an individual patient state-transition simulation (i.e., microsimulation) to estimate lifetime clinical and economic outcomes associated with the use of CFTRms in the indicated patient populations. Although more computationally intensive than other state-transition models (i.e., Markov model), the microsimulation structure is well-suited for modelling CF, as it captures the heterogeneity of the disease and tracks specific time-dependent patient characteristics and treatment effects that influence survival.

The model structure is outlined in Figure 84, and is consistent with the model submitted to NICE for LUM/IVA (TA398) in 2016 (301).

Figure 84. Model schematic for patient-level simulation



Note: Clinical measures tracked include $ppFEV_1$, the occurrence of PEx, weight-for-age z-score, and CF-related diabetes. Modelled variables can be classified as follows: 1) treatment-independent variables: age, gender, CF-related diabetes, pancreatic sufficiency status; 2) variables causally affected by treatment: $ppFEV_1$, PEx, weight-for-age z-score; and 3) variables estimated as function of those causally affected by treatment: risk of death, annual number of PEX, lung transplant.
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; LY, life year; $ppFEV_1$, percent predicted forced expiratory volume in one second; PEx, pulmonary exacerbation; QALY, quality-adjusted life year.

Two cohorts with identical baseline characteristics were simulated to estimate the long-term costs and health outcomes of patients treated with CFTRm or with the comparator. The simulated cohort was derived from patient-level baseline data collected in the clinical trials evaluating CFTRms (see Section B.3.3.1).

Survival predictions are based on the Cox proportional hazards (CPH) model from Liou et al. (64) that relates survival to the clinical characteristics of pwCF in the absence of the CFTRm treatment. The cohort assigned to the CFTRm treatment in the model was identical at baseline to the cohort treated with the comparator to ensure that any differences in modelled outcomes between the two cohorts were attributable to treatment received, rather than to differences in patient baseline characteristics.

Consistent with the previous models, a total of 2,000 individual patient profiles were simulated for each treatment cohort in deterministic analysis (301), as this is the number of profiles needed to achieve stable model outputs (i.e., a negligible change in the cohort-level result was seen when simulating more than 2,000 patients).

Individual patient survival predictions were derived by combining survival estimates in the overall CF population in the UK with the CPH model from Liou et al. (64) that links survival in CF to nine risk factors, namely:

- Age
- Gender
- $ppFEV_1$
- Annual number of PEx
- Respiratory infections (*Staphylococcus aureus [S. aureus]* and *Burkholderia cepacia [B. cepacia]*)
- CFRD
- Weight-for-age z-score (WFAZ)
- Pancreatic sufficiency status.

This methodology allows mortality to be influenced by changes in individual patient characteristics that predict survival, as some of these characteristics evolve over time (64). Therefore, values for these characteristics are needed at baseline for the patient population entering the model. Age, gender, $ppFEV_1$ and WFAZ were derived from patient-level baseline data collected in the relevant genotype-specific pivotal trials in which patients were CFTRm naïve at baseline. Survival differences between treatment

cohorts are achieved based on differences in $ppFEV_1$, annual number of PEx, and WFAZ, as treatment with a CFTRm has been shown to impact these three characteristics.

The simulated patients are tracked through the model in four-week cycles for the first two years of the model horizon to capture shorter-term outcomes observed in the CFTRm clinical trials, and one-year cycles thereafter. During each cycle, patients' age, $ppFEV_1$, WFAZ, annual PEx rate, eligibility and occurrence of lung transplantation, development of CFRD, and treatment discontinuation are updated for patients aged ≥6 years. For patients aged 2-5 years, only age and treatment discontinuation are updated during each cycle; $ppFEV_1$ is not tracked in the model until age 6, as it is not considered a reliable measure in the younger age group.

After the microsimulation completes for all simulated patients, the model aggregates the clinical characteristics across the cohort (e.g., totalling the number of life years spent in each $ppFEV_1$ disease strata across the cohort). Costs are then assigned to the cohort, rather than to individual patients. Since cost calculations are not occurring at each model cycle, the microsimulation component can operate much more quickly, reducing model run time significantly, while delivering computationally equivalent cost calculations as if they were assigned during each cycle of the microsimulation.

The model reports life years (LYs), quality-adjusted life years (QALYs), and costs per treatment cohort, as well as incremental outcomes and incremental cost-effectiveness ratios (ICERs). The model also reports mean and median predicted survival, proportion of undiscounted LYs in each $ppFEV_1$ state, cumulative change in $ppFEV_1$, total number and annual rate of PEx, proportion of patients receiving a lung transplant, and mean and median time to lung transplant among the transplanted. As the model outcomes are presented for the licenced indication for each CFTRm under economic evaluation, in the case of IVA/TEZ/ELX and TEZ/IVA, the indicated populations comprise four and two genotype subgroups, respectively. Therefore, the weighted average of subgroups defined by genotypes is used to represent the overall patient populations for IVA/TEZ/ELX and TEZ/IVA.

B.3.2.2.1 Discount rate

A differential annual discount rate of 1.5% for health outcomes and 3.5% for costs is applied in the base case.

Uniform discounting of costs and benefits leads to prioritisation of treatments with immediate health benefits and works against preventative health programmes and other interventions characterised by early investment and late accrual of health benefits. The national HTA guidelines of Belgium, Poland and the Netherlands, recommend using a lower discount rate for outcomes (1.5%, 1.5% and 3.5%, respectively) compared with costs (3%, 4% and 5%, respectively), arguing that this is a normative decision taken to "avoid too strong penalisation of interventions such as screening or vaccination programmes" where uniform discounting could lead to perpetual deferral of investment (11-14).

It has been shown that equal discount rate for costs and outcomes is appropriate for decision making in a society maximising the present value of health under the conditions of a fixed NHS budget and a constant willingness-to-pay threshold (136). However, it is likely that the value of health over time will increase due to rising social expectations regarding maintaining good health and income growth (16). The increase in the threshold would mean that future additional costs will displace less health; a lower discount rate for health outcomes vs costs would account for such future increase in the value of health benefits (15, 17).

Table 81 summarises the features of the economic model.

Table 81. Features of the economic analysis

Factor	Current appraisal	
	Chosen values	Justification
Time horizon	Lifetime	Chronic progressive disease
Were health effects measured in QALYs; if not, what was used?	Health effects were measured using QALYs	NICE reference case (10)
Discount of 3.5% for utilities and costs	1.5% utilities / 3.5% costs	Differential discounting of costs and benefits was chosen to avoid penalisation of treatments for rare, chronic diseases such as CFTRms, which generate health benefits over long periods; decision is in line with the national HTA guidelines of Belgium, Poland and the Netherlands (11, 12, 14)
Perspective (NHS)	NHS and PSS	NICE reference case (10)
Cycle length	4 weeks for the first 2 years and then annual thereafter	To capture shorter-term clinical outcomes with accuracy and granularity that reproduces results of clinical trials
Half-cycle correction	Yes	NICE reference case (10)

Factor	Current appraisal	
	Chosen values	Justification
Costs	NHS reference costs; CFTRm list prices; UK-based studies; non-UK studies where UK sources unavailable	Where possible, costs relate to NHS and PSS resources and are valued using the prices relevant to the NHS and PSS
Utilities	Baseline utilities by disease severity	Health state utilities stratified by $ppFEV_1$ from [redacted] (Section B.3.4.4).
	Treatment-specific utility increment in pwCF (all *CFTR* genotypes) treated with IVA/TEZ/ELX	[redacted] (Section B.3.4.4)
	Treatment-specific utility increment in pwCF with F/RF genotypes treated with TEZ/IVA	[redacted] (Section B.3.4.4)
	Caregiver treatment-specific utility increment in pwCF who initiate treatment with IVA/TEZ/ELX during ages 6-11 until they turn 12 years old	[redacted] (Section B.3.4.4)
Effectiveness	CFTRm studies, ITCs and assumptions	Evidence selection based on a systematic review
Abbreviations: CF, cystic fibrosis; CFTRm, CF transmembrane conductance regulator modulator; HTA, health technology assessment; ITC, indirect treatment comparison; QALY, quality-adjusted life year; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; $ppFEV_1$, percent predicted forced expiratory volume in one second; PSS, Personal Social Services; pwCF, people with CF; UK, United Kingdom.		

B.3.2.3 Intervention technology and comparators

In clinical trials, CFTRms are administered as add-on to the individualised ECM. The model evaluates costs and benefits of CFTRms in addition to ECM compared to ECM alone and assumes that patients treated with any CFTRm have continued access to ECM, including mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, anti-inflammatory agents and physiotherapy. The doses of the intervention and comparator treatments were implemented as per their marketing authorisation.

B.3.2.3.1 IVA/TEZ/ELX

Within its marketing authorisation, the relevant comparators for IVA/TEZ/ELX include ECM (all *CFTR* genotypes) and IVA as an add-on to ECM in pwCF with F/Gating genotype, as per the 2012 NHS Clinical Commissioning Policy (63). LUM/IVA and TEZ/IVA, on the other hand, are currently prescribed in accordance with a temporary NHS Clinical Commissioning Policy, an extension of which is contingent on this appraisal (6). The reasons why neither treatment is an appropriate comparator for triple combination therapy are outlined in the decision problem table in Section B.1.1.

Established clinical management, comprising components of best supportive care, is the relevant comparator in all four genotypes considered in the IVA/TEZ/ELX model,

as explained in B.3.2.1.1. CF patients with F/Gating genotype receive IVA monotherapy as standard care on NHS, which is thus an additional comparator in this subgroup. Hereinafter, SoC represents the treatment mix of ECM in all subgroups and IVA in F/Gating. The model outcomes with SoC are calculated as a weighted average of the comparators used in each genotype based on market shares first, and then weighted further by genotype prevalence in the overall population of pwCF based on data obtained from the UK CF Registry 2021 (166). As explained in Section B.3.2.1.1, pwCF who are heterozygous for *F508del-CFTR* with a second allele that is unknown and/or has not yet been characterised as MF, RF, or gating are captured in the prevalence estimate for F/MF. The market shares for IVA and ECM in F/Gating are [redacted] and [redacted], respectively (Vertex Pharmaceuticals, unpublished communication). The genotype prevalence and comparator market shares used in the IVA/TEZ/ELX model are presented in Table 82.

Table 82. Genotype prevalence and comparator market shares for IVA/TEZ/ELX

Genotype	Genotype prevalence	Comparators	Market share
F/F	54.28%	ECM	100%
F/MF	28.96%	ECM	100%
F/Gating	10.57%	ECM	[redacted]
		IVA	
F/RF	6.19%	ECM	100%
Source	Data on file obtained from the UK CF Registry 2021 (166)	Unpublished communication with Vertex Pharmaceuticals	
Abbreviations: CF, cystic fibrosis; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; UK, United Kingdom.			

B.3.2.3.2 LUM/IVA

For the population of pwCF aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene, the NICE guideline recommends components of ECM (150). Hence, ECM is the only relevant comparator within the licenced indication for LUM/IVA.

B.3.2.3.3 TEZ/IVA

For the population of pwCF aged 6 years and older who are either homozygous for the *F508del* mutation (F/F genotype) or who are heterozygous for the *F508del* mutation and have one of the RF mutations in the *CFTR* gene (F/RF genotype), the NICE guideline recommends components of ECM (150). Therefore, in the CF population in which TEZ/IVA is indicated, ECM alone is the only relevant comparator.

Model outcomes with ECM are calculated as a weighted average of outcomes for each genotype based on the genotype prevalence data obtained from the UK CF Registry 2021 (**Table 83**) (166).

Table 83. Genotype prevalence used in TEZ/IVA model

Genotype	Genotype prevalence
F/F	89.76%
F/RF	10.24%
Source	Data on file obtained from the UK CF Registry 2021 (166)

B.3.3 Clinical parameters and variables

Clinical inputs for the economic models were derived from clinical trials and ITCs. Where data were not available, assumptions were made.

IVA/TEZ/ELX

Model inputs for patients initiating treatment at age ≥12 were derived from phase 3/3b studies of IVA/TEZ/ELX conducted in populations with F/F (study 445-109), F/MF (study 445-102), F/Gating and F/RF (study 445-104) genotypes. For patients initiating treatment at age 6-11, model inputs were derived from study 445-116 conducted in a CF population with F/MF genotype and study 445-106 conducted in populations with F/F and F/MF genotypes. Model inputs were also informed or supported by data from the interim analyses of the OLE studies, in which patients enrolled in RCTs continued treatment after the end of the randomised phase. Specifically, patients from studies 445-102 and 445-103 (CF patients with F/F or F/MF genotypes aged ≥12 years) were enrolled in OLE 445-105 and patients from study 445-106 (CF patients with F/F or F/MF genotypes aged 6-11 years) were enrolled in study 445-107.

Study 445-102 was designed to demonstrate the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele (Section B.2.5.1.1.1) (53). Since most of the enrolled patients (~78%) had a Class I MF mutation on the other *CFTR* allele which is considered unresponsive to IVA/TEZ/ELX, the clinical benefit derived from IVA/TEZ/ELX is due to the responsiveness of *F508del-CFTR* alone (7). Accordingly, it is expected that any CF patient with at least one *F508del-CFTR* mutation would experience a similar or greater treatment benefit based on the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele, regardless of the mutation on the second allele. Where data on specific endpoints in other populations needed for the model was not available from the studies, such as the PEx treatment effect on patients with F/F, F/Gating and F/RF genotypes aged ≥12 years treated with IVA/TEZ/ELX (Section B.3.3.5.1), the efficacy demonstrated in the F/MF population (PBO-adjusted from study 445-102) was used to estimate the expected efficacy in these patient populations.

The model requires PBO-adjusted estimates of clinical efficacy for CFTRms, since the assignment of baseline mortality hazard is based on a CFTRm-naïve population. To derive PBO-adjusted estimates for IVA/TEZ/ELX in patients with F/F, F/Gating and

F/RF genotypes aged ≥12 years, since the corresponding IVA/TEZ/ELX studies involved active comparators, and in patients with F/F genotype aged 6-11 years, since study 445-106 was a single arm trial, ITCs were conducted using individual patient data from the relevant phase 3 randomised-controlled clinical trials (Section B.2.8), as indicated in Table 84.

Table 84. Indirect treatment comparisons conducted by age group and genotype

Genotype	Age 6-11	Age 12+	Section
F/F	✓ 445-106B (IVA/TEZ/ELX) 809-109 (LUM/IVA vs PBO) 809-011B (LUM/IVA) 661-113B (TEZ/IVA)	✓ 445-109 (IVA/TEZ/ELX vs TEZ/IVA) TRAFFIC (LUM/IVA vs PBO) TRANSPORT (LUM/IVA vs PBO) EVOLVE (TEZ/IVA vs PBO)	6-11: B.2.8.2 12+: B.2.8.3
F/MF	× (direct trial evidence from study 445-116 available)	× (direct trial evidence from study 445-102 available)	
F/Gating	× (no trial evidence for IVA/TEZ/ELX)	✓ 445-104 (IVA/TEZ/ELX vs IVA) STRIVE (IVA vs PBO) KONNECTION (IVA vs PBO) KONDUCT (IVA vs PBO)	12+: B.2.8.5
F/RF	× (no trial evidence for IVA/TEZ/ELX)	✓ 445-104 (IVA/TEZ/ELX vs TEZ/IVA) EXPAND (TEZ/IVA vs PBO)	12+: B.2.8.4

Abbreviations: IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; LUM/IVA, lumacaftor/ivacaftor; PBO, placebo; TEZ/IVA, tezacaftor/ivacaftor.

While IVA/TEZ/ELX clinical efficacy data is not available for the populations with F/Gating and F/RF genotypes aged 6-11 years, IVA/TEZ/ELX has demonstrated robust benefits in patients with F/Gating and F/RF genotypes aged ≥12 years in study 445-104 (168). IVA/TEZ/ELX has demonstrated comparable pharmacokinetic exposures and a consistent safety profile across studied genotypes and age groups. Furthermore, the disease process in CF patients of all age groups stems from a common underlying impairment in CFTR function, and therefore the therapeutic benefit is expected to be comparable between younger age groups and adolescents or adults. The consistency of the therapeutic benefit with IVA/TEZ/ELX across varying age groups has been established in patients with both F/F genotypes (age ≥12 in study 445-103 and study 445-109, age 6-11 in study 445-106) and F/MF genotypes (age ≥12 in study 445-102, age 6-11 in study 445-106 and study 445-116). Thus, the clinical efficacy of IVA/TEZ/ELX in patients with F/Gating and F/RF genotypes aged ≥12 years was used to generate estimates of efficacy in the paediatric population, as described further below. Extrapolating model inputs from clinical trial data in older age groups to younger age groups with the same genotype was considered clinically plausible and appropriate by consulted health economists in an advisory board (324). It was also

considered appropriate by EMA when issuing the marketing authorisation for IVA/TEZ/ELX that covers all genotypes in patients aged 6-11 years.

LUM/IVA

The efficacy inputs for LUM/IVA were derived from phase 3 clinical trials and their corresponding OLE studies, where data is available. For patients initiating treatment at age ≥12, model inputs were derived from the PBO-controlled studies TRAFFIC and TRANSPORT (158). For patients initiating treatment at age 6-11, model inputs were derived from the PBO-controlled study 809-109 (159). Model inputs were also informed or supported by data from the OLE studies PROGRESS (155), where patients from TRAFFIC/TRANSPORT were enrolled, and study 809-110 (156), where patients from studies 809-011B and 809-109 were enrolled. For patients initiating treatment at age 2-5, model inputs were derived from studies 809-115B (162) and 809-116 (161).

TEZ/IVA

Model inputs for patients initiating treatment at age ≥12 were derived from phase 3 studies of TEZ/IVA conducted in populations with F/F (EVOLVE) and F/RF (EXPAND) genotypes (157, 164). Long-term efficacy inputs for TEZ/IVA in patients of this age group with F/F and F/RF genotypes were informed by OLE study EXTEND (222, 325). For patients with F/F and F/RF genotypes treated with TEZ/IVA aged 6-11 years, since EMBRACE was neither designed nor powered for between-group comparisons with the control arms, the model uses the within-group change from baseline (326).

B.3.3.1 Baseline characteristics

As described in B.3.2.2, survival predictions are based on a CPH model that relates survival to clinical characteristics in pwCF in the absence of treatment with CFTRms (64). Therefore, values for these characteristics are needed at baseline for the patient population entering the model.

The rate of PEx requiring IV antibiotics and/or hospitalisation occurring in the year preceding baseline was predicted conditional on $ppFEV_1$ and age using the relationship derived by Whiting et al. (128) from the 2004 US Cystic Fibrosis

Foundation Patient Registry (CFFPR) data published by Goss et al. (87). Additional details are provided in the Section B.3.3.5.

CFRD status was assigned based on patients' age at model start using age-specific prevalence of CFRD derived from the 2021 UK CF Registry annual data report: 8.3% for patients aged <16 years and 35.2% for patients aged ≥16 years (59). Whilst there is an ongoing risk of developing diabetes from baseline (Section B.3.3.2), pancreatic sufficiency and respiratory infection status are assumed to remain unchanged from baseline over time. Thus, the baseline values for pancreatic sufficiency and respiratory infection status do not contribute to the calculation of mortality hazard which compares patient characteristics from one cycle to the next. [redacted] assuming a constant rate of respiratory infections from baseline constitutes a conservative approach (8, 327, 328).

Four of the characteristics used to predict survival, namely age, gender, ppFEV$_1$ and WFAZ, were derived from patient-level baseline data collected from the appropriate genotype-specific pivotal trials in which patients were CFTRm naïve at baseline.

B.3.3.1.1 Population with F/F genotype

Baseline patient characteristics were derived from 1,998 CF patients aged ≥6 years with F/F genotype who participated in one of the following eight phase 3 trials which required patients to be naïve to CFTRm treatment at baseline:

- Study **661-106 (EVOLVE)**, the TEZ/IVA trial in ≥12 age group (N=503) (157)
- Studies **809-103** and **809-104 (TRAFFIC/TRANSPORT)**, the LUM/IVA trials in ≥12 age group (N=1,097) (158)
- Studies **809-011B** and **809-109**, the LUM/IVA trials in 6-11 age group (N=257) (159, 214)
- The subset of CF patients with F/F genotype from studies **661-113** and **661-115 (EMBRACE)**, the TEZ/IVA trials in CF patients with F/F or F/RF genotypes aged 6-11 years (N=113) (165, 329)
- The subset of CF patients with F/F genotype from study **445-106**, the IVA/TEZ/ELX trial in CF patients with F/F or F/MF genotypes aged 6-11 years (N=28) (174).

The CF patients with F/F genotype aged 6-11 years from study 661-113, EMBRACE, and study 445-106 may have had a prior history of CFTRm use before enrolling in the clinical trials, and therefore were required to undergo a 28-day washout period prior to screening.

The patient profiles from IVA/TEZ/ELX trials conducted in the CF population with F/F genotype, studies 445-103 and 445-109, were not included in the model because these patients were not CFTRm-naïve at baseline (170, 172). The clinical profile of patients at baseline would not reflect expected characteristics in the absence of CFTRm treatment, as required for the model.

When pooling the individual patient profiles from the trials, the proportion of patients aged 6-11 years (20.2%) was found to be lower than in the UK real-world setting. Thus, a weighted trial population was derived, whereby the patient profiles of this age group were oversampled to match the age distribution of the CF patients with F/F genotype in the 2018 UK CF Registry (20.7% aged 6-11, 79.3% aged ≥12 years) (330).

B.3.3.1.1.1 Population with F/F genotype in LUM/IVA model

$ppFEV_1$ is not available for patients aged 2-5 years, since it is not a reliable clinical measure in young children (331). Baseline risk profiles for patients aged 2-5 years were derived by sampling patient-level baseline data (i.e., gender, $ppFEV_1$ and WFAZ) from the profiles of patients aged 6-11 years and randomly assigning an integer baseline age of either 2, 3, 4, or 5 years. The assigned $ppFEV_1$ is the measure of lung function expected in the absence of a CFTRm when a patient turns 6 years of age in the model (the age at which the model starts tracking $ppFEV_1$).

The number of generated profiles for patients aged 2-5 years was based on the age distribution of patients aged 2-5 vs ≥6 years from the 2018 UK CF Registry (11.4% aged 2-5, 88.6% aged ≥6 years) (330).

B.3.3.1.2 Population with F/MF genotype

Baseline patient characteristics were derived from 563 CF patients aged ≥6 years with F/MF genotype who participated in one of the following three phase 3/3b trials:

- Study **445-102**, the IVA/TEZ/ELX trial in ≥12 age group (N=403) (7)

- The subset of CF patients with F/MF genotype from study **445-106**, the IVA/TEZ/ELX trial in CF patients with F/F or F/MF genotypes aged 6-11 years (N=39) (174)
- Study **445-116**, the IVA/TEZ/ELX trial in 6-11 age group (N=121) (204).

When pooling the individual patient profiles from the trials, the proportion of patients aged 6-11 years (28.4%) was found to be greater than in the UK real-world setting. Thus, the synthesised dataset of trial patients was weighted to match the age distribution of CF patients with at least one *F508del* mutation in the 2018 UK CF registry (20.1% aged 6-11, 79.9% aged ≥12 years) (330).

B.3.3.1.3 Population with F/Gating genotype

Baseline patient characteristics were derived from 321 CF patients aged ≥6 years with F/Gating genotype enrolled in one of the following four phase 3 trials:

- Study **770-102 (STRIVE)**, the IVA trial in CF patients with a *G551D* mutation aged ≥12 years (N=161) (332)
- Study **770-103 (ENVISION)**, the IVA trial in CF patients with a *G551D* mutation aged 6-11 years (N=52) (333)
- Study **770-111 (KONNECTION)**, the IVA trial in CF patients with a non-*G551D* gating mutation aged ≥6 years (N=39) (334)
- Study **770-110 (KONDUCT)**, the IVA trial in CF patients with a *R117H* mutation aged ≥6 years (N=69) (335).

The patient profiles from study 445-104 (IVA/TEZ/ELX trial in CF populations with F/Gating, including F/R117H, or F/RF genotypes) were not included in the model because these patients had prior exposure to IVA or TEZ/IVA at baseline.

These four trials of IVA were selected to create a pool of patients for the model similar to those enrolled in study 445-104. However, the IVA trials did not require patients to have a *F508del-CFTR* mutation on the second allele. Limiting to this subset of patients would have decreased the pool of available patients and thereby increased the variability of the model cohort. Since several studies have demonstrated the consistency of the burden of disease and disease progression between CF patients with gating and *F508del* mutations, including patients from trials enrolling subjects with

a gating mutation was not expected to have a significant impact on model outcomes (336, 337).

A synthesised dataset of trial patients was weighted to match the age distribution of CF patients with a gating and *R117H* mutation in the 2018 UK CF registry, respectively (gating: 16.1% aged 6-11, 83.9% aged ≥12 years; *R117H*: 24.9% aged 6-11, 75.1% aged ≥12 years) (330). The number of resulting R117H profiles (69 of 417) closely matches the composition of CF patients with F/Gating genotype in study 445-104 (16 patients with F/R117H genotype of the 95 CF patients in the IVA arm).

B.3.3.1.4 Population with F/RF genotype

Baseline patient characteristics were derived from 268 CF patients aged ≥6 years with F/RF genotype who participated in one of the following three phase 3 trials:

- Study **661-108 (EXPAND)**, the TEZ/IVA trial in ≥12 age group (N = 244) (164)
- The subset of CF patients with F/RF genotype from study **661-113** (N = 9) and **EMBRACE** (N = 15), the TEZ/IVA trials in CF patients with F/F and F/RF genotypes aged 6-11 years (165, 329).

When pooling the individual patient profiles from the trials, the proportion of patients aged 6-11 years (9.0%) was found to be lower than in the UK real-world setting. Thus, a weighted trial population was derived, whereby the patient profiles of this age group were oversampled to match the age distribution of the CF patients with F/RF genotype in the 2018 UK CF Registry (15.6% aged 6-11, 84.4% aged ≥12 years) (330).

A summary of the baseline characteristics of patients entering the models are shown in Table 85.

Table 85. Mean baseline characteristics of patients entering the models

Characteristic	F/F		F/MF	F/Gating	F/RF
	Age ≥6	Age ≥2			
Number of patient profiles available from trials	1998		563	321	268
Number of patient profiles after weighting to match the UK age distribution	2019	2279	780	417	289
Age (Years)	22.4	20.3	22.7	23.6	31.2
Gender (Female)	50.8%	50.7%	50.6%	53.0%	55.0%
WFAZ	-0.37	-0.34	-0.36	-0.13	0.32
$ppFEV_1$	66.5	68.9	67.5	70.2	66.7

Characteristic	F/F		F/MF	F/Gating	F/RF
	Age ≥6	Age ≥2			
Trials	TRAFFIC/TRANSPORT (158), EVOLVE (157), 809-011B (214), 809-109 (159), 445-106 (174), 661-113 (329), EMBRACE (165)		445-102 (7), 445-106 (174), 445-116 (204)	STRIVE (332), ENVISION (333), KONNECTION (334), KONDUCT (335)	EXPAND (164), 661-113 (329), EMBRACE (165)
Abbreviations: $ppFEV_1$, percent predicted forced expiratory volume in one second; UK, United Kingdom; WFAZ, weight-for-age z-score.					

B.3.3.2 Diabetes

Patients who do not have diabetes at baseline can potentially develop diabetes in each subsequent model cycle. It is assumed that patients initiating treatment at age 2-5 years are not at risk of developing CFRD prior to age of 6 years. The risk of developing diabetes in each model cycle was estimated based on an annual age- and gender-specific incidence of CFRD, derived from a UK CF Registry study in the period 1996-2005 (101). This was a longitudinal study conducted across 50 UK CF clinics; the study followed 8,029 patients, ranging from 0-64 years of age, in which a total of 526 patients developed diabetes over a total follow-up of 15,010 person-years. In the absence of genotype-specific estimates, the annual incidence of CFRD derived from this study was applied across all genotypes (Table 86).

The risk of developing CFRD is assumed to be equal for patients treated with a CFTRm and those treated with ECM alone. However, both the LUM/IVA and IVA long-term safety studies have demonstrated that CFTRm therapies are associated with a reduction in the incidence of diabetes (338, 339). Over four years of follow-up, the IVA disease progression cohort from the long-term safety study had a [redacted] reduction in the risk of developing CFRD vs the matched registry control group (340). Additionally, a recent medical chart review study reported that approximately one-third of patients at a CF clinic in the US who were on CFTRm therapy had resolution or near resolution of CFRD (341). Incorporating a CFRD-treatment effect into the model would increase the incremental survival benefit provided by CFTRms; thus, assuming no treatment effect is a conservative approach.

Table 86. Annual incidence of CFRD per person-year by age and gender

Age (years)	Males	Females
2–5	N/A	N/A
6–9	0.008	0.016
10–19	0.039	0.060
20–29	0.049	0.071
30–39	0.065	0.072
40+	0.051	0.029
Source: Adler et al. (101). Abbreviations: CFRD, cystic fibrosis-related diabetes; NA, not applicable.		

B.3.3.3 Acute increase in ppFEV$_1$

CFTRms are assumed to impact ppFEV$_1$ in the model in two ways: 1) an acute increase in ppFEV$_1$ immediately after treatment initiation, and 2) a slowing of the rate of lung function decline over the longer term. A lower bound of 15 percentage points is applied to avoid implausible ppFEV$_1$ values.

The magnitude and duration over which the acute ppFEV$_1$ improvement was applied, were informed by the respective age- and genotype-specific clinical trial data. In cases where clinical trial data were not available, assumptions were made. As the inputs for the CFTRm treatment effect were PBO-adjusted, patients treated with ECM alone had no change in ppFEV$_1$ over the initial time period.

B.3.3.3.1 IVA/TEZ/ELX

Depending on the age of IVA/TEZ/ELX initiation and the *CFTR* genotype, modelled patients experience different rates of improvement in ppFEV$_1$ relative to PBO informed by clinical trial data, as summarised in Table 87 and Table 88.

The acute increase in ppFEV$_1$ in patients with F/MF genotype initiating IVA/TEZ/ELX at ages ≥12 and 6-11 was informed by studies 445-102 and 445-116, respectively (Table 87 and Table 88). In the absence of head-to-head comparisons of IVA/TEZ/ELX vs PBO in patients with F/F, F/Gating and F/RF genotypes, the estimates of PBO-adjusted effect of IVA/TEZ/ELX on ppFEV$_1$ were derived by means of ITCs in patients aged ≥12 years with F/F, F/Gating and F/RF genotypes (Sections B.2.8.3 - B.2.8.5), and patients aged 6-11 years with F/F genotype (Section B.2.8.2). A summary of inputs used in the IVA/TEZ/ELX model for the acute increase in ppFEV$_1$ for patients initiating treatment with a CFTRm at ages ≥12 and 6-11 is reported in Table 87 and Table 88, respectively.

In the absence of data in patients with F/Gating and F/RF genotypes aged 6-11 years treated with IVA/TEZ/ELX, efficacy for IVA/TEZ/ELX was extrapolated from study 445-104 that included patients with F/Gating and F/RF genotypes aged ≥12 years (168). Given that the safety and efficacy of IVA/TEZ/ELX in patients aged 6-11 years in study 445-106 were comparable to those reported for patients aged ≥12 years, the clinical efficacy of IVA/TEZ/ELX in patients with F/Gating and F/RF genotypes aged ≥12 years was used to generate estimates of efficacy in the paediatric populations with F/Gating

and F/RF genotypes. Such paediatric patients generally have experienced less lung disease progression than adolescent or adult patients, and hence have higher mean baseline ppFEV$_1$ as well as a smaller magnitude of mean change from baseline with use of IVA/TEZ/ELX. The magnitude of the IVA/TEZ/ELX treatment impact on ppFEV$_1$ in patients with F/MF and F/F genotypes aged 6-11 years was approximately [redacted] and [redacted] of the efficacy in patients aged ≥12 years of the same genotype. Assuming the relative relationship observed in F/MF and F/F is applicable across other genotypes, simulated patients with F/Gating genotype initiating IVA/TEZ/ELX at age 6-11 are predicted to experience an acute increase in ppFEV$_1$ of between [redacted] and [redacted] percentage points over the first 8 weeks of the model simulation, based on the IVA/TEZ/ELX effect in patients with the same genotype aged ≥12 years ([redacted] to [redacted] of the [redacted] PBO-adjusted change derived from the ITC in F/Gating). Accordingly, patients with F/RF genotype initiating IVA/TEZ/ELX at age 6-11 are predicted to experience an acute increase in ppFEV$_1$ of between [redacted] and [redacted] percentage points over the first 8 weeks of the model simulation, based on the IVA/TEZ/ELX effect observed in patients with F/RF genotype aged ≥12 years ([redacted] to [redacted] of the [redacted] PBO-adjusted change derived from the ITC in F/RF). The model uses the midpoint of the plausible estimate ranges – that is, a [redacted] and [redacted] percentage point change over 8 weeks in patients initiating IVA/TEZ/ELX at age 6-11 with F/Gating and F/RF genotype, respectively, as indicated in Table 88.

Table 87. IVA/TEZ/ELX model inputs for acute increase in ppFEV$_1$ by genotype and CFTRm for patients initiating treatment at age ≥12

CFTRm	PBO-adjusted ppFEV$_1$ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	ITC (342) (B.2.8.3)
F/MF			
IVA/TEZ/ELX	14.3 (12.7-15.8)	24	Study 445-102 (7)
F/Gating			
IVA/TEZ/ELX	[redacted]	8	ITC (343) (B.2.8.5)
IVA	[redacted]	8	ITC (343) (B.2.8.5)
F/RF			
IVA/TEZ/ELX	[redacted]	8	ITC (344) (B.2.8.4)

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in one second.

Table 88. IVA/TEZ/ELX model inputs for acute increase in ppFEV$_1$ by genotype and CFTRm for patients initiating treatment at age 6-11

CFTRm	PBO-adjusted ppFEV$_1$ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	ITC (345) (B.2.8.2)

CFTRm	PBO-adjusted ppFEV$_1$ increment (95% CI)	Acute period duration (weeks)	Source
F/MF			
IVA/TEZ/ELX	11.0 (6.9 to15.1)	24	Study 445-116 (204)
F/Gating			
IVA/TEZ/ELX	[redacted]	8	Assumption
IVA	10.0 (4.5 to 15.5)	48	ENVISION (333)
F/RF			
IVA/TEZ/ELX	[redacted]	8	Assumption

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in one second.

B.3.3.3.2 LUM/IVA

Patients who initiate LUM/IVA at age ≥12 are assumed to experience an acute increase of 2.8 percentage points in ppFEV$_1$ over the first 24 weeks of the model simulation, based on the PBO-adjusted change from baseline in ppFEV$_1$ observed in TRAFFIC/TRANSPORT (95% CI: 1.8 to 3.8) (158). Patients who initiate LUM/IVA at age 6-11 years are assumed to experience an acute increase of 2.4 percentage points in ppFEV$_1$ over the first 24 weeks of the model simulation, based on the PBO-adjusted change from baseline in ppFEV$_1$ observed in study 809-109 (95% CI: 0.4 to 4.4) (159). [redacted] Since ppFEV$_1$ is not explicitly tracked in the model during age 2-5, simulated patients who initiate LUM/IVA at age 2-5 are also assumed to experience an acute increase in ppFEV$_1$ of 2.4 percentage points immediately upon turning age 6 years, when ppFEV$_1$ tracking starts.

B.3.3.3.3 TEZ/IVA

Depending on the age of TEZ/IVA initiation and the *CFTR* genotype, modelled patients experience different rates of improvement in ppFEV$_1$ relative to PBO informed by clinical trial data, as summarised in Table 89.

Patients with F/F and F/RF genotypes who initiate TEZ/IVA treatment at age 6-11 are assumed to experience an acute increase in ppFEV$_1$ based on the mean within-group change from baseline through Week 8 for the TEZ/IVA arm of EMBRACE. Given the small numbers of patients randomised to the control group (N = 10 PBO for F/F, N = 3 IVA for F/RF) of EMBRACE, the study was neither designed nor powered for between-group comparisons (326). In an advisory board, a consulted health

economist agreed that the most appropriate model input for acute increase in $ppFEV_1$ is the mean within-group change observed across both F/F and F/RF genotypes of EMBRACE, as it is line with the protocol-specified analysis and the interpretation of genotype-specific comparator-controlled analyses would be limited due to the small sample size (347). Additionally, utilising the within-group change in $ppFEV_1$ for the model input while assuming the $ppFEV_1$ for patients treated with ECM alone remains flat for the acute period is a conservative estimate of the efficacy of TEZ/IVA, since it is expected that $ppFEV_1$ in patients treated with ECM alone will decline annually by -1.32 and -0.80 for patients aged 6-11 years with F/F and F/RF genotype, respectively (348).

Table 89. TEZ/IVA model inputs for acute increase in $ppFEV_1$ for TEZ/IVA across genotypes by treatment initiation age

Age of treatment initiation	PBO-adjusted $ppFEV_1$ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
≥12 years	4.0 (3.1 to4.8)	24	EVOLVE (157)
6-11 years*	2.8 (1.0 to 4.6)	8	EMRACE (165)
F/RF			
≥12 years	6.8 (5.7 to 7.8)	8	EXPAND (164)
6-11 years*	2.8 (1.0 to 4.6)	8	EMBRACE (165)

Note: *Based on the within-group change observed across both F/F and F/RF genotypes in EMBRACE (165).
Abbreviations: $ppFEV_1$, percent predicted forced expiratory volume in one second.

B.3.3.4 Long-term decline in $ppFEV_1$

Given the extensive evidence documenting long-term decline of lung function in pwCF, an age-dependent annual decline in $ppFEV_1$ was applied over the lifetime horizon. Estimates of annual lung function decline in the absence of CFTRm treatment were derived from a retrospective cohort study of patients with F/RF (n = 1,242 patients) or F/F genotype (n=11,916 patients) in the US CF Foundation Patient Registry (US CFFPR) from 2006 to 2014 (Table 90) (348).

In the absence of genotype-specific rates for the populations with F/MF and F/Gating genotypes, the rates of $ppFEV_1$ decline reported for the population with F/F genotype in the Sawicki et al. (2022) study were applied (Table 90) (348). This is a reasonable assumption given the similar burden of disease and disease progression seen among patients with F/F and other *F508del*-containing genotypes, such as F/MF (349) and F/Gating (336, 337). Furthermore, in a systematic review, wherein eight studies evaluated the effect of *CFTR* genotype on lung function decline, overall results suggested that patients homozygous or heterozygous for *F508del* mutation had a

similar rate of decline over time (350). Results from the Canadian CF Patient Registry analysis revealed a ~10% decline in $ppFEV_1$ over a 9-year period in both *F508del* homozygous and heterozygous patients (351).

The annual decline in lung function for all modelled patients begins at the conclusion of the acute period (i.e., trial duration), except for patients entering the model at age 2-5 for whom that is upon turning age 6. The rates of decline for simulated patients not receiving CFTRms are reported in Table 90.

Table 90. Model inputs for age-dependent annual change in $ppFEV_1$ in absence of CFTRm treatment

Age	F/F (also applied to F/MF and F/Gating)	F/RF
6 – 8 years	-1.32	-0.80
9 – 12 years	-1.32	-0.80
13 – 17 years	-2.37	-0.57
18 – 24 years	-2.52	-1.85
≥25 years	-1.86	-1.06

Source: Sawicki et al. (348).
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; $ppFEV_1$, percent predicted forced expiratory volume in one second.

To model the effect of CFTRms on long-term disease progression, a percent reduction in rate of $ppFEV_1$ decline is applied to the rates of decline observed among untreated patients for each patient receiving a CFTRm regardless of the genotype. A 100% reduction in rate of $ppFEV_1$ decline would mean no decline in $ppFEV_1$ over time, a >100% reduction would indicate an increase in $ppFEV_1$ over time, and in case of 0% reduction, $ppFEV_1$ would decline at the same rate as with ECM alone.

B.3.3.4.1 IVA/TEZ/ELX

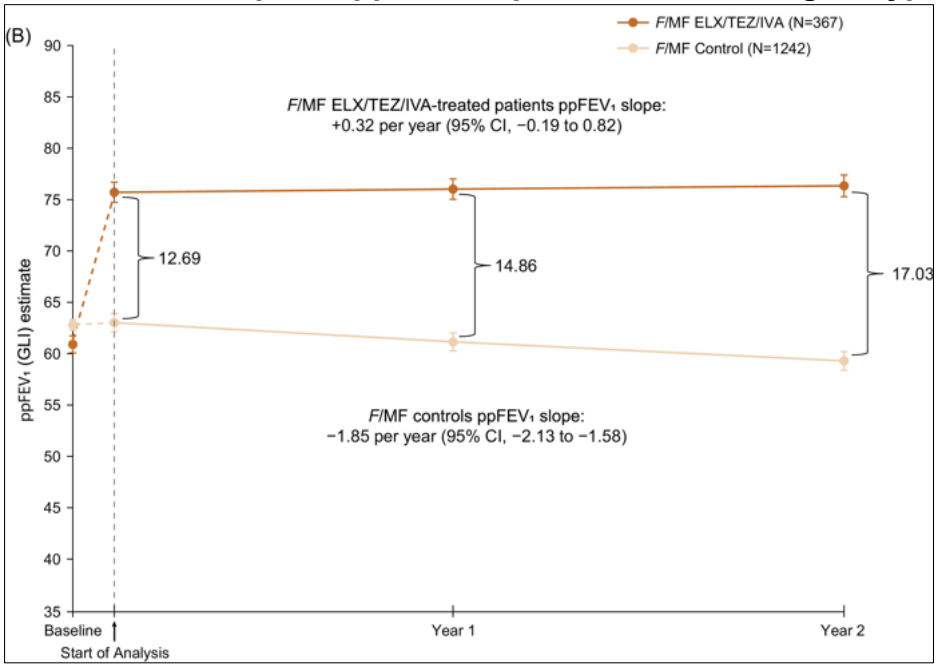
Estimates of the reduction in the rate of lung function decline for CFTRms are based on post-hoc analyses of OLE studies, namely study 445-105 for IVA/TEZ/ELX and PERSIST for IVA, relative to untreated matched controls from the US CFFPR.

The IA 4 (IA4) of study 445-105, performed when all subjects reached the Week 144 visit, demonstrates the robustness and durability of the IVA/TEZ/ELX effect on lung function, with the improvements seen in the parent studies 445-102 and 445-103 being maintained through Week 144 of the OLE period (see Section B.2.5.1.1.5) (236).

Although IA4 data of study 445-105 have not been matched to untreated controls, results indicate no loss of pulmonary function on average across F/MF and F/F

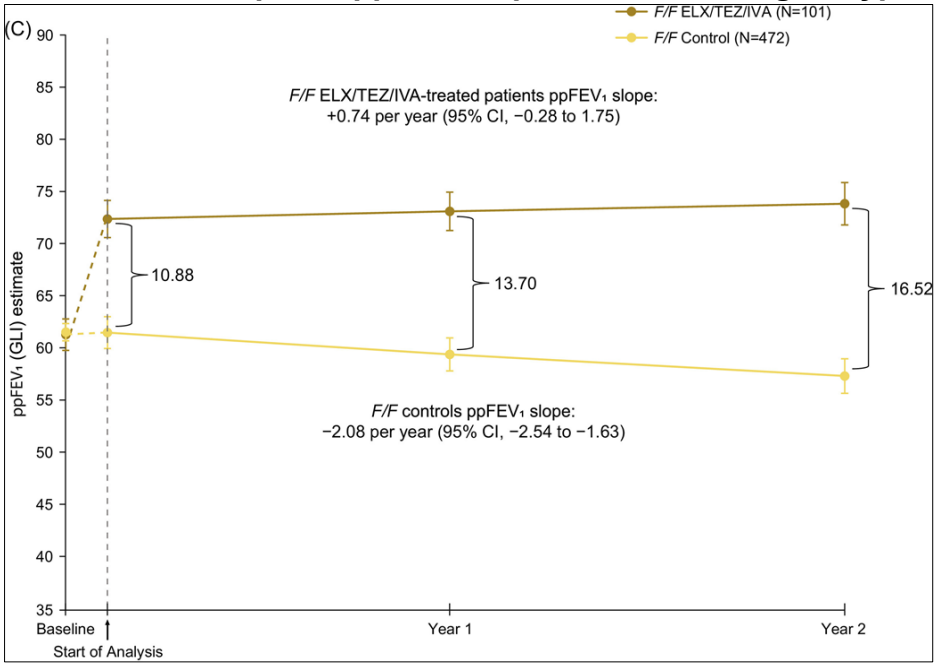
genotypes over the 144-week analysis period (236). In a registry-matched cohort analysis of IVA/TEZ/ELX, which utilised IA3 of 445-105, a total of 468 (367 patients with F/F genotype and 101 with F/MF genotype) pwCF aged ≥12 years treated with IVA/TEZ/ELX for up to 120 consecutive weeks were matched via propensity score to 1,714 untreated registry patients (1,242 F/MF and 472 F/F patients) from the US CFFPR (352). The estimated annualised rate of change in $ppFEV_1$ among patients with F/MF genotype treated with IVA/TEZ/ELX during the study period was +0.32 percentage points (95% CI: -0.19 to 0.82) compared with a -1.85-percentage point (95% CI: -2.13 to -1.58) decline observed in the corresponding matched control group, amounting to a 117.3% (95% CI: 89.7% to 145.7%) reduction in the rate of lung function decline (Figure 85) (352). Among patients with F/F genotype, the estimated annualised rate of change in $ppFEV_1$ was +0.74 percentage points (95% CI: -0.28 to 1.75) among IVA/TEZ/ELX-treated patients vs -2.08-percentage points (95% CI: -2.54 to -1.63) decline in the matched control – a 135.6% (95% CI: 86.4% to 188.3%) reduction in the rate of lung function decline (Figure 86) (352).

Figure 85. Annualised slope for $ppFEV_1$ in patients with F/MF genotype



Abbreviations: CI, confidence interval; ELX, elexacaftor, IVA, ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in one second; TEZ, tezacaftor.
Source: Lee et al. 2022 (352); Figure 1(B).

Figure 86. Annualised slope for ppFEV$_1$ in patients with F/F genotype



Abbreviations: CI, confidence interval; ELX, elexacaftor, IVA, ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in one second; TEZ, tezacaftor.
Source: Lee et al. 2022 (352); Figure 1(C).

In line with the results of 445-105 IA4 OLE (236), and the IA3 registry-matched rate of change analysis (352), the model applies a 100% reduction for patients treated with IVA/TEZ/ELX across all genotypes after the acute period (Table 91). [redacted]

In the absence of the rate of change in ppFEV$_1$ with IVA/TEZ/ELX vs ECM in pwCF aged 6-11 years, the model conservatively assumes the reduction in the annual rate of ppFEV$_1$ decline is consistent with the estimates used in patients aged ≥12 years. IA of the OLE 445-107 conducted in pwCF aged 6-11 years showed the improvements in ppFEV$_1$ observed over 24 weeks of treatment in 445-106 (LS mean difference: 10.2, 95% CI: 7.9 to 12.6) were sustained over 96 additional weeks of treatment (LS mean change from parent study baseline to Week 96 of OLE study 445-107: 11.2; 95% CI: 8.3 to 14.2) (201).

Given the sustained treatment effect from the OLE study conducted in patients aged 6-11 years which is consistent with the 12+ population, as well as the clear linkage that exists between early disease markers and future ppFEV$_1$ trajectory, a 100%

reduction in annual rate of ppFEV$_1$ decline to patients initiating IVA/TEZ/ELX treatment at age 6-11 was assumed, consistent with what is applied to the 12+ poulation.

In the registry-matched observational cohort analysis of IVA, a total of 189 patients aged ≥6 years with the *G551D* mutation, treated with IVA for up to 144 weeks were matched via propensity score to 886 untreated controls with F/F genotype from the US CFFPR (353). Patients treated with IVA experienced a mean annual decline in ppFEV$_1$ of -0.91 percentage points over the study period that was 47.1% lower than the -1.72 percentage point decline observed in matched controls receiving ECM alone. Thus, all simulated patients treated with IVA regardless of age were assumed to experience a 47.1% long-term reduction in the annualised rate of ppFEV$_1$ decline compared to simulated patients treated with ECM alone, as indicated in Table 91. Real-world use of IVA has consistently demonstrated long-term improvements in lung function (354). Further, results from the disease progression cohorts of the IVA long-term safety study demonstrated better-preserved lung function with 5 years of IVA treatment relative to a comparator cohort that did not receive a CFTRm, in both the US and the UK (338).

A summary of inputs used in IVA/TEZ/ELX model for long-term reduction in ppFEV$_1$ decline rate for patients treated with CFTRm treatment is reported in Table 91.

Table 91. IVA/TEZ/ELX model inputs for long-term reduction in rate of ppFEV$_1$ decline for patients treated with CFTRm (aged 6-11 and ≥12 years)

CFTR modulator	Reduction in rate of ppFEV$_1$ decline relative to ECM alone	Source
F/F		• IVA/TEZ/ELX: Assumption based on study 445-105 IA4 (236); the 445-103 IA3 registry-matched rate of change analysis (352); [redacted] • IVA: Based on the registry-matched observational cohort analysis of IVA (353)
IVA/TEZ/ELX	100.0%	
F/MF		
IVA/TEZ/ELX	100.0%	
F/Gating		
IVA/TEZ/ELX	100.0%	
IVA	47.1%	
F/RF		
IVA/TEZ/ELX	100.0%	

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in one second.

B.3.3.4.2 LUM/IVA

The reduction in the rate of lung function decline for patients who initiate LUM/IVA at age ≥12 is based on the results of a retrospective observational analysis assessing the rate of change in lung function for patients treated with LUM/IVA relative to untreated matched controls from the US CFFPR (155). The patients receiving LUM/IVA who contributed sufficient non-missing ppFEV$_1$ records during the 24-week

clinical trial periods of TRAFFIC/TRANSPORT and the 96-week extension period of PROGRESS (n=455) were matched by propensity scores, baseline age, and baseline ppFEV$_1$ to controls homozygous for the *F508del* mutation identified in the US CFFPR (n=1,588). Patients receiving LUM/IVA experienced a mean annual decline in ppFEV$_1$ of -1.33 percentage points (95% CI: -1.80 to -0.85), which was a 42% reduction compared with the decline of -2.29 percentage points (95% CI: -2.56 to -2.03) observed in untreated matched controls. Thus, the LUM/IVA model assumes that the rate of decline for patients who initiated LUM/IVA at age ≥12 is 42% lower than the decline in patients treated with ECM alone.

Several recent real-world studies have demonstrated equal or greater reductions in rate of lung function decline with long-term use of LUM/IVA. One of the largest such studies is the IA3 of the Orkambi Post-Authorization Safety Study (PASS IA3), which reported clinical outcomes for a cohort of 2,287 patients in the US CFFPR who received LUM/IVA for an average of 2.9 years (355). Over the three-year follow-up period, the average change from baseline in ppFEV$_1$ for the cohort treated with LUM/IVA was -3.7 percentage points (95% CI: -4.2 to -3.3), a 46% reduction relative to the untreated comparator cohort (-6.9 percentage points; 95% CI: -7.2 to -6.5). Six additional real-world studies from five different countries across Europe and Australia reported substantial reductions in the rate of lung function decline following longer-term treatment with LUM/IVA (356-361). In several studies, treatment with LUM/IVA was associated with a stabilisation or improvement in ppFEV$_1$ over the treatment period, in contrast with the progressive lung function decline expected in the absence of CFTR modulation. These analyses provide further support that the long-term real-world use of LUM/IVA modified the disease trajectory in CF patients, and that the 42% reduction in the rate of lung function decline used in the LUM/IVA model's base case analysis may be a conservative assumption.

In the absence of rate of change in ppFEV$_1$ analysis to estimate the effect of LUM/IVA on ppFEV$_1$ decline vs ECM in patients initiating treatment at age 6-11, the model conservatively assumes the reduction in the annual rate of ppFEV$_1$ decline is consistent with the estimates in patients aged ≥12 years. Data from the OLE study 809-110 in patients aged 6-11 years showed that annualised rate of change in ppFEV$_1$, starting from day 15 after the first dose of LUM/IVA up to 120 weeks of treatment,

remained stable or increased, resulting in a positive rate of lung function change (0.58 percentage points per year; 95% CI: 0.02 to 1.14) over the study period (156). In contrast, a decline in lung function of 1-2 percentage points per year is expected in untreated patients aged 6-11 years (348, 362). Given the sustained treatment effect from the OLE study 809-110 and a clear link between early disease markers and future $ppFEV_1$ trajectory, applying a 42.0% reduction in annual rate of $ppFEV_1$ decline to patients initiating LUM/IVA at age 6-11 is considered a conservative assumption.

To reflect the preservation of lung function with early use of LUM/IVA, patients initiating LUM/IVA at age 2-5 are assumed to have avoided a proportion of lung function decline before age of 6. The proportion of lung function decline avoided during the age of 2-5 with LUM/IVA treatment relative to ECM alone, is assumed to be 42%, based on the LUM/IVA registry-matched analysis conducted in patients aged ≥12 years (155). The preserved lung function in patients initiating LUM/IVA at age 2-5 compared with their counterparts receiving ECM alone is calculated by multiplying the number of years a patient is in the model before turning 6 by the annual change in $ppFEV_1$ observed during age 2-5 receiving ECM and the proportion of $ppFEV_1$ decline avoided (i.e., 42%). The -1.32 $ppFEV_1$ decline rate during age 6-8 (348) is assumed to be a proxy for the average decline experienced during age 2-5 (Table 90). For instance, a patient who initiates LUM/IVA at age 2 and who would have a $ppFEV_1$ of 90 at age 6 if they remained untreated, would have a $ppFEV_1$ of 92.2 at age 6 after four years of treatment with LUM/IVA, calculated as: 90 + [(1.32 x 4) x 42%] = 92.2.

B.3.3.4.3 TEZ/IVA

B.3.3.4.3.1 Population with F/F genotype aged ≥12 years

The reduction in the rate of lung function decline for patients treated with TEZ/IVA was derived from a post-hoc analysis assessing the rate of change in lung function for patients with F/F genotype treated with TEZ/IVA relative to untreated matched controls. Patients receiving TEZ/IVA with sufficient non-missing $ppFEV_1$ records during the 24-week EVOLVE and the 96-week OLE study, EXTEND, were included in this analysis. The 407 eligible CF patients with F/F genotype receiving TEZ/IVA were matched by propensity scores, baseline age, and baseline $ppFEV_1$ to untreated controls with F/F genotype identified in the US CFFPR (n= 1,383). The annualised rate

of lung function decline was significantly less for patients treated with TEZ/IVA vs matched controls: -0.80 percentage points per year (95% CI: -1.31 to -0.30) vs -2.08 percentage points per year (95% CI: -2.34 to -1.82) (222). Thus, the model assumes that the rate of decline in patients with F/F genotype receiving TEZ/IVA is 61.5% lower than the decline in patients treated with ECM alone.

B.3.3.4.3.2 Population with F/RF genotype aged ≥12 years

Patients with F/RF genotype treated with TEZ/IVA are also assumed to experience a 61.5% reduction in the rate of $ppFEV_1$ decline, based on the treatment effect observed in patients with F/F genotype treated with TEZ/IVA (222). This is likely a conservative assumption considering that the acute improvement in $ppFEV_1$ experienced by F/RF patients who received TEZ/IVA for 8 weeks in EXPAND was sustained through 96 weeks in the OLE study EXTEND (LS mean absolute change in $ppFEV_1$ at Week 96: 7.5; 95% CI: 5.6 to 9.4) (222). However, an assessment of the reduction in the rate of $ppFEV_1$ decline for patients with F/RF genotype treated with TEZ/IVA relative to untreated controls was not feasible due to the limited number of untreated patients with this genotype in the US CFFPR, which did not allow for robust propensity score matched analysis with sufficient power.

B.3.3.4.3.3 Populations with F/F and F/RF genotypes aged 6-11 years

In the absence of rate of change in $ppFEV_1$ analysis to directly estimate the effect of TEZ/IVA on $ppFEV_1$ decline vs ECM in patients initiating treatment at age 6-11, the model conservatively assumes a reduction in the annual rate of $ppFEV_1$ decline of 61.5%, in line with the estimate used in patients aged ≥12 years (222).

A summary of inputs used in TEZ/IVA model for long-term reduction in $ppFEV_1$ decline rate for patients treated with TEZ/IVA is reported in Table 92.

Table 92. TEZ/IVA model inputs for long-term reduction in rate of $ppFEV_1$ decline for patients treated with CFTRm (aged 6-11 and ≥12 years)

Genotype	Reduction in rate of $ppFEV_1$ decline relative to ECM alone	Source
F/F	61.5%	Registry-matched observational cohort analysis of TEZ/IVA in patients with F/F genotype (222)
F/RF	61.5%	

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; $ppFEV_1$, percent predicted forced expiratory volume in one second.

B.3.3.5 Pulmonary exacerbations

The simulation model tracks PEx requiring either treatment with IV antibiotics and/or hospitalisation, as these are the types of PEx that are predictive of survival in pwCF (64). The occurrence of PEx in each model cycle is predicted contingent on patients' $ppFEV_1$ and age from a relationship derived from the 2004 US CFFPR, based on a publication by Goss et al. (87) in which increased PEx rates were associated with lower $ppFEV_1$. The data were fitted to an exponential regression function, to provide a continuous relationship between the PEx rates and $ppFEV_1$ (128):

$$rate = a * exp(-b \times ppFEV_1)$$

where *rate* is the annual rate of PEx. Two equations are applied: one for patients aged 6-17 years (a=8.594, b=0.035), and another for patients aged ≥18 years (a=3.789, b=0.026). The rate of PEx for ECM is not genotype-specific. For patients aged 2-5 years, PEx rate is not estimated, since $ppFEV_1$ data are not available for this age group; this is a reasonable assumption, given PEx events are relatively infrequent in this age group.

PEx rates for patients aged ≥6 years treated with ECM alone are predicted conditional on $ppFEV_1$ in each cycle over the model time horizon using the relationship above. For simulated patients aged ≥12 years treated with CFTRms, the derived PEx rate is multiplied by a RR to reflect the benefit of treatment on this outcome. The RRs were derived from the pivotal trials conducted in patients aged ≥12 years for each CFTRm.

For patients aged ≥12 years, CFTRms positively impact both $ppFEV_1$ and PEx. Given these two clinical outcomes are interrelated, the impact of CFTRms on PEx may be partially explained by the observed improvements in $ppFEV_1$. To adjust for the potential of double-counting $ppFEV_1$ and PEx treatment effects in the model, calibration techniques were used to derive a RR for the PEx experienced on CFTRm treatment relative to ECM that account for the acute improvement in $ppFEV_1$. For each patient population and CFTRm, a cohort of patients was simulated, and the PEx treatment effect model input was calibrated, such that the resulting relative rate of PEx between patients receiving a CFTRm and those receiving ECM alone matched the treatment effect on PEx requiring IV antibiotics and/or hospitalisation observed in the pivotal trials (for more detail, see Appendix N).

Based on the results from the CFTRm OLE studies conducted in patients aged ≥12 years (155, 222, 236, 353), which demonstrated that the annualised rate of PEx from the shorter-term clinical trials were sustained over longer treatment duration, the calibrated PEx RRs were applied over the model time horizon.

For patients initiating CFTRms at age 6-11, no treatment effect is assumed on PEx requiring IV antibiotics and/or hospitalisation, since pivotal trials conducted in this age group were not powered to detect a difference in PEx rates (studies 809-109 and 770-103) or did not collect PEx as an efficacy endpoint (studies 445-116 and 661-115) (159, 165, 204, 333). While the treatment effect in younger patients is likely consistent with that observed in adolescents and adults, the lower event rates in younger patients make the treatment effect harder to detect in a clinical trial. Assuming no PEx effect in patients aged 6-11 years is a conservative assumption, [redacted]

B.3.3.5.1 IVA/TEZ/ELX

For CF patients with F/MF genotype treated with IVA/TEZ/ELX aged ≥12 years, the PEx RR was derived from study 445-102, as indicated in Table 93 (7). Patients with F/F, F/Gating and F/RF genotypes of the same age group treated with IVA/TEZ/ELX are assumed to experience the PEx treatment effect demonstrated in patients with the F/MF genotype from study 445-102 (Table 93).

[redacted] In study 445-105 IA4, the estimated annualised mean PEx rate for participants with F/MF genotype treated with IVA/TEZ/ELX for at least 144 weeks was 0.20 (95% CI: 0.16 to 0.24), which was consistent with the low rate observed with IVA/TEZ/ELX in study 445-102 (7, 236).

For patients with F/Gating genotype treated with IVA aged ≥12 years, the PEx RR was derived from STRIVE. In STRIVE, patients treated with IVA experienced PEx requiring IV antibiotics (0.40 for IVA vs 0.71 for PBO; RR: 0.56; P=0.078) and PEx requiring hospitalisation (0.31 for IVA vs 0.49 for PBO; RR: 0.63; P=0.195) less frequently than

patients in the PBO group (332). The study was not powered to detect differences in PEx requiring IV antibiotics and hospitalisation. However, the OLE study PERSIST demonstrated that the reduction in PEx seen with IVA was maintained over time (363). Thus, a PEx RR of 0.56 was assumed for patients with F/Gating genotype treated with IVA (Table 93).

Based on results from extension studies of IVA/TEZ/ELX and IVA conducted in patients aged ≥12 years, which demonstrated that the annualised rate of PEx from the shorter-term clinical trials were sustained over longer durations of treatment in the OLE studies, the PEx RRs are applied for CFTRms over the model time horizon (236, 353). This assumption is supported by [redacted], and a recent study of IVA/TEZ/ELX conducted in the US CFFPR (365). [redacted]

As explained above, for patients treated with IVA/TEZ/ELX or IVA during ages 6-11, no treatment effect on PEx requiring IV antibiotics and/or hospitalisation was assumed, as pivotal trials in this age group did not estimate RR vs PBO (175, 366). An ITC to derive a PBO-adjusted PEx event rate was not feasible.

The uncalibrated and calibrated PEx RRs used in IVA/TEZ/ELX model are reported in Table 93 below.

Table 93. IVA/TEZ/ELX model inputs for PEx rate ratio in patients treated with CFTRm aged ≥12 years (uncalibrated and calibrated)

CFTR modulator	Uncalibrated PEx rate ratio	Source	Calibrated PEx rate ratio
F/F			
IVA/TEZ/ELX	0.22	Assumption, study 445-102	[redacted]
F/MF			
IVA/TEZ/ELX	0.22	Study 445-102 (7)	[redacted]
F/Gating			
IVA/TEZ/ELX	0.22	Assumption, study 445-102	[redacted]
IVA	0.56	STRIVE (332)	[redacted]
F/RF			
IVA/TEZ/ELX	0.22	Assumption, study 445-102	[redacted]

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PEx, pulmonary exacerbation.

B.3.3.5.2 LUM/IVA

Patients aged ≥12 years treated with LUM/IVA in TRAFFIC/TRANSPORT experienced a 61% reduction in the rate of PEx requiring hospitalisation and a 56% reduction in the rate of PEx requiring IV antibiotics compared to PBO (both comparisons P<0.001) (158). To adjust for the potential of double-counting $ppFEV_1$ and PEx treatment effects in the model, the PEx treatment effect input was calibrated, such that the resulting relative rate of PEx between patients receiving LUM/IVA and those receiving ECM alone matched the treatment effect of 0.44 from the pivotal trial. This yielded a calibrated PEx RR of [redacted] ([redacted] reduction) for the patients treated with LUM/IVA aged ≥12 years.

Results from the OLE study PROGRESS demonstrated that the annualised rate of PEx from TRAFFIC/TRANSPORT was sustained over longer treatment period (24 weeks of TRAFFIC/TRANSPORT, 96 weeks of PROGRESS) (155). A sustained LUM/IVA effect on the rate of PEx was also observed over three years in the safety study PASS IA3 (355). This evidence supported the implementation of the calibrated RR over the lifetime horizon.

For patients treated with LUM/IVA during ages 6-11, no treatment effect was assumed on the PEx rate, as study 809-109 was not powered to detect a difference in PEx rates and no statistically significant difference was observed (159).

B.3.3.5.3 TEZ/IVA

B.3.3.5.3.1 Population with F/F genotype aged ≥12 years

CF patients treated with TEZ/IVA in EVOLVE experienced significantly fewer PEx requiring treatment with IV antibiotics and/or hospitalisation compared to PBO: 0.29 PEx events per year vs 0.54 per year for PBO, resulting in a RR of 0.53 (95% CI: 0.34 to 0.82) (157). The calibration yielded a PEx RR of [redacted] for the patients aged ≥12 years treated with TEZ/IVA (Table 94).

B.3.3.5.3.2 Population with F/RF genotype aged ≥12 years

Although EXPAND was not powered to evaluate changes in PEx rate, the observed rate was approximately 45% lower with TEZ/IVA (0.34 events per year) compared to

PBO (0.63 events per year) albeit not statistically significant (RR: 0.54; 95% CI: 0.26 to 1.13) (Table 94) (164). However, continued treatment with TEZ/IVA for an additional 96 weeks in the OLE study EXTEND resulted in a PEx rate of 0.22 (95% CI: 0.14 to 0.35), a 65% reduction compared with the event rate observed in the PBO arm during the parent study EXPAND (163). Based on findings of a continued reduction in PEx, the expert opinion was that the CFTRm treatment effects observed in EXPAND were reasonable, if not conservative, model inputs for the effect on PEx.

Based on the PEx results from the OLE study EXTEND, the calibrated PEx RRs are applied over the model time horizon (163). [redacted]

B.3.3.5.3.3 Populations with F/F and F/RF genotypes aged 6-11 years

For patients initiating treatment with TEZ/IVA during ages 6-11, no treatment effect on PEx rate was assumed, as PEx were not included as an efficacy endpoint in EMBRACE (326).

The uncalibrated and calibrated PEx RRs used in TEZ/IVA model are reported in Table 94 below.

Table 94. TEZ/IVA model inputs for PEx rate ratio in patients treated with TEZ/IVA aged ≥12 years (uncalibrated and calibrated)

Genotype	Uncalibrated PEx rate ratio	Source	Calibrated PEx rate ratio
F/F	0.53	EVOLVE (157)	[redacted]
F/RF	0.54	EXPAND (164)	[redacted]
Abbreviations: PEx, pulmonary exacerbation; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.			

B.3.3.6 Weight-for-age Z-score

Simulated patients treated with CFTRms experience an acute change in WFAZ upon treatment initiation. The magnitude and duration of the acute change in WFAZ were informed by respective age- and genotype-specific clinical trial data, assuming growth statistics of 20-year-olds could be applied to all patients aged >20 years. If clinical trial data were not available, assumptions were made. Because the inputs for the treatment effect are PBO-adjusted, patients treated with ECM alone have no change in WFAZ

over the initial period. Following the period of acute change, a patient's WFAZ is assumed to be constant for the remainder of the model simulation.

B.3.3.6.1 IVA/TEZ/ELX

The acute increase in WFAZ in patients with F/MF genotype initiating IVA/TEZ/ELX at ages ≥12 and 6-11 was informed by studies 445-102 and 445-116, respectively (Table 95 and Table 96). In the absence of head-to-head comparison of IVA/TEZ/ELX vs PBO in patients with F/F, F/Gating and F/RF genotypes, the estimates of PBO-adjusted effect of IVA/TEZ/ELX on WFAZ were derived by means of ITCs in patients aged ≥12 years with F/F, F/Gating and F/RF genotypes (Sections B.2.8.3 - B.2.8.5), and patients aged 6-11 years with F/F genotype (Section B.2.8.2). A summary of inputs used in the IVA/TEZ/ELX model for the acute increase in WFAZ for patients initiating treatment with a CFTRm at ages ≥12 and 6-11 is reported in Table 95 and Table 96, respectively.

The relative change in WFAZ from baseline at Week 8 for IVA/TEZ/ELX vs IVA derived from the ITC in F/Gating was [redacted] (95% CI: [redacted] to [redacted]) (Section B.2.8.5). The PBO-adjusted change in WFAZ from baseline at Week 8 for the pooled patients treated with IVA was [redacted] (95% CI: [redacted] to [redacted]), with the derived indirect estimate of change in WFAZ for IVA/TEZ/ELX vs PBO being [redacted] (95% CI: [redacted] to [redacted]). [redacted] (Table 95). This is a conservative assumption, given that study 445-104 was not powered to detect a statistically significant change in this endpoint and the impact of IVA/TEZ/ELX on nutritional parameters is expected to increase with longer treatment duration, as observed over 24 weeks in study 445-102.

In the absence of data in patients with F/Gating and F/RF genotypes aged 6-11 years treated with IVA/TEZ/ELX, efficacy for IVA/TEX/ELX was extrapolated from study 445-104 (168). The magnitude of the IVA/TEZ/ELX impact on WFAZ in patients with F/F and F/MF genotypes aged 6-11 years was approximately [redacted] and [redacted] of the efficacy demonstrated in the populations with F/F and F/MF genotypes aged ≥12, respectively. Assuming the relative relationship observed in F/F and F/MF is applicable across other genotypes, simulated patients with F/Gating genotype initiating IVA/TEZ/ELX at age

6-11 are predicted to experience an acute increase in WFAZ of between [redacted] and [redacted] units over the first 8 weeks of the model simulation, based on the IVA/TEZ/ELX effect in patients aged ≥12 years with the same genotype ([redacted] to [redacted] of the [redacted] PBO-adjusted change derived from the ITC in F/Gating). Accordingly, patients with F/RF genotype initiating IVA/TEZ/ELX at age 6-11 are predicted to experience an acute increase in WFAZ of between [redacted] and [redacted] units over the first 8 weeks of the model simulation, based on the IVA/TEZ/ELX effect in patients aged ≥12 years with the same genotype ([redacted] to [redacted] of the [redacted] PBO-adjusted change derived from the ITC in F/RF). The model uses the midpoint of the plausible estimate ranges – that is, a [redacted] and [redacted] unit increase in WFAZ over 8 weeks in patients initiating IVA/TEZ/ELX at age 6-11 with F/Gating and F/RF genotype, respectively, as indicated in Table 96.

Table 95. IVA/TEZ/ELX model inputs for acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age ≥12

CFTRm	PBO-adjusted WFAZ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	ITC (342) (B.2.9.3)
F/MF			
IVA/TEZ/ELX	[redacted]	24	Study 445-102 (367)
F/Gating			
IVA/TEZ/ELX	[redacted]	8	Assumption, ITC (343) (B.2.9.5)
IVA	[redacted]	8	ITC (343) (B.2.9.5)
F/RF			
IVA/TEZ/ELX	[redacted]	8	ITC (344)

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; WFAZ, weight-for-age z-score.

Table 96. IVA/TEZ/ELX model inputs for acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age 6-11

CFTRm	PBO-adjusted WFAZ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	ITC (345) (B.2.9.2)
F/MF			
IVA/TEZ/ELX	[redacted]	24	Study 445-116 (368)
F/Gating			
IVA/TEZ/ELX	[redacted]	8	Assumption
IVA	[redacted]	48	ENVISION (366)
F/RF			
IVA/TEZ/ELX	[redacted]	8	Assumption

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; WFAZ, Weight-for-age z-score.

B.3.3.6.2 LUM/IVA

Patients initiating LUM/IVA at age ≥12 are assumed to experience an acute increase of [redacted] from baseline in WFAZ by Week 24 of the simulation, based on the PBO-adjusted improvement in WFAZ observed in TRAFFIC/TRANSPORT (95% CI: [redacted] to [redacted]) (369).

Patients initiating LUM/IVA treatment at age 6-11 are assumed to experience an acute increase of [redacted] from baseline in WFAZ by Week 24 of the simulation, based on the PBO-adjusted improvement in WFAZ derived from a post-hoc analysis in which patient-level data from study 809-109 and study 809-011 Part B were pooled (95% CI: [redacted] to [redacted]) (346).

The treatment effect for patients initiating LUM/IVA at age 2-5 was derived from study 809-115, in which patients treated with LUM/IVA experienced a statistically significant within-group improvement of 0.26 (95% CI: 0.15 to 0.38) in WFAZ by Week 24 (162).

B.3.3.6.3 TEZ/IVA

The acute increase in WFAZ in patients with F/RF genotype initiating TEZ/IVA at age ≥12 was derived from EXPAND, as shown in Table 97. The model assumes no impact of TEZ/IVA on WFAZ in patients with F/F genotype initiating treatment at age ≥12. This is a conservative assumption given the continued increase in nutritional outcomes observed in EXTEND (163). [redacted]. The inputs for the acute increase in WFAZ for patients initiating TEZ/IVA are reported in Table 97.

Table 97. TEZ/IVA model inputs for acute increase in WFAZ for TEZ/IVA by genotype by treatment initiation age

Age of treatment initiation	PBO-adjusted WFAZ increment (95% CI)	Acute period duration (weeks)	Source
F/F			
≥12 years	0.00	24	EVOLVE (157)
6-11 years	[redacted]	8	EMRACE (326)
F/RF			
≥12 years	[redacted]	8	EXPAND (370)
6-11 years	[redacted]	8	EMBRACE (326)
Abbreviations: WFAZ, Weight-for-age z-score.			

B.3.3.7 Mortality

Survival predictions for patients aged ≥6 years were calculated at the patient-level and were based on the following:

- A reference survival curve of the overall population with CF in the absence of CFTR modulation in the UK
- A CPH model that links survival in CF to nine risk factors: age, gender, $ppFEV_1$, annual number of PEx, respiratory infections (*S. aureus* and *B. cepacia*), diabetes, WFAZ, and pancreatic sufficiency status (64)
- The general population survival for England and Wales to set an upper bound on survival (371).

This methodology allows mortality to be impacted by differences in individual patient characteristics that predict survival as these characteristics evolve over time. The model assumes 100% survival for patients during the age of 2-5, as $ppFEV_1$ is not tracked in the model until the age of 6. This is considered a reasonable assumption, as the UK mortality rate for this age group is negligible (372).

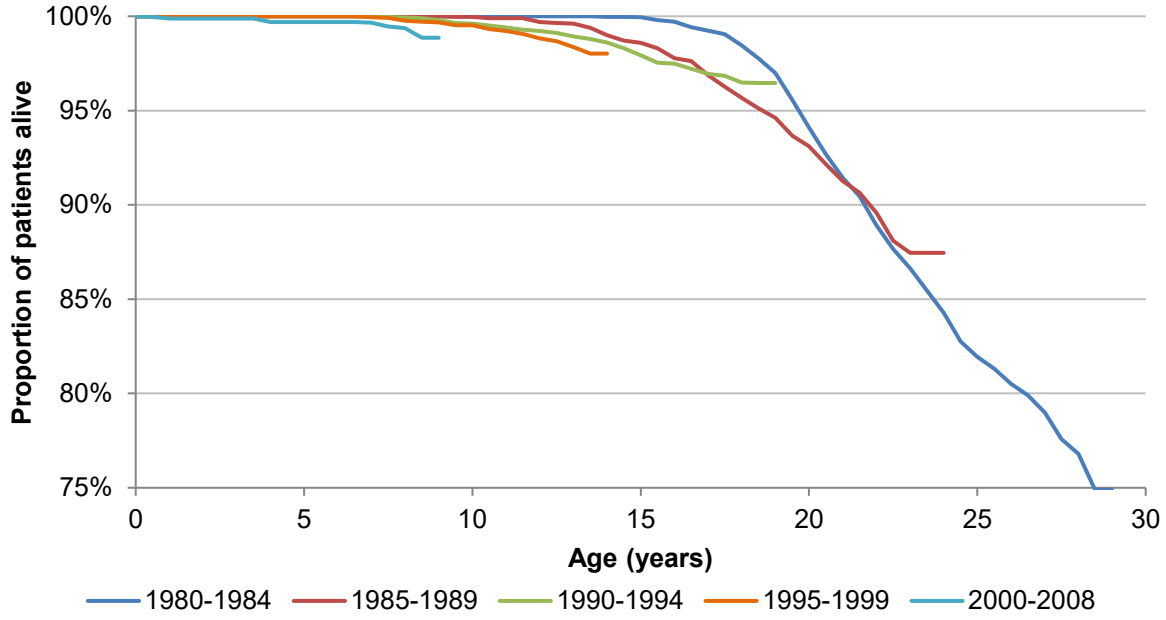
A patient's baseline mortality hazard is estimated based on the age-specific mortality from the survival curve of the underlying CF population. In prior cost-effectiveness models of CFTRms, the baseline mortality hazard was adjusted by comparing a patient's baseline clinical characteristics to the mean characteristics of the underlying population with CF. Removing the adjustment of baseline hazard improves the overall predictive nature of the model, as demonstrated by a validation study which compared the 5-year projections of survival from a Vertex survival model of IVA to the 5-year mortality rates observed in a long-term safety study (LTSS) of IVA (373).

B.3.3.7.1 Reference survival curve of the overall population with CF

The underlying survival of the CF population in the absence of CFTR modulation is based on data published in the 2008 UK CF Registry (372) (before CFTRms had entered the market). Parametric equations were fitted to the observed survival data from the registry to derive a reference curve that provides survival probabilities over a lifetime. These projected curves were then used to estimate the background mortality risk in pwCF.

The analyses are based on published Kaplan-Meier curves of CF survival from the 2008 UK CF Registry annual report, which reported survival for 6,082 patients grouped into five birth cohorts ranging from 1980 to 2008 (Figure 87). The published curves were digitised. Simulated patient-level Kaplan-Meier data were generated based on the digitised curve and the number of patients in each birth cohort were derived using methods described by Ishak et al. (374) and Tierney et al. (375). Various parametric functions (exponential, Weibull, Gompertz, Log-logistic, Log-normal, and generalised gamma) were tested to arrive at the best parametric fit that was visually and statistically credible, as well as clinically plausible.

Figure 87. Kaplan-Meier curves of survival in the UK CF Registry birth cohorts, 1980-2004



Source: UK CF Registry 2008 report (372)
Abbreviations: CF, cystic Fibrosis; UK, United Kingdom.

Analyses of the UK data presented the following challenges: (1) long flat periods in older birth cohorts, potentially due to the lack of information earlier in the samples' lifetime, represent artificial "immortal" time, which can distort fits and projections, and (2) survival observed in the more recent birth cohorts is relatively short, making projection potentially unreliable.

In separate analyses of each birth cohort, median predicted survival estimates for the most recent birth cohorts were either clinically unrealistically high (e.g., more than 100 years) or unrealistically low (approximately 25 years). Thus, combining data from birth cohorts was required. Two possible groupings were considered to obtain the most

plausible overall reference curve: 1990–2008 and 1985–2008. The fits were compared to assess which group provided the most reasonable output. Projections from the 1990–2008 grouping were not reasonable: the median estimated survival, using a Gompertz distribution, was around [redacted] years of age, but the projection declined so rapidly that no patients would be predicted to survive beyond [redacted] years of age. In contrast, the projection using a Gamma distribution was more realistic, but implied a median predicted survival of [redacted] years, which is considerably higher than estimates from analyses of other cohorts. Thus, final analyses were based on a Weibull fit to the 1985–2008 birth cohorts, which produced a median predicted survival of [redacted] years (Table 98) (376).

Diagnostic plots for each of the distributions considered for the UK CF Registry's combined 1985-2008 are shown in Figure 88. The closer the transformed, observed data are to the dashed linear regression in these plots, the better the fit (374). The median predicted survival and fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) are presented in Table 98. Lower test fit statistics (AIC and BIC) indicate a better statistical fit (374). The UK test statistics suggest that Weibull, Gompertz, and Gamma distributions offer comparable fit, with AIC statistics within one point of each other. Median estimates from the three distributions, while plausible, imply a broad range of possible values: from [redacted] years with a Gompertz fit to [redacted] years with Weibull (Table 98).

Figure 88. Diagnostic plots to determine best fits to UK CF Registry population survival data (all genotypes) — birth cohort 1985–2008

[redacted]

[redacted]

Abbreviations: GRP, group; h, hazard; haz, hazard; LN, natural log; S, survival, surv, survival; t, time.

For the UK CF Registry analysis using the 1985-2008 cohort, long-term predictions using the Gompertz and Gamma distribution suggest an unrealistically rapid decline; all patients are predicted to die by age [redacted]. The Weibull fit produces more plausible projections, with predicted survival reaching [redacted] near [redacted] years of age and a predicted median survival of [redacted] years (Figure 89) (376). The validity of predictions was appraised by clinical experts, who agreed that Weibull projections for this UK population were clinically plausible (376).

Figure 89. KM curve and parametric fits to the UK CF Registry population, birth cohort 1985–2008

Abbreviations: CF, cystic fibrosis; KM, Kaplan-Meier; UK, United Kingdom.

Table 98. Median estimates and fit statistics for fits to the UK CF Registry population, birth cohort 1985–2008

Distribution	Predicted 50th Percentile (Median)	Predicted 90th Percentile	Predicted 99th Percentile	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; CF, cystic fibrosis; UK, United Kingdom.

B.3.3.7.2 Relating individual patient characteristics to survival

For simulated patients aged ≥6 years, baseline mortality hazard is estimated based on the age-specific mortality from the underlying CF population survival curve.

After baseline, a patient's mortality hazard is re-calculated in each model cycle by adjusting for changes in patient clinical characteristics using a CPH model developed by Liou et al. (64). Liou et al. developed the model based on data collected from 1993 to 1998 by the US CFFPR on 11,630 individuals aged 5.5 to 71.1 years and the following nine characteristics of pwCF were found to predict survival: age, $ppFEV_1$, gender, weight-for-age z-score, pancreatic sufficiency, diabetes, *S. aureus* infection, *B. cepacia* infection, and number of acute PEx per year. It is worth noting that the presence of zero, one, or two *F508del* alleles was tested for inclusion in the model. However, this covariate was not found to be a significant predictor of mortality, indicating that the effect of genotype on mortality is mediated through the phenotypic characteristics that were identified as significant predictors of mortality in the analysis (64). Covariates included in the Liou et al. CPH model and the corresponding coefficients are presented in Table 99. Risk factors were measured only at baseline in the Liou et al. (64) analysis; changes over time were not taken into account.

While the CPH model has not been updated since its publication in 2001, the authors presented an updated validation in 2015 of the original logistic regression (232, 377). The updated logistic regression used US CFFPR data from 1993–2010. This analysis concluded that, while there were some minor changes to coefficients, the factors predicting mortality in pwCF have remained stable. These results support continued use of the 2001 CPH model in these simulations.

Although the Liou et al. (64) model was based on US CF registry data, it has broader applicability. CF is a disease found mostly in individuals of Caucasian descent, and there is reason to believe that the projections and conclusions are relevant to Europe, especially considering the similar modalities of care in both geographies (378). The validity of the Liou et al. CPH model is supported by other survival models that have used many of the same prognostic factors (379, 380).

Table 99. CPH model covariates and coefficients

Covariate	Coefficient	Standard error
Age (per year)	0.011	0.0049
$ppFEV_1$ (per percentage point)	-0.042	0.0025
Gender (female = 1)	0.15	0.074
WFAZ	-0.28	0.041
Pancreatic sufficiency (yes = 1)	-0.14	0.23
Diabetes mellitus (yes = 1)	0.44	0.098
S.aureus (yes = 1)	-0.25	0.09
B.cepacia (yes = 1)	1.41	0.19
Annual number of acute PEx (max 5)	0.35	0.024
PEx × *B.cepacia*	-0.28	0.06

Covariate	Coefficient	Standard error
Abbreviations: *B.cepacia, Burkholderia cepacia*; CPH, Cox proportional hazards; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in one second; *S.aureus, Staphylococcus aureus*; WFAZ, weight-for-age z-score.		

An individual's baseline mortality hazard provides a starting point for the projection of survival over the model horizon. In each model cycle, the patient's mortality hazard is adjusted to reflect changes in any of the included risk factors (e.g., increasing age, deterioration of lung function) for that patient. This is achieved by calculating a hazard ratio with respect to that patient's own values from the previous model cycle. The hazard ratio is computed as follows:

$$HR_i = e^{\beta_1(x_1-\overline{x_1})+\beta_2(x_2-\overline{x_2})+\cdots+\beta_9(x_9-\overline{x_9})}$$

where β_j is the CPH model coefficient from Liou et al. (64) for risk factor *j*, the x_j are the values of the individual patient's risk factors in the current cycle, and $\overline{x_j}$ are the individual patient's risk factors from the preceding cycle. This hazard ratio is then applied to the patient's hazard from the previous cycle to derive the hazard in the current cycle. By repeating this process over many time steps, the (annual) mortality hazard of patients with any given initial risk factor profile can be estimated over time.

This methodology of calculating the hazard over time is applied both to simulated patients receiving intervention and those receiving comparator. Thus, as the clinical characteristics of a patient receiving intervention diverge from their "clone" who is receiving comparator, their hazards will also diverge over time.

The per-cycle probability of death for each simulated patient is computed from the calculated annual mortality hazard each cycle using the following formula:

$$p = 1 - e^{-h/t}$$

where *h* is the annual mortality hazard calculated at that cycle and t is the cycle length (in years) (381). The probability of death is compared to a random number each cycle to determine if the individual patient will die. After death, the patient exits the model and the next patient profile runs through the model calculation.

B.3.3.7.3 General population of England and Wales

The mortality hazard for pwCF estimated in the model is assumed to be no lower than that of the general population of England and Wales. Age- and gender-specific national life table data from England and Wales are used to impose this bound (371).

As such, at each model cycle, the calculated mortality hazard for a simulated patient is compared with the mortality hazard of the general population for a person of the same age and gender. In any given cycle, the assigned mortality hazard is the greater of the calculated hazard or the age- and gender-specific hazard retrieved from the general population of England and Wales.

B.3.3.7.4 Aggregated population mortality

To calculate a population survival curve from the predicted survival of each patient run through the model, the number of patients at risk of death for each age (i.e., the number of patients who were alive and had a baseline age less than or equal to the age in question) as well as the number of deaths at each age were calculated. From this, the survival curve was calculated using the Kaplan-Meier product-limit formula (382):

$$S(t) = S(t-1) \times \left(1 - \frac{n\ deaths_{(t-1,t)}}{n\ at\ risk_{(t-1,t)}}\right)$$

where survival at time zero (i.e., S(0)) is defined as 100%. This formula illustrates the methodology that the model uses to generate the survival curve and derive the median predicted survival estimate.

B.3.3.8 Adverse events

Each model considered AEs (excluding PEx) that occurred in at least 5% of patients treated with CFTRm and had at least 1%-point difference between patients treated with a CFTRm and PBO in the relevant clinical trial(s). This rule was applied to include events more likely to occur in patients receiving CFTRm than those receiving ECM alone. The probabilities observed over the respective trial durations were converted to constant event rates to be used as inputs in the model.

B.3.3.8.1 IVA/TEZ/ELX

In IVA/TEZ/ELX model, AEs from study 445-102 that occurred in at least 5% of treated patients and had at least 1%-point difference between patients treated with a CFTRm and PBO, were considered (7). As a simplifying assumption, the AE rates observed in the PBO arm of study 445-102 (7) in CF patients with F/MF genotype aged ≥12 years were applied to all patients aged ≥12 years receiving ECM alone across all genotypes.

The AE rates for patients of this age group treated with a CFTRm were derived from individual trials as indicated in Table 100.

For patients initiating treatment at age 6-11, the AE rates observed in the PBO arm of the LUM/IVA study 809-109 in CF patients with F/F genotype aged 6-11 years were applied to all patients in this age group receiving ECM alone across all genotypes (159). The PBO data from the LUM/IVA study were selected over the IVA pivotal trial and IVA/TEZ/ELX study 445-116, which also included a PBO arm, given the larger sample size (N=101 vs N=26 and N=61, respectively) (159, 175, 333). The AE rates for patients of this age group treated with a CFTRm were derived from individual trials as indicated in Table 101. Due to the small sample size of study 445-106 and the low incidence of AEs, it was not feasible to derive genotype-specific AE rates for CF patients with F/F or F/MF genotype treated with IVA/TEZ/ELX from this study (174).

Table 100. IVA/TEZ/ELX model inputs for annual AE incidence rates by genotype and comparator for patients aged ≥12 years

Adverse event	ECM alone, across all genotypes	IVA/TEZ/ELX			IVA in F/Gating
		F/F	F/MF	F/Gating, F/RF	
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source	445-102 (194)	445-109 (383)	445-102 (194)	445-104 (237)	STRIVE (384)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/ tezacaftor/elexacaftor and ivacaftor; URTI, upper respiratory tract infection.

Table 101. IVA/TEZ/ELX model inputs for annual AE incidence rates by genotype and comparator for patients aged 6-11 years

Adverse event	ECM alone, across all genotypes	IVA/TEZ/ELX		IVA in F/Gating
		F/F, F/RF, F/Gating	F/MF	
Headache	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event	ECM alone, across all genotypes	IVA/TEZ/ELX		IVA in F/Gating
		F/F, F/RF, F/Gating	F/MF	
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]
Source	809-109 (244)	445-106 (199)	445-116 (175)	ENVISION (366)
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/ tezacaftor/elexacaftor and ivacaftor; URTI, upper respiratory tract infection.				

B.3.3.8.2 LUM/IVA

In LUM/IVA model, AEs from TRAFFIC/TRANSPORT that met the inclusion criteria for AEs were considered (385). The age-specific AE rates for patients treated with LUM/IVA or ECM alone were derived from individual trials as indicated in Table 102. Since study 809-115 was a single-arm study (245), the AE rates in the PBO arm from study 809-109 were applied to patients aged 2-5 years receiving ECM alone (244).

Table 102. LUM/IVA model inputs for annual AE incidence rates by age group and comparator

Adverse event	Age ≥12		Age 6-11		Age 2-5	
	LUM/IVA	ECM	LUM/IVA	ECM	LUM/IVA	ECM
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiration abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source	TRAFFIC/ TRANSPORT(385)		809-109 (244)		809-115 (245)	809-109 (244)
Abbreviations: AE, adverse event; ECM, established clinical management; LUM/IVA, lumacaftor/ivacaftor.						

B.3.3.8.3 TEZ/IVA

In TEZ/IVA model, AEs from EMBRACE, EVOLVE, or EXPAND that met the inclusion criteria for AEs were considered (246, 247, 326). The genotype- and age-specific AE rates for CF patients with F/F or F/RF genotype treated with TEZ/IVA or ECM alone were derived from individual trials as indicated in Table 103.

Table 103. TEZ/IVA model inputs for annual AE incidence rates by age group, genotype and comparator

Adverse event	Age ≥12				Age 6-11	
	F/F		F/RF		F/F and F/RF	
	TEZ/IVA	ECM	TEZ/IVA	ECM	TEZ/IVA	ECM
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sputum increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event	Age ≥12				Age 6-11	
	F/F		F/RF		F/F and F/RF	
	TEZ/IVA	ECM	TEZ/IVA	ECM	TEZ/IVA	ECM
Cough						
Productive cough						
Gastroenteritis						
Vomiting						
Abdominal pain						
Nasal congestion						
Rhinorrhea						
Source	EVOLVE (246)		EXPAND (247)		EMBRACE (326)	
Abbreviations: AE, adverse event; ECM, established clinical management; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.						

B.3.3.9 Treatment discontinuation

Annualised CFTRm treatment discontinuation rates for the acute period (i.e., trial duration) were obtained from the relevant phase 3 trials. The annualised treatment discontinuation rates for the post-acute period were derived from the respective OLE studies, when data were available. After the post-acute period, no discontinuation of CFTRms was assumed in the model.

Upon discontinuation, patients no longer receive the benefits of CFTRm treatment. If a patient discontinues treatment, they retain the acute increase in $ppFEV_1$ and WFAZ they achieved up until the point of discontinuation. Since these efficacy measures were determined from intention-to-treat analyses, the mean treatment effects derived from the trials already take into account patients who discontinued during trial periods. In the post-acute period, the $ppFEV_1$ for a discontinued patient declines according to the age-dependent values assumed for the patients treated with ECM alone of each respective population (i.e., no reduction applied). If patients discontinue treatment during age 2-5, they receive the acute $ppFEV_1$ increment at age 6, but only the lung preservation achieved up until the point of discontinuation. Additionally, all patients who discontinue treatment are assumed to experience PEx at the same rate as patients treated with ECM alone (i.e., no relative reduction applied).

B.3.3.9.1 IVA/TEZ/ELX

The trials with the longest duration of follow-up for IVA/TEZ/ELX in each genotype and IVA in F/Gating were chosen as sources of treatment discontinuation rate for the acute period, while longer term discontinuation rates were based on OLEs where possible. The treatment discontinuation rates used in the IVA/TEZ/ELX model by genotype and CFTRm for patients initiating treatment with CFTRm at ages ≥12 and 6-11 are reported in Table 104 and Table 105, respectively.

For patients with F/Gating or F/RF genotype initiating treatment with IVA/TEZ/ELX at age ≥12, treatment discontinuation rate for the acute period was derived from study 445-104 (168). Due to the high retention in study 445-104, treatment discontinuation rate was calculated for the pooled population rather than by genotype.

Due to the small sample size and low number of discontinuations in study 445-106, an annualised treatment discontinuation rate was calculated for the pooled populations with F/F and F/MF genotypes aged 6-11 years (174). In the absence of data in patients with F/Gating and F/RF genotypes aged 6-11 years treated with IVA/TEZ/ELX, it was assumed that the attrition observed in patients of the same age from study 445-106 was applicable for the acute period (174).

In the absence of OLE data in patients with F/Gating and F/RF genotypes aged 6-11 years treated with IVA/TEZ/ELX, the corresponding post-acute discontinuation rates were derived from study 445-107 (202).

Table 104. IVA/TEZ/ELX model inputs for annual treatment discontinuation rate in patients initiating CFTRm at age ≥12

CFTR modulator	Acute period (weeks)	Annual rate (per pt-year)	Source	Post-acute period (weeks)	Annual rate (per pt-year)	Source
F/F						
IVA/TEZ/ELX	24	0.025	Study 445-109 (172)	144	[redacted]	Study 445-105 (188)
F/MF						
IVA/TEZ/ELX	24	0.033	Study 445-102 (7)	144	[redacted]	Study 445-105 (188)
F/Gating						
IVA/TEZ/ELX	8	0.049	Study 445-104 (168)	96	[redacted]	Study 445-110 (191)
IVA	48	0.081	STRIVE (332)	96	0.036	PERSIST (363)
F/RF						
IVA/TEZ/ELX	8	0.049	Study 445-104 (168)	96	[redacted]	Study 445-110 (191)

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PT, patient.

Table 105. IVA/TEZ/ELX model inputs for annual treatment discontinuation rate in patients initiating CFTRm at age 6-11

CFTR modulator	Acute period (weeks)	Annual rate (per pt-year)	Source	Post-acute period (weeks)	Annual rate (per pt-year)	Source
F/F						
IVA/TEZ/ELX	24	0.067	Study 445-106 (174)	96	0.026	Study 445-107 (201)
F/MF						
IVA/TEZ/ELX	24	0.036	Study 445-116 (204)	96	0.026	Study 445-107 (201)
F/Gating						
IVA/TEZ/ELX	24	0.067	Assumption, study 445-106	96	0.026	Assumption, study 445-107
IVA	48	0.000	ENVISION (333)	96	0.043	PERSIST (363)
F/RF						
IVA/TEZ/ELX	24	0.067	Assumption, study 445-106	96	0.026	Assumption, study 445-107

Abbreviations: CFTR, Cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PT, patient.

B.3.3.9.2 LUM/IVA

The sources of treatment discontinuation rate for patients initiating LUM/IVA at age ≥12 over the first 24 weeks of simulation were TRAFFIC/TRANSPORT (158), while the following 72 weeks are informed by PROGRESS (155) (Table 106). For patients initiating LUM/IVA at age 6-11, treatment discontinuation rate for the acute period was derived from study 809-109 (159), and from study 809-110 for the post-acute period (156). Discontinuation rates in the age group of 2-5 years for the acute and post-acute period were derived from study 809-115 (162) and study 809-116 (161), respectively (Table 106).

Table 106. LUM/IVA model inputs for annual treatment discontinuation rate for patients treated with LUM/IVA by treatment initiation age

Age of treatment initiation	Acute period (weeks)	Annual rate (per pt-year)	Source	Post-acute period (weeks)	Annual rate (per pt-year)	Source
≥12 years	24	0.152	TRAFFIC/ TRANSPORT(158)	72	0.140	PROGRESS (155)
6-11 years	24	0.130	809-109 (159)	96	0.047	809-110 (156)
2-5 years	24	0.149	809-115 (162)	96	0.104	809-116 (161)
Abbreviations: PT, patient.						

B.3.3.9.3 TEZ/IVA

Treatment discontinuation rate for the acute period of pwCF with F/F or F/RF genotypes initiating TEZ/IVA at age ≥12 was derived from EVOLVE (157) and EXPAND (164), respectively. Discontinuation rate in the post-acute period for the same populations was derived from EXTEND (325). In the age group 6-11 years, discontinuations in the acute and post-acute period were derived from EMBRACE (165) and 661-116 (386) for pwCF with F/F and F/RF genotypes, respectively (Table 107).

Table 107. TEZ/IVA model inputs for annual treatment discontinuation rate for patients treated with TEZ/IVA by genotype and treatment initiation age

Age of treatment initiation	Acute period (weeks)	Annual rate (per pt-year)	Source	Post-acute period (weeks)	Annual rate (per pt-year)	Source
F/F						
≥12 years	24	0.143	EVOLVE (157)	96	[redacted]	EXTEND (325)
6-11 years	8	0.121	EMBRACE (165)	96	[redacted]	661-116 (386)
F/RF						
≥12 years	8	0.081	EXPAND (164)	96	[redacted]	EXTEND (325)
6-11 years	8	0.121	EMBRACE (165)	96	[redacted]	661-116 (386)
Abbreviations: PT, patient.						

B.3.3.10 Compliance

Based on data from pill counts in the phase 3 trials, treatment-specific compliance rates were applied to the cost of CFTRms over the initial trial period. Following the acute period, a compliance rate of 80% was applied to all CFTRm therapies and age groups (2-5, 6-11 and ≥12 years) to reflect treatment compliance expected in a real-world setting, informed by the retrospective cohort study of a US administrative claims database by Suthoff et al (387). The only available data source that analysed both the efficacy and the impact of IVA on health resource utilisation, the study found that among 79 CF patients prescribed IVA between January 1, 2012 and July 31, 2014, the average medication possession ratio was 0.8. Despite compliance lower than that observed in trial settings, this study demonstrated clinical benefits consistent with those reported from trials and other observational studies. The efficacy of CFTRms over time was therefore not adjusted.

The post-acute compliance rate of 80% is further supported by a real-world multi-site non-interventional study of clinical outcomes in CF patients prescribed IVA/TEZ/ELX across eight clinical sites in the UK and Ireland. The six-month analysis, using the electronic Medication Electronic Monitoring System (MEMS®), reported adherence rates for IVA/TEZ/ELX (based on 16 patients) and IVA (based on 16 patients) of 82.7% and 83.1%, respectively (388). In addition, an analysis of adherence for IVA/TEZ/ELX, LUM/IVA, TEZ/IVA and IVA using retail pharmacy claims from a US pharmacy chain for 2020 was conducted. Proportion of days covered (PDC) was evaluated for 980 CF patients who were on a single CFTRm therapy, with 688 of these using IVA/TEZ/ELX. The mean PDC estimates for IVA/TEZ/ELX, LUM/IVA and IVA were similar and varied between 78.2-79.1%, while for TEZ/IVA was 73.0% (389).

B.3.3.10.1 IVA/TEZ/ELX

The inputs for compliance during acute period used in IVA/TEZ/ELX model for patients initiating treatment with CFTRm at ages ≥12 and 6-11 are summarised in Table 108 and Table 109, respectively. In the absence of trial data for IVA/TEZ/ELX in patients with F/Gating or F/RF genotype aged 6-11 years, the IVA/TEZ/ELX pill count for the combined population of patients with F/F and F/MF genotypes from study 445-106 was applied (199).

Table 108. IVA/TEZ/ELX model inputs for compliance during acute period for patients initiating CFTRm treatment at age ≥12

CFTR modulator	Compliance	Duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	Study 445-109 (383)
F/MF			
IVA/TEZ/ELX	[redacted]	24	Study 445-102 (194)
F/Gating			
IVA/TEZ/ELX	[redacted]	8	Study 445-104 (237)
IVA	[redacted]	48	STRIVE (384)
F/RF			
IVA/TEZ/ELX	[redacted]	8	Study 445-104 (237)

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor.

Table 109. IVA/TEZ/ELX model inputs for compliance during acute period for patients initiating CFTRm treatment at age 6-11

CFTR modulator	Compliance	Duration (weeks)	Source
F/F			
IVA/TEZ/ELX	[redacted]	24	Study 445-106 (199)
F/MF			
IVA/TEZ/ELX	[redacted]	24	Study 445-116 (175)
F/Gating			
IVA/TEZ/ELX	[redacted]	24	Assumption, study 445-106
IVA	[redacted]	48	ENVISION (366)
F/RF			
IVA/TEZ/ELX	[redacted]	24	Assumption, study 445-106

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor.

B.3.3.10.2 LUM/IVA

The inputs for compliance during acute period used in LUM/IVA model for patients treated with LUM/IVA by treatment initiation age are summarised in Table 110.

Table 110. LUM/IVA model inputs for compliance during acute period for patients treated with LUM/IVA by treatment initiation age

Age of treatment initiation	Compliance	Duration (weeks)	Source
≥12 years	[redacted]	24	TRAFFIC/TRANSPORT (390)
6-11 years	[redacted]	24	Study 809-109 (244)
2-5 years	[redacted]	24	Study 809-115 (245)

B.3.3.10.3 TEZ/IVA

The inputs for compliance during acute period used in TEZ/IVA model for patients treated with TEZ/IVA by genotype and age of treatment initiation are reported in Table 111.

Table 111. TEZ/IVA model inputs for compliance during acute period for patients treated with TEZ/IVA by genotype and treatment initiation age

Age of treatment initiation	Compliance	Duration (weeks)	Source
F/F			
≥12 years	[redacted]	24	EVOLVE (246)
6-11 years	[redacted]	8	EMBRACE (326)
F/RF			
≥12 years	[redacted]	8	EXPAND (247)
6-11 years	[redacted]	8	EMBRACE (326)

B.3.3.11 Lung transplantation

The UK clinical guideline for transplantation suggests referral for a lung transplantation for patients with $ppFEV_1$ <30% (391, 392). This threshold was accepted by NICE as an appropriate threshold for lung transplantation eligibility (128). Therefore, the model assumes that once a patient's $ppFEV_1$ drops below 30%, that patient becomes eligible to receive a lung transplant. Simulated patients aged 2-5 years are not eligible for lung transplantation since $ppFEV_1$ is not tracked in that age group.

The percentage of eligible patients who receive a lung transplant was estimated to be 6.4%, based on data from the UK CF Registry's annual report for 2021, which indicated that 5 CF patients received a lung transplant (<5 bilateral transplants and <5 "other" assumed to be single-lung transplants) among the 78 patients evaluated (59). The probability of receiving a lung transplant is applied equally to all patients in the cycle in which their $ppFEV_1$ falls below the 30% threshold. If a patient is not transplanted in that cycle, they are assumed not to receive a transplant for the remainder of the lifetime simulation.

The consequences of receiving a lung transplant are reflected in the applied mortality risk, costs accrued, and utilities assigned based on the time since transplantation. The post-lung transplantation mortality risk assumes constant annual mortality of 14.2% in the first year after transplantation and 5.4% in each subsequent year. These inputs were informed by survival data from 9,428 adult pwCF (all genotypes) who received a lung transplantation between January 1992 and June 2017, with median post-transplant survival of 9.9 years (393).

B.3.4 Measurement and valuation of health effects

CF is a chronic, life-limiting disease associated with substantially reduced HRQoL for both pwCF and their families and caregivers (115, 138, 143). For pwCF, disease progression leads to impaired physical and mental HRQoL, particularly in older individuals and those with poorer lung function (115, 136, 143). Up to 29% of children and adolescents with CF have depression, and up to 33% of adults with CF report either anxiety or depression (139). pwCF also perceive barriers to forming relationships, feelings of isolation, and limited independence (142). Furthermore,

caring for children with CF represents a major challenge for parents and caregivers, especially with increasing child age and treatment burden (115, 144, 394, 395).

B.3.4.1 HRQoL data from clinical trials

Utility scores are used in the model to convert time spent in health states defined by lung function ($ppFEV_1$), into estimates of QALYs. The NICE reference case requires that utility values used in economic analyses are generated using the European Quality of Life-Five Dimensions (EQ-5D), a generic (i.e., not disease-specific) instrument whereby scores are weighted by general population preferences (396). However, alternative preference-based methods for generating health state utility values (such as condition-specific preference-based measures) can be considered if it can be demonstrated that EQ-5D data are inappropriate (10).

B.3.4.1.1 Limitations of generic HRQoL Instruments in trials of CFTR modulators

Cystic fibrosis affects multiple body systems, but the largest impact is from progressive respiratory impairment. Evidence from clinical trials of CFTRms suggests that the EQ-5D is not sensitive to meaningful differences in lung function and that it does not capture the value of broader HRQoL benefits resulting from the restoration of CFTR function (397-399).

In the IVA pivotal trial, STRIVE, patients with mild and severe lung function impairment self-reported mean EQ-5D scores at baseline (prior to treatment initiation) of 0.92 and 0.87, respectively (399); these scores are higher than UK general population norms (0.86) (400). Similarly, data from the TRAFFIC/TRANSPORT trials of LUM/IVA confirmed the limitation of the EQ-5D in pwCF. The mean EQ-5D-5L index scores at baseline were similarly above population norms in both the LUM/IVA (0.908) and PBO (0.903) arms (397), suggesting ceiling effects limited the discrimination between subjects and thus the ability to observe a difference in outcomes. Analysis of the EQ-5D scores pooled across treatment arms and timepoints showed the instrument was not sensitive to meaningful differences in lung function, as measured by $ppFEV_1$ (Figure 90).

Figure 90. EQ-5D-5L index scores by ppFEV$_1$ pooled across timepoints in TRAFFIC/TRANSPORT trials of LUM/IVA

Abbreviations: LUM/IVA, lumacaftor/ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in 1 second. Taken from: Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. Slide-deck report- TRAFFIC TRANSPORT EQ-5D Analysis_200_13April2015.ppt.

The limitations of generic instruments in measuring CF-related changes in HRQoL were also observed with the Short Form-Six Dimension (SF-6D) instrument in the TEZ/IVA pivotal trial EVOLVE, where the mean SF-6D utility value at baseline was [redacted] (401). Both clinical experts and HTA reviewers have noted that these baseline utility scores in the CF population lack face validity.

Further supporting the limitations of the EQ-5D in this population is a crosswalk study that mapped the CFQ-R (263, 402) to the EQ-5D (403). The respiratory dimension of the CFQ-R was not found to be a significant predictor of EQ-5D utility and was not included in the mapping algorithm, despite this being a key symptom in pwCF which impacts on patient quality of life.

B.3.4.1.2 Need for a disease-specific preference-based measure in CF

The improbably high utility values observed in CF reflect patients' adaptation to life with a chronic condition. This causes them to rate their quality of life higher with less regard for the impact of the disease than is consistent with societal values and is known as a response shift. Response shift has been observed in serious chronic diseases, particularly those that are present from birth (404, 405). In addition, the ceiling effect limits the ability to detect a treatment benefit using a generic health utility measure, since a baseline EQ-5D utility of 1.0 allows no room for improvement with treatment.

The lack of sensitivity of the EQ-5D in the trial data of CFTRms, given the meaningful differences in respiratory function and HRQoL measured by CFQ-R, suggested that alternative approaches were needed to estimate utility values from CF clinical trial

data. For this reason, the pivotal trials of IVA/TEZ/ELX, LUM/IVA and TEZ/IVA collected QoL data using the CFQ-R, a disease-specific instrument, in addition to or instead of EQ-5D or SF-6D (for more detail, see Appendix H).

Although CFQ-R is a validated, reliable, and sensitive measure of HRQoL widely used in CF clinical research to evaluate treatments, it is not a direct measure of utility (402). To be able to generate CF-specific utility values with good sensitivity across the spectrum of CF severity, a CF-specific preference-based scoring algorithm for the CFQ-R adult and adolescent version was developed by Acaster and colleagues (406). Whereas a mapping algorithm permits the estimation of a preference-based score on measure X (e.g., EQ-5D) from the score on a non-preference-based measure Y (e.g., CFQ-R), the development of a preference-based scoring algorithm allows a preference-based score to be directly calculated from measure Y (e.g., CFQ-R). Utilities calculated from this disease-specific measure are intended to better capture both respiratory and non-respiratory effects of CFTRms on HRQoL and allow for calculation of QALYs in cost-effectiveness analyses. Additional details on the development of the preference-based scoring algorithm for the CFQ-R, known as the CFQ-R-8D, are presented in Section B.3.4.2.

B.3.4.1.3 Sources of CFQ-R data to inform utilities

Systematic searches for relevant HRQoL data, described in Appendix H, identified 29 clinical trials of CFTRms which reported HRQoL results. Of these trials, all except one (VX14-809-106) excluded patients with $ppFEV_1$ <40% at screening due to concerns around increased risk of AEs. For this reason, the IVA/TEZ/ELX and TEZ/IVA pivotal trials had so few patients with $ppFEV_1$ <40% during follow-up that it was not possible to use the CFQ-R data collected in these trials to estimate the effect of $ppFEV_1$ on utility at the lower end of the $ppFEV_1$ range. In TRAFFIC/TRANSPORT trials, a substantial number of patients had FEV_1 values that had fallen to below 40% of predicted at baseline (post-screening) thus allowing assessment of utility values by $ppFEV_1$ category. However, to achieve consistency across all three models and all subpopulations of pwCF with different *CFTR* genotypes, the economic model base case uses utility values estimated from the [redacted] (407).

Caregivers of children with CF struggle with the emotional and mental impact of their child's diagnosis as well as the complex nature of CF management (138). Providing nearly 75 hours of informal care per week to their children can be a distressing and burdensome experience (115, 394), linked to a two-to three-fold increase in the rate of anxiety (36%-48%) and depression (31%-37%) among parents of children (i.e., age ≤18) with CF, compared with the general population (176). The burden on caregivers of patients treated with IVA/TEZ/ELX, LUM/IVA or TEZ/IVA in the UK [redacted] (408).

[redacted]

B.3.4.1.4 TRAJECTORY

As described in Section B.2.2.4.2, [redacted] Study methodology and results are described in detail in Sections B.2.2 to B.2.5. [redacted] as described in detail in Section B.3.4.2.

B.3.4.1.5 MAGNIFY

[redacted]

[redacted] The methodology and results of MAGNIFY are described in detail in Sections B.2.2to B.2.5.

B.3.4.2 Mapping

Derivation of health state utilities for the economic model did not involve the use of a mapping algorithm to estimate preference-based EQ-5D scores from CFQ-R scores. Instead, the [redacted]:

- [redacted]
- [redacted]

B.3.4.2.1 Development of the CFQ-R-8D

To develop CFQ-R-8D, methods originally developed in the estimation of a preference-based measure of health from the SF-36 were applied (410, 411). The same methods were used with condition specific measures in urinary incontinence (412), overactive bladder (413), cancer (414), diabetes (415) and myelofibrosis (416).

The development of a preference-based measure from an existing instrument such as the CFQ-R uses factor, psychometric and Rasch analysis to derive dimensions and identify suitable items for a 'health state classification system'. The classification system identifies the minimum number of health dimensions necessary to describe the primary impacts of a condition (411). Selected health states described by the classification system are then valued by members of the general public and these values are modelled to produce utility values for all health states defined by the classification system. The valuation methods using time trade-off (TTO) mirror those

used to value the EQ-5D and follow published guidelines (417). The development of CFQ-R-8D progressed in three phases described in a recent publication (406).

Phase 1 involved development of a health state classification system, as a combination of items that represent dimensions and their response options (e.g., no difficulty to a lot of difficulty) by which every patient can be classified. The subset of items for valuation was identified from secondary analysis of four CFTRm trials (STRIVE, TRAFFIC/TRANSPORT and EXPAND/EVOLVE) that administered the CFQ-R (adult/adolescent version), as well as a measure of utility (either EQ-5D or SF-6D). Items in the CFQ-R were evaluated using standard analytic techniques and were further evaluated for Item/Response Option wording to ensure suitability for valuation by the general public. The draft classification system was reviewed by UK residents with CF (N = 5) and clinicians (N = 4) from the UK, the US, Canada and Australia. Reviewers were interviewed and asked to assess the relevance and importance of the selected CFQ-R items; the 9 items were endorsed by all reviewers.

In phase 2, a subset of 32 health states was selected for the valuation using statistical methods. The subjects recruited to perform health state valuation and included in the final analysis comprised 345 adult members of the UK general population enrolled through a general population panel, with quotas to ensure that the sample was a reasonable reflection of the UK general population (e.g., mean age, 46.5 in sample vs 49.1 in the UK; female 50.1% vs 54.1%; white 85.8% vs 76.1%). The sample was drawn from the general population rather than from pwCF, in line with the NICE reference case, to reflect societal preferences (10). Only adults were included in the valuation thus fulfilling the HTA requirement related to ‘potential taxpayer’ and because the interviews are considered too cognitively and conceptually challenging for children. Currently all pediatric preference-based measures derive their utility weights from adult populations. Valuation was conducted via face-to-face interview with a trained interviewer using the TTO approach to assign utility values to each health state, consistent with utility theory and methodology for EQ-5D valuation.

Finally, a variety of regression models were fitted to individual-level data and to mean health state values from the valuation exercise in phase 3. Performance of regression models was assessed using several criteria, such as the number of significant and non - significant coefficients, the consistency of the coefficients with the classification

system, root mean squared error (RMSE) at the individual level and mean absolute error (MAE) at the state level. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were also examined. Predicted values, observed values and errors by health state were plotted and examined for any patterns. The final preferred model, selected through consideration of logical consistency of coefficients, predictive performance, and the ability to reflect variation at the individual level, was the Tobit heteroscedastic–ordered model (Table 112).

Table 112. Tobit heteroscedastic–ordered model estimating preference weights based on reduction in utility associated with dimension and response level

Dimension and reference	Response level	Disutility
Physical function Climbing one flight of stairs (ref: no difficulty)	A little difficulty	0.0409*
	Some difficulty	0.0593‡
	A lot of difficulty	0.1036‡
Role Functioning Able to complete daily activities (ref: always)	Often	0.0482†
	Sometimes	0.0883‡
	Never	0.1081‡
Emotion You felt worried or sad (ref: never)	Sometimes	0.0631‡
	Often	0.0960‡
	Always	0.1041‡
Vitality You felt exhausted (ref: never)	Sometimes	0.0396†
	Often	0.0708‡
	Always	0.1083‡
Breathing difficulty You had trouble breathing (ref: never)	Sometimes	0.0515†
	Often	0.0700‡
	Always	0.1268‡
Cough Coughing during the day (ref: not at all)	A little	0.0250
	Sometimes	0.0426†
	A great deal	0.1003‡
Abdominal pain You had abdominal pain (ref: never)	Sometimes	0.0586‡
	Often	0.0586‡
	Always	0.0847‡
Body image You feel bad about your appearance (ref: false)	True	0.0280†
* $P<0.1$; † $P<0.05$; ‡ $P<0.01$		

The utility values generated by the TTO process have good face validity across the spectrum of CF severity. As expected, the coefficients are all positive, indicating that less than full health resulted in lower HRQoL, and all dimensions and all levels were significant predictors of HRQoL. The model algorithm has a predicted range of health state utilities from 0.236 to 1 (418). Model coefficients define the algorithm used to convert the relevant CFQ-R items to a utility score, which is implemented by subtracting the sum of all disutilities from 1. Validation of the CFQ-R-8D scoring algorithm has been completed in collaboration with the Sheffield University and the manuscript is in preparation (418).

B.3.4.3 HRQoL studies

Appendix H describes the details of the methods used for the systematic searches for relevant health-related quality-of-life data. Briefly, a systematic review was conducted to identify any randomised or non-randomised studies reporting HRQoL data of pwCF and their carers, and any studies reporting utility values of pwCF stratified by $ppFEV_1$ range that could inform the health state utilities in the cost-effectiveness model. The searches were run in the period from 31 August to 2 September 2022. A total of 139 unique studies were identified, and of these, 91 were retained for extraction. Studies describing HRQoL of pwCF treated with specific components of ECM were not extracted, since data from the PBO arm of trials or observational studies of CFTRms adequately capture the HRQoL associated with individualised ECM. Of the extracted studies, 16 report HRQoL as utilities. Of those, five studies reported a unique set of utilities stratified by $ppFEV_1$ from the UK (128, 293, 399, 403, 419), and two studies reported UK-specific disutilities for PEx (293, 419). Three studies reported utilities post-lung transplantation in the UK (128, 293, 420).

Acaster et al. (2015) (403) reported the most recent UK EQ-5D data stratified by $ppFEV_1$ (Table 113). Acaster et al. conducted a cross-sectional observational study in the UK in which 401 pwCF aged over 18 years completed the CFQ-R, the EQ-5D and a demographic/clinical background form (403). The clinical background form, which asked participants to rate their CF severity as mild ($ppFEV_1$ ≥70%), moderate ($ppFEV_1$ 40-70%) or severe ($ppFEV_1$ <40%), provided the necessary data to stratify reported utilities by $ppFEV_1$. The mean EQ-5D utility for the total sample was 0.67 (SD: 0.28), with utility values ranging from -0.35 to 1.0 (403).

Table 113. EQ-5D utilities by $ppFEV_1$ strata from Acaster et al. (403)

Disease severity	Utility value	Source
$ppFEV_1$ ≥70%	0.74	Acaster et al. (2015) (403)
$ppFEV_1$ 40%-69%	0.70	
$ppFEV_1$ <40%	0.54	
Abbreviations: ppFEV1, percent predicted forced expiratory volume in one second.		

Alternative utility values by $ppFEV_1$ have been reported in the following studies:

- Tappenden et al. (293) cited EQ-5D utility values by $ppFEV_1$ from Bradley et al. (419), a study that investigated the EQ-5D and CFQ-R scores of 94 CF patients

aged over 16 years who presented with a chronic Pseudomonas aeruginosa infection, taking oral or nebulised antibiotics recruited from UK clinics

- Whiting et al. (128) performed a cost-effectiveness analysis using UK-based utility scores by $ppFEV_1$ derived from the SF-36 index by Gee et al. (421)
- Solem et al. (2014) (422) and Solem et al. (2016) (399) are post-hoc analyses of STRIVE (332) that reported EQ-5D by $ppFEV_1$ in patients aged ≥12 years with CF.

Tappenden et al. (293) and the post-hoc analysis of STRIVE (399) are the two studies which provide estimates of disutility for the occurrence of a PEx; STRIVE EQ-5D data were collected more recently from a clinical trial and provide disutility estimates for PEx requiring and those not requiring hospitalisation.

The three studies identified in the SLR that report post-transplant utilities in the UK (128, 293, 420) cited Anyanwu et al. (423), which is the source used in the models presented in this submission. Anyanwu et al. (423) was not identified in the SLR due to the restriction on the search publication year, but was identified as the source of data in studies retrieved by the SLR.

The observational studies TRAJECTORY (407), source of baseline utilities stratified by $ppFEV_1$ and the utility benefit of treatment with IVA/TEZ/ELX, and MAGNIFY (408), which is the source of caregiver utility used in the cost-effectiveness analysis, were not identified in the SLR, as these studies have not been published yet.

B.3.4.4 HRQoL data used in the cost-effectiveness analysis

B.3.4.4.1 Utilities by disease severity

As described in Section B.3.4.2, the validated CFQ-R 8D algorithm was used to derive health state utilities stratified by $ppFEV_1$ from the CFQ-R data [redacted] The mean CFQ-R 8D utility values at baseline (i.e., prior to treatment with IVA/TEZ/ELX) stratified by $ppFEV_1$ shown in Table 114 were used as inputs in the model.

Table 114. Health state utilities by disease severity

Disease severity	CFQ-R-8D utility value	Source
$ppFEV_1$ ≥70%	[redacted]	[redacted] (249)
$ppFEV_1$ 40%-69%	[redacted]	
$ppFEV_1$ <40%	[redacted]	

Abbreviations: IA, interim analysis; $ppFEV_1$, percent predicted forced expiratory volume in one second.

B.3.4.4.2 Disutility associated with a pulmonary exacerbation

The pivotal studies for IVA/TEZ/ELX and TEZ/IVA did not include measures of utility (e.g., EQ-5D or SF-6D). Therefore, the models of IVA/TEZ/ELX and TEZ/IVA apply a disutility of 0.07 for the occurrence of a PEx requiring treatment with IV antibiotics and/or hospitalisation based on the EQ-5D utility decrement observed for such events among patients in the IVA pivotal trial, STRIVE (399). For consistency, the LUM/IVA model applies the same disutility value. Each PEx was assumed to last for 30 days, based on the mean duration of PEx across both treatment arms in STRIVE (399).

The duration of PEx disutility was applied to both simulated patients receiving a CFTRm and those receiving ECM alone. This is a conservative assumption, since CFTRms have demonstrated a reduction in the length of PEx as well as the frequency.

B.3.4.4.3 Adverse events

The AEs included in the economic model were not serious in general, and therefore no utility decrement was applied.

B.3.4.4.4 Utility benefit of treatment

[redacted]

[redacted]

[redacted]

B.3.4.4.5 Post-lung transplant utilities

Assumptions for post-lung transplantation utility were based on cost-effectiveness analysis in CF (128), which reported a weighted EQ-5D post-lung transplant utility based on a study by Anyanwu et al. (423). Anyanwu et al. investigated patient's post-lung transplant utility regardless of previous treatment and clinical status prior to transplantation. The study included 255 patients after single or bilateral lung or heart-lung transplant from four of seven UK lung transplant centres. Whiting et al. analysed

the measurements from patients who received bilateral lung transplantation in the study conducted by Anyanwu et al. because these patients were deemed most likely to have CF (128). The number of months since the transplantation was used to weight mean utility values measured at different time periods after bilateral lung transplantation. The resulting EQ-5D utility value applied to all patients post-lung transplant is 0.81 (128).

A health technology assessment by NHS later assessed the cost-effectiveness of IVA in CF patients and adopted the utilities by Anyanwu et al. and reported the weighted average of these post transplantation utilities (423). Whiting et al. (128) was identified from the SLR for HRQoL data. There were no additional relevant studies identified from the SLR for HRQoL data to inform lung transplant utilities.

B.3.4.4.6 Caregiver utility

Day-to-day care of pwCF imposes a considerable burden on their caregivers and families. Multiple studies have demonstrated that caregiving for pwCF has a substantial impact on caregiver QoL, particularly for caregivers of paediatric patients and during PEx episodes (140, 248, 395). 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 methodologies [redacted] (408, 426). [redacted]

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

A systematic review was conducted to identify economic evidence associated with management of pwCF as described in Appendix I. The SLR identified 36 unique studies of costs and healthcare resource use relevant for decision making in England, and four economic evaluations reporting relevant cost and health care resource use inputs. Their summary is presented in Appendix I.

The cost of managing CF in the UK in the absence of active intervention, stratified by disease severity, was not identified from the SLR. An additional hand search on this topic identified Ramagopalan et al. (116), a UK study presented at the 15th Biennial European Meeting at the Society for Medical Decision Making in 2014 based on an earlier study by Lambrelli et al. (427). This source was used to inform both PEx- and non-PEx-related disease management costs (116). The impact of CFTRms on non-PEx-related inpatient and pharmacotherapy costs was informed by Simmonds et al., an observational study of the effect of long-term IVA on healthcare resource utilisation in pwCF in the UK, Italy and the Netherlands (428). Post lung transplantation costs were derived from a UK study by Anyanwu et al. (423) and were cited by Whiting et al. (128) identified in this SLR. Other costs were derived from the 2020/21 National Cost Collection for the NHS (429) and the Personal Social Services Research Unit (PSSRU) (430). The current costs in the model were derived by inflating the previously published values to year 2021 using the UK Consumer Price Inflation (431). A complete list of all the costs included in the model is provided in Table 115.

Table 115. Summary of cost inputs

	Point Estimate (£)		Source
CFTRm and ECM treatment cost, annual			
IVA/TEZ/ELX	200,187		Calculated values based on the NHS list prices (432)
IVA	182,625		
LUM/IVA	104,357		
TEZ/IVA	173,414		
ECM	0		Assumption
Monitoring cost, CFTRm, first year	387		2020/21 National Cost Collection (429)
Monitoring cost, CFTRm, subsequent years	2		
Non-PEx-related disease management cost, annual			
Cost item, ppFEV$_1$ category	CFTRm	ECM	
Inpatient, <40	6,579	21,928	Ramagopalan et al. (2014) (116); impact of CFTRms on inpatient and pharmacotherapy costs derived from Simmonds et al. (2022) (428)
Inpatient, 40-69	2,524	8,415	
Inpatient, ≥70	418	1,393	
Outpatient, <40	5,454	5,454	
Outpatient, 40-69	5,228	5,228	
Outpatient, ≥70	4,826	4,826	
Pharmacotherapy, <40	3,475	11,582	

	Point Estimate (£)		Source
Pharmacotherapy, 40-69	3,234	10,780	
Pharmacotherapy, ≥70	652	2,173	
Other, <40	921	921	
Other, 40-69	497	497	
Other, ≥70	356	356	
PEx-related disease management cost, per event			
$ppFEV_1$ category	CFTRm	ECM	
<40	10,018	10,018	Ramagopalan et al. (2014) (116)
40-69	8,159	8,159	
≥70	7,813	7,813	
Lung transplant cost			
Transplant procedure	91,778		2020/21 National Cost Collection (429)
First year follow-up	26,239		Anyanwu et al. (2002) (423)
Second year follow-up	16,469		
Third year follow-up	17,314		
Years 4–9 follow-up (annual)	10,400		
Years 10+ follow-up (annual)	5,787		
AE cost			
AE cost per event	70.13		PSSRU Unit Costs of Health & Social Care 2021 (430)
Abbreviations: AE, adverse event; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; NHS, National Health Service; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; PSSRU, Personal Social Services Research Unit.			

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

The annual acquisition cost of each CFTRm is based on the corresponding NHS list price, as shown in Table 116 (432).

Table 116. Annual acquisition costs by CFTR modulator regimen

	IVA/TEZ/ELX regimen		IVA regimen	LUM/IVA regimen	TEZ/IVA regimen	
	IVA/TEZ/ELX	IVA			TEZ/IVA	IVA
Cost per pack	£8,346	£7,000	£14,000	£8,000	£6,294	£7,000
Doses per pack	56	28	56	112	28	28
Doses per day	2	1	2	4	1	1
Annual acquisition cost	£200,187		£182,625	£104,357	£173,414	
Source	NHS list price (432)					
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; LUM/IVA, lumacaftor/ivacaftor; NHS, National Health Service; TEZ/IVA, tezacaftor/ivacaftor.						

Traditional cost-effectiveness frameworks assume that the price of a therapy will be unchanged for the full duration of the model time horizon, although real-world pricing patterns demonstrate significant price reductions when branded drugs lose exclusivity and generic options become available (314, 433). According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Drug Cost Task Force, in case of a long model time horizon, the expected market realities of changes in drug prices should be accounted for in the model, along with the impact of generic entry and related price erosion (434). Assuming that drug prices remain unchanged after the loss of exclusivity would misrepresent the long-term cost of drugs to society.

At the very least, plausible assumptions about genericization should be explored in sensitivity analysis (435).

In the context of CFTRms, it is unrealistic to assume that the price will remain constant for the entire lifetime horizon, which can be decades for many simulated patients in the model, especially given the likely advent of generic options entering the market at patent expiry. Although it was conservatively assumed in the base-case that the price of CFTRms would remain unchanged after the loss of exclusivity, a companion set of analyses was conducted to examine how results change with the inclusion of genericization. In the companion analyses it was assumed that the price of CFTRms would decrease at the time of loss of exclusivity (LoE), which was assumed to be 15 years from model start for IVA/TEZ/ELX, 11 years for TEZ/IVA, 8 years for LUM/IVA and 4.5 years for IVA, based on the projected expiration of European Union patents (Vertex Pharmaceuticals, unpublished communication). The reduction in drug price in the first year following LoE was assumed to be 39.4%, followed by a 65.1% drop the year after, based on published literature of UK pricing trends (436).

Treatment monitoring costs

The cost of liver function tests and ophthalmologist visits were only applied to patients receiving CFTRms, as per the Summary of Product Characteristics for each CFTRm. Patients receiving ECM are assumed to have no monitoring costs. The tests included a liver function test for bilirubin, aspartate transaminase and alanine transaminase at three, six, nine, and twelve months after treatment initiation, and two ophthalmologist visits in the first year of initiation. In subsequent years, a liver function test is performed once annually. No additional physician visits were assumed to accompany the liver function tests since CF patients were routinely monitored on a quarterly basis. The annual treatment monitoring costs presented in Table 117, were applied to all patients receiving CFTRm irrespective of age.

Table 117. Annual treatment monitoring costs

Type of cost	Unit cost (£)	Frequency		Total cost (£)		Source
		CFTRms	ECM	CFTRms	ECM	
Monitoring cost, first year						
Liver function tests	1.85	4	0	7.40	0	2020/21 National Cost Collection (429)
Initial visit ophthalmologist	213.13	1	0	213.13	0	
Follow-up visit ophthalmologist	166.35	1	0	166.35	0	
Monitoring cost, subsequent years						

Liver function test	1.85	1	0	1.85	0	2020/21 National Cost Collection (429)
Abbreviations: CFTRms, cystic fibrosis transmembrane conductance regulator modulators; ECM, established clinical management.						

B.3.5.2 Health-state unit costs and resource use

Disease management costs

Disease management costs are included in the model to capture the cost of routine medical care for CF, including clinic visits, hospitalisations, infection prevention and management of comorbidities. Disease management costs are applied in the model by disease severity, defined by $ppFEV_1$ thresholds, and are split by non-PEx-related annual costs and PEx-related costs, to ensure the model does not double count costs of PEx events.

Cost inputs were derived from a retrospective chart review of 200 CF patients aged ≥6 years carrying the *G551D* mutation or homozygous for the *F508del* mutation across eight specialist CF centres in the UK (116). Full 24-month data were extracted for each patient, including patient characteristics, pharmacotherapy, and healthcare resource use. Individual costs were aggregated into five categories: surgeries, hospitalisations, outpatient visits, pharmacotherapy, and diagnosis. Since the cost of PEx was included in the estimates, the annual cost associated with hospitalisation and pharmacotherapy was adjusted to exclude the potential cost of PEx events. The reduced hospitalisation costs together with the surgery costs were captured in the economic model as annual non-PEx-related inpatient costs. The categories of outpatient visits, pharmacotherapy and diagnosis in the chart review were captured as annual non-PEx-related outpatient, pharmacotherapy, and other costs, respectively, in the economic model.

The cost estimates in the chart review were reported by the following disease severity strata (116):

- Normal: $ppFEV_1$ ≥90%
- Mildly impaired: $ppFEV_1$ 70% to <90%
- Moderately impaired: $ppFEV_1$ 40% to <70%
- Severely impaired: $ppFEV_1$ <40%.

To be incorporated into the model that allows maximum three disease severity groups, the “normal” and “mildly impaired” $ppFEV_1$ groups were merged ($ppFEV_1$ ≥70%) using a weighted average approach based on the number of patients in each stratum. The UK chart review also included the costs of a PEx episode by lung function severity,

which was stratified into three ppFEV$_1$ categories, following the same approach. The cost of a PEx event is applied in the model during the cycle in which the PEx occurs, and not as an annual cost. Model inputs for disease management costs applied to simulated patients receiving ECM alone is summarised in Table 118.

Table 118. Disease management costs for patients receiving ECM alone

	Non-PEx-related disease management cost, annual				PEx-related disease management cost, per event
ppFEV$_1$ Category	Inpatient	Outpatient	Pharmacotherapy	Other	
ppFEV$_1$ ≥70	£1,393	£4,826	£2,173	£356	£7,813
ppFEV$_1$ 40-69	£8,415	£5,228	£10,780	£497	£8,159
ppFEV$_1$ <40	£21,928	£5,454	£11,582	£921	£10,018
Source	Ramagopalan et al. (2014) (116)				

Abbreviations: ECM, established clinical management; PEx, pulmonary exacerbation, ppFEV$_1$, percent predicted forced expiratory volume in one second.

A real-world study by Simmonds et al. (2022) demonstrated the positive long-term effect of IVA on healthcare resource utilisation in CF patients aged ≥6 years with non-*G551D-CFTR* gating mutations (428). All-cause hospitalisations and courses of oral or inhaled antibiotics during the first 12 months after IVA initiation were compared with 12 months prior to IVA. For the annualised hospitalisation rate per CF patient post IVA, the study reported an estimated RR of 0.3 (95% CI: 0.2 to 0.7) vs prior to IVA initiation (428). For the annualised medication course rate of oral or inhaled antibiotics per CF patient post IVA, the study reported an estimated RR of 0.3 (95% CI: 0.1 to 0.6) vs prior to IVA initiation (428). The observed reduction in oral or inhaled antibiotic use following the initiation of IVA was assumed to represent the reduction in pharmacotherapy costs incurred by CF patients treated with CFTRms. Thus, based on the study by Simmonds et al., the model applies a 70% reduction to both inpatient and pharmacotherapy costs for patients treated with a CFTRm.

Several real-world studies conducted in the UK have demonstrated the positive impact of CFTRms on hospitalisation rates due to PEx (327, 338, 428, 437). However, the model conservatively assumes the cost of a PEx episode to be the same for patients treated with a CFTRm and patients treated with ECM alone to not overestimate the impact of treatment on PEx (given a reduction in the PEx rate is explicitly tracked in the model).

Although a large portion of healthcare resource use is attributable to outpatient visits and diagnostic costs, due to the absence of data on the impact of CFTRms on these costing elements, the costs were assumed to be the same for patients treated with a

CFTRm and patients treated with ECM alone. Model inputs for disease management cost applied to simulated patients receiving a CFTRm is summarised in Table 119.

Table 119. Disease management costs for patients receiving CFTRm

	Non-PEx-related disease management cost, annual				PEx-related disease management cost, per event
$ppFEV_1$ Category	Inpatient	Outpatient	Pharmacotherapy	Other	
$ppFEV_1$ ≥70	£418	£4,826	£652	£356	£7,813
$ppFEV_1$ 40–70	£2,524	£5,228	£3,234	£497	£8,159
$ppFEV_1$ <40	£6,579	£5,454	£3,475	£921	£10,018
Source	Impact of a CFTRm on inpatient and pharmacotherapy costs derived from Simmonds et al. (2022) (428)				Ramagopalan et al. (2014) (116)
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second.					

Treatments such as CFTRms that extend life also, by definition, extend the period during which the patient receives non-interventional supportive care (i.e., ECM). As CF is associated with substantial disease management costs, increasing survival in CF is costly, independent of the cost of a CFTRm. As a result, counting these supportive care costs during the life years gained by patients treated with a CFTRm substantially devalues life-extending therapies, which is counterintuitive to how society values these medicines. However, conservatively, disease management costs for patients treated with CFTRms accrued during prolonged survival (i.e., after the ECM-treated "identical counterpart" dies), have been included in the cost estimates.

B.3.5.3 Adverse reaction unit costs and resource use

AEs are considered to be acute conditions which result in a one-time cost for each occurrence of the event. The cost of each AE was conservatively assumed to be equal to the cost of a single general practitioner consultation (£39.23) and one generic prescription (£30.90), totalling £70.13 per event (430).

B.3.5.4 Miscellaneous unit costs and resource use

Lung transplantation costs

In the model, pwCF who receive a lung transplant no longer incur CF-related disease management costs (since $ppFEV_1$ is no longer tracked post-transplant) and instead incur the cost of post-transplant care.

Costs associated with lung transplantation considered in the model are shown in Table 120. The cost of transplantation is a weighted average of elective hospitalisations, non-elective long stays, and non-elective short hospital stays for patients receiving lung transplantation in the UK based on the 2020/21 National Cost Collection for the

NHS (429). The costs associated with follow-up care are based on a study by Anyanwu et al. (2002), which reported costs for up to 15 years post-lung transplant (423). The average costs per year for patients who received lung transplant were adjusted to reflect costs only for patients still alive in the given year, with the values inflated to year 2021.

Table 120. List of lung transplantation costs

Item	Value (£)	Source
Transplant Procedure	£91,778	2020/21 National Cost Collection (429)
First Year Follow-up	£26,239	Anyanwu et al. (2002) (423)
Second Year Follow-up	£16,469	
Third Year Follow-up	£17,314	
Years 4–9 Follow-up (Annual)	£10,400	
Years 10+ Follow-up (Annual)	£5,787	

B.3.6 Severity

The severity of CF and whether the CFTRms under evaluation meet the criteria for a severity weight were assessed by calculating the associated absolute and proportional QALY shortfall, based on NICE's health technology evaluation guidance development manual (10). For the calculation of expected total QALYs for the general population, the survival was based on the 2018-20 National life tables for England and Wales from the Office for National Statistics (2021) (371), while the population EQ-5D-3L data by age and sex were derived from the HSE 2014 dataset, as recommended in the NICE DSU report from Hernández Alava et al. (2022) (438). QALYs were discounted using the base-case annual discount rate of 1.5% for health outcomes.

As described in Section B.3.3.7, for patients aged ≥6 years, the survival predictions in the model were based on a reference survival curve of the overall population with CF in the absence of CFTR modulation in the UK, a CPH model by Liou et al. (64) and the general population survival for England and Wales from ONS 2021 to set an upper bound on survival (371). The model reasonably assumes 100% survival for patients during the age of 2-5, as ppFEV$_1$, which is the key parameter needed to estimate survival, is not tracked in the model until the age of 6, and the UK mortality rate for this age group is negligible (372).

B.3.6.1 IVA/TEZ/ELX

The features by genotype used in the QALY shortfall analysis of IVA/TEZ/ELX model are summarised in Table 121.

The discounted values of absolute and proportional QALY shortfalls weighted by genotype prevalence were calculated at 21.50 and 0.64, respectively (Table 122). Since the weighted absolute QALY shortfall is ≥18, IVA/TEZ/ELX meets the criteria for a severity weight of 1.7 (10).

Table 121. Summary features of QALY shortfall analysis in IVA/TEZ/ELX model

Feature	F/F	F/MF	F/Gating	F/RF	Reference
Starting age (Years)	22.4	22.7	23.6	31.2	Table 85
Gender (Female)	50.77%	50.64%	53.00%	55.02%	Table 85
Genotype prevalence	54.28%	28.96%	10.57%	6.19%	Table 82

Table 122. Summary of results of QALY shortfall analysis in IVA/TEZ/ELX model

Feature	F/F	F/MF	F/Gating	F/RF
Expected total QALYs for the general population	33.84	33.42	33.00	29.92
Total QALYs that CF patients would be expected to have with current treatment	11.43	11.47	15.81	11.23
Absolute QALY shortfall	22.41	21.95	17.19	18.70
Weighted absolute QALY shortfall	21.50			
Weighted proportional QALY shortfall	0.64			

B.3.6.2 LUM/IVA

The features used in the QALY shortfall analysis of LUM/IVA model are summarised in Table 123.

The discounted values of absolute and proportional QALY shortfalls were calculated at 21.73 and 0.63, respectively (Table 124). Since the absolute QALY shortfall is ≥18, LUM/IVA meets the criteria for a severity weight of 1.7 (10).

Table 123. Summary features of QALY shortfall analysis in LUM/IVA model

Feature	Value	Reference
Starting age (Years)	20.3	Table 85
Gender (Female)	50.68%	Table 85

Table 124. Summary of results of QALY shortfall analysis in LUM/IVA model

Feature	Value
Expected total QALYs for the general population	34.66
Total QALYs that CF patients would be expected to have with current treatment	12.93
Absolute QALY shortfall	21.73
Proportional QALY shortfall	0.63

B.3.6.3 TEZ/IVA

The features by genotype used in the QALY shortfall analysis of TEZ/IVA model are summarised in Table 125.

The discounted values of absolute and proportional QALY shortfalls weighted by genotype prevalence were calculated at 22.04 and 0.66, respectively (Table 126).

Since the weighted absolute QALY shortfall is ≥18, TEZ/IVA meets the criteria for a severity weight of 1.7 (10).

Table 125. Summary features of QALY shortfall analysis in TEZ/IVA model

Feature	F/F	F/RF	Reference
Starting age (Years)	22.4	31.2	Table 85
Gender (Female)	50.77%	55.02%	Table 85
Genotype prevalence	89.76%	10.24%	Table 83

Table 126. Summary of results of QALY shortfall analysis in TEZ/IVA model

Feature	F/F	F/RF
Expected total QALYs for the general population	33.84	29.92
Total QALYs that CF patients would be expected to have with current treatment	11.42	11.23
Absolute QALY shortfall	22.42	18.70
Weighted absolute QALY shortfall	22.04	
Weighted proportional QALY shortfall	0.66	

B.3.7 Uncertainty

The rarity of CF and the ethical concerns related to randomised controlled trial design have an impact on the generation of high-quality evidence. Indeed, the relatively small pool of participants available for clinical trial enrolment limits an investigator's ability to power studies to detect small (i.e., potentially clinically insignificant) treatment differences (439). The requirement of participants with specific genotypes further restricts the already limited CF populations eligible for clinical trials beyond the normally imposed eligibility criteria, such as $ppFEV_1$ ≥40% at baseline and age (440).

Given the small numbers of patients randomised to the control (PBO for F/F, N = 10; IVA for F/RF, N = 3) EMBRACE was neither designed nor powered for between-group comparisons, with the most appropriate model input for acute increase in $ppFEV_1$ being the mean within-group change observed across both F/F and F/RF genotypes (326, 347). The pooling of data from patients with F/F and F/RF genotypes was partially based on the limited number of trial participants with RF mutations. An assessment of the reduction in the rate of $ppFEV_1$ decline for patients with F/RF genotype treated with TEZ/IVA based on a post-hoc analysis of EXTEND relative to untreated controls was not feasible due to the limited number of untreated patients with this genotype in the US CFFPR, which did not allow for robust propensity score matched analysis.

PEx rate as an efficacy endpoint in CF clinical trials requires relatively large number of patients; while this can be mitigated by enriching a study population for subjects with a higher risk of PEx, such a study could be poorly generalisable to the wider CF

population (441). The relative infrequency of PEx in children precludes its use as an end point in paediatric trials due to sample size requirements (442). Indeed, for patients initiating CFTRms at age 6-11, no treatment effect is assumed on PEx, since the pivotal trials of LUM/IVA (study 809-109) and IVA (study 770-103) conducted in this age group were not powered to detect a difference in PEx rates (159, 333), while the pivotal trials of IVA/TEZ/ELX (study 445-116) and TEZ/IVA (study 661-115) did not collect PEx as an efficacy endpoint (165, 204).

In clinical investigations of IVA/TEZ/ELX, lengthy PBO-controlled comparisons are considered unethical, since patients would be required to washout their therapy with the approved CFTRm and, if randomised to PBO, to stay off a highly effective treatment for the duration of the trial (440). Even for patients willing to washout from previous CFTRm, only trial designs with short washout and short double-blind PBO periods would be acceptable (443). However, the incorporation of a short washout period also raises uncertainty about whether it would be sufficient to avoid a carry-over treatment effect of the previous CFTRm (442, 443).

Although active-comparator trials enable evaluation of efficacy within the context of standard care, there is a challenge to this design relative to a more traditional PBO-controlled trial: increased sample size (440). Comparisons with existing drugs can be powered for superiority or non-inferiority, potentially requiring large numbers of patients depending on the hypothesis and the trial endpoints (184).

B.3.8 Managed access proposal

A managed access agreement (MAA) between NHS and Vertex is presently in existence. However, the current submission does not propose an MAA to enable future access to the CFTRms.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Base-case analysis inputs used in all three economic models, their corresponding measure of uncertainty (i.e., SE) and distribution are reported in Table 127.

Table 127. Base-case analysis inputs used in all three models

Variable	Value	SE	Distribution	Reference to section
Exponential PEx equation				
Parameter a – Age <18	8.59	1.72*	Normal	B.3.3.5
Parameter a – Age ≥18	3.79	0.76*	Normal	B.3.3.5
Lung transplant				
$ppFEV_1$ threshold for lung transplant	30	6*	Gamma	B.3.3.11
Prob of transplant	6.41%	1.28%*	Normal	B.3.3.11
Prob of death – Yr 1 post-transplant	14.20%	2.84%*	Beta	B.3.3.11
Prob of death – Yr 2+ post-transplant	5.40%	1.08%*	Beta	B.3.3.11
Annual non-PEx-related medical cost for patients receiving ECM alone				
Inpatient – Mild disease	£1,393	£279*	Gamma	B.3.5.2
Inpatient – Moderate disease	£8,415	£1,683*	Gamma	B.3.5.2
Inpatient – Severe disease	£21,928	£4,386*	Gamma	B.3.5.2
Outpatient – Mild disease	£4,826	£965*	Gamma	B.3.5.2
Outpatient – Moderate disease	£5,228	£1,046*	Gamma	B.3.5.2
Outpatient – Severe disease	£5,454	£1,091*	Gamma	B.3.5.2
Pharmacotherapy – Mild disease	£2,173	£435*	Gamma	B.3.5.2
Pharmacotherapy – Moderate disease	£10,780	£2,156*	Gamma	B.3.5.2
Pharmacotherapy – Severe disease	£11,582	£2,316*	Gamma	B.3.5.2
Other – Mild disease	£356	£71*	Gamma	B.3.5.2
Other – Moderate disease	£497	£99*	Gamma	B.3.5.2
Other – Severe disease	£921	£184*	Gamma	B.3.5.2
Annual non-PEx-related medical cost for patients receiving a CFTRm				
Inpatient – Mild disease	£418	£84*	Gamma	B.3.5.2
Inpatient – Moderate disease	£2,524	£505*	Gamma	B.3.5.2
Inpatient – Severe disease	£6,579	£1,316*	Gamma	B.3.5.2
Outpatient – Mild disease	£4,826	£965*	Gamma	B.3.5.2
Outpatient – Moderate disease	£5,228	£1,046*	Gamma	B.3.5.2
Outpatient – Severe disease	£5,454	£1,091*	Gamma	B.3.5.2
Pharmacotherapy – Mild disease	£652	£130*	Gamma	B.3.5.2
Pharmacotherapy – Moderate disease	£3,234	£647*	Gamma	B.3.5.2
Pharmacotherapy – Severe disease	£3,475	£695*	Gamma	B.3.5.2
Other – Mild disease	£356	£71*	Gamma	B.3.5.2
Other – Moderate disease	£497	£99*	Gamma	B.3.5.2
Other – Severe disease	£921	£184*	Gamma	B.3.5.2
Cost of a PEx episode for patients receiving ECM alone				
PEx – Mild disease	£7,813	£1,563*	Gamma	B.3.5.2
PEx – Moderate disease	£8,159	£1,632*	Gamma	B.3.5.2
PEx – Severe disease	£10,018	£2,004*	Gamma	B.3.5.2
Cost of a PEx episode for patients receiving a CFTRm				
PEx – Mild disease	£7,813	£1,563*	Gamma	B.3.5.2
PEx – Moderate disease	£8,159	£1,632*	Gamma	B.3.5.2
PEx – Severe disease	£10,018	£2,004*	Gamma	B.3.5.2
Lung transplantation costs				
Cost of lung transplantation	£91,778	£18,356*	Gamma	B.3.5.4
Post-transplant cost – Yr 1	£26,239	£5,248*	Gamma	B.3.5.4
Post-transplant cost – Yr 2	£16,469	£3,294*	Gamma	B.3.5.4
Post-transplant cost – Yr 3	£17,314	£3,463*	Gamma	B.3.5.4
Post-transplant cost – Yr 4-9	£10,400	£2,080*	Gamma	B.3.5.4
Post-transplant cost – Yr 10+	£5,787	£1,157*	Gamma	B.3.5.4
Other costs				
CFTRm monitoring cost – Yr 1	£387	£77*	Gamma	B.3.5.1
CFTRm monitoring cost – Yr 2+	£1.85	£0.37*	Gamma	B.3.5.1
Utility				
Utility strata – Mild disease	[redacted]	[redacted]	Beta	B.3.4.4
Utility strata – Moderate disease	[redacted]	[redacted]	Beta	B.3.4.4
Utility strata – Severe disease	[redacted]	[redacted]	Beta	B.3.4.4
PEx disutility	-0.07	0.02	Normal	B.3.4.4
Duration of PEx (days)	30	6*	Normal	B.3.4.4

*Standard error assumed to be 20% of mean.
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second; PSA, probabilistic sensitivity analysis; SE, standard error.

B.3.9.1.1 IVA/TEZ/ELX

Base-case analysis inputs used in the IVA/TEZ/ELX model, their corresponding measure of uncertainty (i.e., SE) and distribution are reported in Table 128.

Table 128. Base-case analysis inputs used in IVA/TEZ/ELX model

Variable	Value	SE	Distribution	Reference to section
Rate of $ppFEV_1$ decline in absence of CFTRm treatment				
Age 6-8 – F/F	-1.32	0.26*	Normal	B.3.3.4
Age 9-12 – F/F	-1.32	0.26*	Normal	B.3.3.4
Age 13-17 – F/F	-2.37	0.47*	Normal	B.3.3.4
Age 18-24 – F/F	-2.52	0.50*	Normal	B.3.3.4
Age ≥25 – F/F	-1.86	0.37*	Normal	B.3.3.4
Age 6-8 – F/MF	-1.32	0.26*	Normal	B.3.3.4
Age 9-12 – F/MF	-1.32	0.26*	Normal	B.3.3.4
Age 13-17 – F/MF	-2.37	0.47*	Normal	B.3.3.4
Age 18-24 – F/MF	-2.52	0.50*	Normal	B.3.3.4
Age ≥25 – F/MF	-1.86	0.37*	Normal	B.3.3.4
Age 6-8 – F/Gating	-1.32	0.26*	Normal	B.3.3.4
Age 9-12 – F/Gating	-1.32	0.26*	Normal	B.3.3.4
Age 13-17 – F/Gating	-2.37	0.47*	Normal	B.3.3.4
Age 18-24 – F/Gating	-2.52	0.50*	Normal	B.3.3.4
Age ≥25 – F/Gating	-1.86	0.37*	Normal	B.3.3.4
Age 6-8 – F/RF	-0.80	0.16*	Normal	B.3.3.4
Age 9-12 – F/RF	-0.80	0.16*	Normal	B.3.3.4
Age 13-17 – F/RF	-0.57	0.11*	Normal	B.3.3.4
Age 18-24 – F/RF	-1.85	0.37*	Normal	B.3.3.4
Age ≥25 – F/RF	-1.06	0.21*	Normal	B.3.3.4
Acute change in $ppFEV_1$ from baseline – Age ≥12				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
F/MF – IVA/TEZ/ELX (24 weeks)	14.30	0.79	Normal	B.3.3.3.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
F/Gating – IVA (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
Acute change in $ppFEV_1$ from baseline – Age 6-11				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
F/MF – IVA/TEZ/ELX (24 weeks)	11.00	2.09	Normal	B.3.3.3.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
F/Gating – IVA (48 weeks)	10.00	2.81	Normal	B.3.3.3.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.3.1
Reduction in rate of $ppFEV_1$ decline – Age ≥12				
F/F – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/MF – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/Gating – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/Gating – IVA	47.1%	0.11	Log-normal	B.3.3.4.1
F/RF – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
Reduction in rate of $ppFEV_1$ decline – Age 6-11				
F/F – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/MF – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/Gating – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
F/Gating – IVA	47.1%	0.11	Log-normal	B.3.3.4.1
F/RF – IVA/TEZ/ELX	100.0%	0.20*	Log-normal	B.3.3.4.1
Acute PEx rate ratio (calibrated) – Age ≥12				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/MF – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/Gating – IVA (48 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.1
Acute PEx rate ratio (calibrated) – Age 6-11				
F/F – IVA/TEZ/ELX (24 weeks)	1.00	Not included in PSA		B.3.3.5.1
F/MF – IVA/TEZ/ELX (24 weeks)	1.00	Not included in PSA		B.3.3.5.1
F/Gating – IVA/TEZ/ELX (8 weeks)	1.00	Not included in PSA		B.3.3.5.1
F/Gating – IVA (48 weeks)	1.00	Not included in PSA		B.3.3.5.1
F/RF – IVA/TEZ/ELX (8 weeks)	1.00	Not included in PSA		B.3.3.5.1
Long-term PEx rate ratio (calibrated) – Age ≥12				
F/F – IVA/TEZ/ELX	[redacted]	[redacted]	Log-normal	B.3.3.5.1

Variable	Value	SE	Distribution	Reference to section
F/MF – IVA/TEZ/ELX	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/Gating – IVA/TEZ/ELX	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/Gating – IVA	[redacted]	[redacted]	Log-normal	B.3.3.5.1
F/RF – IVA/TEZ/ELX	[redacted]	[redacted]	Log-normal	B.3.3.5.1
Long-term PEx rate ratio (calibrated) – Age 6-11				
F/F – IVA/TEZ/ELX	1.00	Not included in PSA		B.3.3.5.1
F/MF – IVA/TEZ/ELX	1.00	Not included in PSA		B.3.3.5.1
F/Gating – IVA/TEZ/ELX	1.00	Not included in PSA		B.3.3.5.1
F/Gating – IVA	1.00	Not included in PSA		B.3.3.5.1
F/RF – IVA/TEZ/ELX	1.00	Not included in PSA		B.3.3.5.1
Acute change from baseline in WFAZ – Age ≥12				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/MF – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/Gating – IVA (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
Acute change from baseline in WFAZ – Age 6-11				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/MF – IVA/TEZ/ELX (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/Gating – IVA (48 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.1
Acute discontinuation rate – Age ≥12				
F/F – IVA/TEZ/ELX (24 weeks)	0.025	Not included in PSA		B.3.3.9.1
F/MF – IVA/TEZ/ELX (24 weeks)	0.033	Not included in PSA		B.3.3.9.1
F/Gating – IVA/TEZ/ELX (8 weeks)	0.049	Not included in PSA		B.3.3.9.1
F/Gating – IVA (48 weeks)	0.081	Not included in PSA		B.3.3.9.1
F/RF – IVA/TEZ/ELX (8 weeks)	0.049	Not included in PSA		B.3.3.9.1
Acute discontinuation rate – Age 6-11				
F/F – IVA/TEZ/ELX (24 weeks)	0.067	Not included in PSA		B.3.3.9.1
F/MF – IVA/TEZ/ELX (24 weeks)	0.036	Not included in PSA		B.3.3.9.1
F/Gating – IVA/TEZ/ELX (24 weeks)	0.067	Not included in PSA		B.3.3.9.1
F/Gating – IVA (48 weeks)	0.000	Not included in PSA		B.3.3.9.1
F/RF – IVA/TEZ/ELX (24 weeks)	0.067	Not included in PSA		B.3.3.9.1
Post-acute discontinuation rate – Age ≥12				
F/F – IVA/TEZ/ELX (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.1
F/MF – IVA/TEZ/ELX (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.1
F/Gating – IVA/TEZ/ELX (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.1
F/Gating – IVA (96 weeks)	0.036	Not included in PSA		B.3.3.9.1
F/RF – IVA/TEZ/ELX (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.1
Post-acute discontinuation rate – Age 6-11				
F/F – IVA/TEZ/ELX (96 weeks)	0.026	Not included in PSA		B.3.3.9.1
F/MF – IVA/TEZ/ELX (96 weeks)	0.026	Not included in PSA		B.3.3.9.1
F/Gating – IVA/TEZ/ELX (96 weeks)	0.026	Not included in PSA		B.3.3.9.1
F/Gating – IVA (96 weeks)	0.043	Not included in PSA		B.3.3.9.1
F/RF – IVA/TEZ/ELX (96 weeks)	0.026	Not included in PSA		B.3.3.9.1
Acute (trial) compliance – Age ≥12				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/MF – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/Gating – IVA/TEZ/ELX (8 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/Gating – IVA (48 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/RF – IVA/TEZ/ELX (8 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
Acute (trial) compliance – Age 6-11				
F/F – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/MF – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/Gating – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/Gating – IVA (48 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
F/RF – IVA/TEZ/ELX (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.1
Post-acute (post-trial) compliance – Age ≥12				
F/F – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
F/MF – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
F/Gating – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
F/Gating – IVA	80.0%	Not included in PSA		B.3.3.10.1
F/RF – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
Post-acute (post-trial) compliance – Age 6-11				
F/F – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
F/MF – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
F/Gating – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1

Variable	Value	SE	Distribution	Reference to section
F/Gating – IVA	80.0%	Not included in PSA		B.3.3.10.1
F/RF – IVA/TEZ/ELX	80.0%	Not included in PSA		B.3.3.10.1
Utility				
Treatment-specific utility increment – IVA/TEZ/ELX	[redacted]	[redacted]	Normal	B.3.4.4
Caregiver treatment-specific utility increment – IVA/TEZ/ELX	[redacted]	[redacted]	Normal	B.3.4.4

*Standard error assumed to be 20% of mean.
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second; PSA, probabilistic sensitivity analysis; SE, standard error; WFAZ, weight-for-age z-score.

B.3.9.1.2 LUM/IVA

Base-case analysis inputs used in the LUM/IVA model, their corresponding measure of uncertainty (i.e., SE) and distribution are reported in Table 129.

Table 129. Base-case analysis inputs used in LUM/IVA model

Variable	Value	SE	Distribution	Reference to section
Rate of $ppFEV_1$ decline in absence of LUM/IVA treatment				
Age 6-8	-1.32	0.26*	Normal	B.3.3.4
Age 9-12	-1.32	0.26*	Normal	B.3.3.4
Age 13-17	-2.37	0.47*	Normal	B.3.3.4
Age 18-24	-2.52	0.50*	Normal	B.3.3.4
Age ≥25	-1.86	0.37*	Normal	B.3.3.4
Acute change in $ppFEV_1$ from baseline – LUM/IVA				
Age ≥12 (24 weeks)	2.80	0.51	Normal	B.3.3.3.2
Age 6-11 (24 weeks)	2.40	1.02	Normal	B.3.3.3.2
Age 2-5 – Applied at age 6	2.40	1.02	Normal	B.3.3.3.2
Reduction in rate of $ppFEV_1$ decline – LUM/IVA				
Age ≥12	42.0%	0.11	Log-normal	B.3.3.4.2
Age 6-11	42.0%	0.11	Log-normal	B.3.3.4.2
Age 2-5 – After age 6	42.0%	0.11	Log-normal	B.3.3.4.2
Age 2-5 – Decline avoided before 6	42.0%	0.11	Log-normal	B.3.3.4.2
PEx rate ratio (calibrated) – LUM/IVA				
Acute – Age ≥12 (24 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.2
Acute – Age 6-11 (24 weeks)	1.00	Not included in PSA		B.3.3.5.2
Post-acute – Age ≥12	[redacted]	[redacted]	Log-normal	B.3.3.5.2
Post-acute – Age 6-11	1.00	Not included in PSA		B.3.3.5.2
Acute change from baseline in WFAZ – LUM/IVA				
Age ≥12 (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.2
Age 6-11 (24 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.2
Age 2-5 – Applied at age 6	0.260	0.060	Normal	B.3.3.6.2
Discontinuation rate – LUM/IVA				
Acute – Age ≥12 (24 weeks)	0.152	Not included in PSA		B.3.3.9.2
Acute – Age 6-11 (24 weeks)	0.130	Not included in PSA		B.3.3.9.2
Acute – Age 2-5 (24 weeks)	0.149	Not included in PSA		B.3.3.9.2
Post-acute – Age ≥12 (72 weeks)	0.140	Not included in PSA		B.3.3.9.2
Post-acute – Age 6-11 (96 weeks)	0.047	Not included in PSA		B.3.3.9.2
Post-acute – Age 2-5 (96 weeks)	0.104	Not included in PSA		B.3.3.9.2
Compliance – LUM/IVA				
Acute – Age ≥12 (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.2
Acute – Age 6-11 (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.2
Acute – Age 2-5 (24 weeks)	[redacted]	Not included in PSA		B.3.3.10.2
Post-acute – Age ≥12	80.0%	Not included in PSA		B.3.3.10.2
Post-acute – Age 6-11	80.0%	Not included in PSA		B.3.3.10.2
Post-acute – Age 2-5	80.0%	Not included in PSA		B.3.3.10.2

*Standard error assumed to be 20% of mean.
Abbreviations: LUM/IVA, lumacaftor/ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; PSA, probabilistic sensitivity analysis; SE, standard error; WFAZ, weight-for-age z-score.

B.3.9.1.3 TEZ/IVA

Base-case analysis inputs used in the TEZ/IVA model, their corresponding measure of uncertainty (i.e., SE) and distribution are reported in Table 130.

Table 130. Base-case analysis inputs used in TEZ/IVA model

Variable	Value	SE	Distribution	Reference to section
Rate of $ppFEV_1$ decline in absence of TEZ/IVA treatment				
Age 6-8 – F/F	-1.32	0.26*	Normal	B.3.3.4
Age 9-12 – F/F	-1.32	0.26*	Normal	B.3.3.4
Age 13-17 – F/F	-2.37	0.47*	Normal	B.3.3.4
Age 18-24 – F/F	-2.52	0.50*	Normal	B.3.3.4
Age ≥25 – F/F	-1.86	0.37*	Normal	B.3.3.4
Age 6-8 – F/RF	-0.80	0.16*	Normal	B.3.3.4
Age 9-12 – F/RF	-0.80	0.16*	Normal	B.3.3.4
Age 13-17 – F/RF	-0.57	0.11*	Normal	B.3.3.4
Age 18-24 – F/RF	-1.85	0.37*	Normal	B.3.3.4
Age ≥25 – F/RF	-1.06	0.21*	Normal	B.3.3.4
Acute change in $ppFEV_1$ from baseline – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	4.00	0.43	Normal	B.3.3.3.3
Age ≥12 – F/RF (8 weeks)	6.80	0.54	Normal	B.3.3.3.3
Age 6-11 – F/F (8 weeks)	2.80	0.92	Normal	B.3.3.3.3
Age 6-11 – F/RF (8 weeks)	2.80	0.92	Normal	B.3.3.3.3
Reduction in rate of $ppFEV_1$ decline – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	61.5%	0.13	Log-normal	B.3.3.4.3
Age ≥12 – F/RF (8 weeks)	61.5%	0.13	Log-normal	B.3.3.4.3
Age 6-11 – F/F (8 weeks)	61.5%	0.13	Log-normal	B.3.3.4.3
Age 6-11 – F/RF (8 weeks)	61.5%	0.13	Log-normal	B.3.3.4.3
Acute PEx rate ratio (calibrated) – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.3
Age ≥12 – F/RF (8 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.3
Age 6-11 – F/F (8 weeks)	1.00	Not included in PSA		B.3.3.5.3
Age 6-11 – F/RF (8 weeks)	1.00	Not included in PSA		B.3.3.5.3
Long-term PEx rate ratio (calibrated) – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.3
Age ≥12 – F/RF (8 weeks)	[redacted]	[redacted]	Log-normal	B.3.3.5.3
Age 6-11 – F/F (8 weeks)	1.00	Not included in PSA		B.3.3.5.3
Age 6-11 – F/RF (8 weeks)	1.00	Not included in PSA		B.3.3.5.3
Acute change from baseline in WFAZ – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	0.00	0.02	Normal	B.3.3.6.3
Age ≥12 – F/RF (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.3
Age 6-11 – F/F (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.3
Age 6-11 – F/RF (8 weeks)	[redacted]	[redacted]	Normal	B.3.3.6.3
Acute discontinuation rate – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	0.143	Not included in PSA		B.3.3.9.3
Age ≥12 – F/RF (8 weeks)	0.081	Not included in PSA		B.3.3.9.3
Age 6-11 – F/F (8 weeks)	0.121	Not included in PSA		B.3.3.9.3
Age 6-11 – F/RF (8 weeks)	0.121	Not included in PSA		B.3.3.9.3
Post-acute discontinuation rate – TEZ/IVA				
Age ≥12 – F/F (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.3
Age ≥12 – F/RF (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.3
Age 6-11 – F/F (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.3
Age 6-11 – F/RF (96 weeks)	[redacted]	Not included in PSA		B.3.3.9.3
Acute (trial) compliance – TEZ/IVA				
Age ≥12 – F/F (24 weeks)	[redacted]	Not included in PSA		B.3.3.10
Age ≥12 – F/RF (8 weeks)	[redacted]	Not included in PSA		B.3.3.10
Age 6-11 – F/F (8 weeks)	[redacted]	Not included in PSA		B.3.3.10
Age 6-11 – F/RF (8 weeks)	[redacted]	Not included in PSA		B.3.3.10
Post-acute (post-trial) compliance – TEZ/IVA				
Age ≥12 – F/F	80.0%	Not included in PSA		B.3.3.10
Age ≥12 – F/RF	80.0%	Not included in PSA		B.3.3.10
Age 6-11 – F/F	80.0%	Not included in PSA		B.3.3.10
Age 6-11 – F/RF	80.0%	Not included in PSA		B.3.3.10
Utility				
Treatment-specific utility increment – TEZ/IVA – F/RF	[redacted]	[redacted]	Normal	B.3.4.4

Variable	Value	SE	Distribution	Reference to section
*Standard error assumed to be 20% of mean. Abbreviations: PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; PSA, probabilistic sensitivity analysis; SE, standard error; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor; WFAZ, weight-for-age z-score.				

B.3.9.2 Assumptions

Assumptions related to all three economic models and the corresponding justifications are summarised in Table 131 below.

Table 131. Assumptions applied to all three models

Parameter	Assumption	Justification	Section
Diabetes	The risk of developing CFRD is assumed to be equal for patients receiving a CFTRm and those receiving ECM alone.	This is a conservative assumption, given that LUM/IVA and IVA long-term safety studies have demonstrated that CFTRm therapies were associated with a reduction in the diabetes incidence (338, 339).	B.3.3.2
Long-term $ppFEV_1$	Long-term reduction in the annual rate of $ppFEV_1$ decline for patients on a CFTRm aged 6-11 years is consistent with the estimates used in CFTRm-treated patients aged ≥12 years.	In a recent advisory board, consulted health economists agreed that, in the absence of age-specific long-term $ppFEV_1$ treatment effect, the use of data from the registry-matched analyses conducted in patients aged ≥12 years was the most appropriate source (347). This is a conservative assumption, given that clinical data from the CFTRm trials conducted in patients aged 6-11 years have demonstrated clinical benefits in LCI, a disease marker predictive of future $ppFEV_1$ trajectory (444, 445). Data for IVA/TEZ/ELX from the OLE study 445-107 in patients aged 6-11 years indicated a sustained treatment effect on $ppFEV_1$ over longer-term use, since the improvements in $ppFEV_1$ observed over 24 weeks of treatment in the parent study 445-106 were sustained over 96 additional weeks of treatment (201).	B.3.3.4
PEx	PEx rate ratios are applied for CFTRms over the model time horizon.	The results from OLE studies of CFTRms conducted in patients aged ≥12 years demonstrated that the annualised rates of PEx observed in the shorter-term clinical trials were sustained over longer durations of treatment in the OLE studies (155, 222, 236, 353). In addition, the assumption of long-term PEx benefit is supported by real-world data, [redacted]	B.3.3.5

Parameter	Assumption	Justification	Section
	For patients aged 6-11 years receiving CFTRms, no treatment effect is assumed on PEx requiring IV antibiotics and/or hospitalisation.	Assuming no PEx effect during ages 6-11 is a conservative assumption; the treatment effect in younger patients is likely consistent with that observed in adolescents and adults, but events occur with less frequency in younger patients and thus a statistically significant treatment effect is harder to detect within a clinical trial. The LUM/IVA and IVA pivotal trials in this age group were not powered to detect a difference in PEx rates (159, 333), while the IVA/TEZ/ELX and TEZ/IVA trials did not collect PEx as an efficacy endpoint (165, 204). [redacted]	B.3.3.5
Mortality	While the CPH model has not been updated since its publication(64), Liou et al. presented an updated validation of the logistic regression that was originally published alongside the CPH model in 2001 (232, 377).	The presence of *F508del* alleles was not found to be a significant predictor of mortality (64), indicating that the effect of the genotype on mortality is mediated through the phenotypic characteristics that were identified as significant predictors in the analysis.	B.3.3.7
	Survival estimates are derived by applying a CPH model published in 2001 (64) to the 2008 UK CF Registry data (372).	The factors identified by Liou et al. to predict survival have since been demonstrated to have remained stable from 1993 to 2010 (232, 377).	B.3.3.7
Treatment discontinuation	No discontinuation of CFTRms is assumed after the post-acute period.	There is no evidence for the long-term discontinuation of CFTRms.	B.3.3.9
Compliance after acute period	Following the initial trial period, a compliance rate of 80% was applied to all CFTRm therapies and age groups (≥2 years) to reflect treatment compliance expected in a real-world setting, informed by a US retrospective cohort study for IVA (387).	The study was selected as it is the only available data source that analysed both the efficacy and the impact of IVA on health resource utilisation, amongst the CFTRm studies. The post-acute compliance rate of 80% is further supported by a real-world multi-site study in the UK and Ireland using MEMS® (388), and a US study using retail pharmacy claims for CFTRms (389).	B.3.3.10
Lung transplantation	Once a patient's $ppFEV_1$ drops below 30 percentage points, the patient becomes eligible to receive a lung transplant.	The UK clinical guideline for transplantation suggests referral for a lung transplantation for patients with $ppFEV_1$ <30% (391, 392). This threshold was accepted by NICE, as shown in a health technology assessment for IVA in the treatment of pwCF and the *G551D* mutation (128).	B.3.3.11
Health state utilities	The CFQ-R-8D preference-based scoring algorithm was used to calculate health state utilities stratified by $ppFEV_1$ from the CFQ-R data collected in IA1 of the TRAJECTORY study (407).	The NICE reference case requires utility values used in economic analyses are generated using the EQ-5D (396). However, evidence from Vertex's clinical trials suggests that generic preference-based measures, such as EQ-5D, are insensitive to meaningful differences in lung function and HRQoL in pwCF (397-399). In these cases, NICE states that alternative preference-based measures (such as condition-specific preference-based measures) can be considered if it can be demonstrated that EQ-5D data are inappropriate (10).	B.3.4.1

Parameter	Assumption	Justification	Section
PEx disutility	A disutility for the occurrence of a PEx requiring treatment with IV antibiotics and/or hospitalisation is applied to both simulated patients receiving a CFTRm and those receiving ECM alone.	The pivotal studies for IVA/TEZ/ELX and TEZ/IVA did not include measures of utility (e.g., EQ-5D or SF-6D). Therefore, the models of IVA/TEZ/ELX and TEZ/IVA apply the disutility and duration of PEx derived from STRIVE (399). For consistency, the LUM/IVA model applies the same disutility value.	B.3.4.4
Costs	Data from UK real-world study of IVA demonstrating resource utilisation and cost reduction (inpatient and pharmacotherapy costs) has been used as a proxy for the likely cost reductions associated with CFTRm use in the UK (428).	Long-term data on the healthcare resource use associated with CFTRms other than IVA are not yet available, therefore IVA has been used as a proxy.	B.3.5.2
	It is assumed that costs associated with a PEx are the same for a patient treated with ECM alone and a patient treated with a CFTRm.	Several real-world studies conducted in the UK have demonstrated the positive impact of CFTRms on hospitalisation rates due to PEx (327, 338, 428, 437). However, the models conservatively assume the cost of a PEx episode to be the same for CFTRms and ECM alone to preclude overestimation of the treatment effect on PEx, given the reduction in the PEx event rate is explicitly tracked in the models.	B.3.5.2

Abbreviations: CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFRD, cystic fibrosis-related diabetes; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CPH, Cox proportional hazards; DCA, Data Collection Agreement; ECM, established clinical management; IA, interim analysis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; IV, intravenous; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; LCI, lung clearance index; LoE, loss of exclusivity; LUM/IVA, lumacaftor/ivacaftor; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor; UK, United Kingdom; US, United States.

B.3.9.2.1 IVA/TEZ/ELX

Assumptions exclusively related to the IVA/TEZ/ELX model and their justifications are summarised in Table 132.

Table 132. Assumptions applied to IVA/TEZ/ELX model

Parameter	Assumption	Justification	Section
Genotype prevalence	Patients with CF who are heterozygous for *F508del-CFTR* with a second allele that is unknown and/or has not yet been characterised as MF, RF, or gating are captured in the prevalence estimate for F/MF.	It is expected that any CF patient with at least one *F508del-CFTR* mutation would experience a similar or greater treatment benefit based on the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele, regardless of the mutation on the second allele	B.3.2.1.1

Parameter	Assumption	Justification	Section
Acute $ppFEV_1$	In the absence of IVA/TEX/ELX data in the populations with F/Gating and F/RF genotypes aged 6-11 years, treatment effect on $ppFEV_1$ in the acute phase is extrapolated from study 445-104, an IVA/TEZ/ELX trial that included patients with F/Gating and F/RF genotypes aged ≥12 years (168).	The safety and efficacy of IVA/TEZ/ELX in CF patients aged 6-11 years with F/F or F/MF genotypes observed in study 445-106 (174) were consistent with those reported for patients aged ≥12 years with the same genotypes in 445-102 and 445-103. Therefore, the clinical efficacy of IVA/TEZ/ELX in patients aged ≥12 years with F/Gating and F/RF genotypes were used to generate estimates of efficacy in patients aged 6-11 years with the same genotypes, by assuming the relative relationship observed in F/F and F/MF is applicable across other genotypes. Paediatric patients generally have slower lung disease progression than adolescents or adults, and therefore have higher mean baseline $ppFEV_1$ and may experience a smaller mean change from baseline upon IVA/TEZ/ELX treatment.	B.3.3.3.1
Long-term $ppFEV_1$	In the absence of data for the populations with F/Gating and F/MF genotypes, the rates of $ppFEV_1$ decline reported for patients with F/F genotype in the Sawicki et al. study are applied (348).	Assumption is supported by similarities in the burden of disease and disease progression seen among patients with F/F and other *F508*del-containing genotypes, such as F/Gating (337) and F/MF (349).	B.3.3.4
	A 100% reduction in the rate of $ppFEV_1$ decline for patients treated with IVA/TEZ/ELX relative to ECM alone across all genotypes is applied after the initial period.	In line with the study 445-105 IA4 OLE data that suggest no loss of pulmonary function on average in patients treated with IVA/TEZ/ELX during longer-term treatment , and the IA3 registry-matched rate of change analysis which demonstrates a >100% reduction in the $ppFEV_1$ decline rate relative to untreated matched controls (352). [redacted]	B.3.3.4.1
PEx	All patients treated with IVA/TEZ/ELX aged ≥12 years are assumed to experience the PEx treatment effect demonstrated in patients with F/MF genotype from study 445-102 (7).	Study 445-102 was designed to demonstrate the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele (7). It is expected that any patient with CF with ≥1 *F508del-CFTR* mutation would experience a similar treatment benefit as that observed in study 445-102, based on the effect of IVA/TEZ/ELX on a single *F508del-CFTR* allele, regardless of the mutation on the second allele and whether it produces any protein.	B.3.3.5.1

Parameter	Assumption	Justification	Section
WFAZ	In the absence of IVA/TEX/ELX data in the populations with F/Gating and F/RF genotypes aged 6-11 years, treatment effect on WFAZ is extrapolated from study 445-104, an IVA/TEZ/ELX trial that included patients with F/Gating and F/RF genotypes aged ≥12 years (168).	The safety and efficacy of IVA/TEZ/ELX in patients aged 6-11 years with F/F or F/MF genotypes in study 445-106 (174) were comparable to those reported for patients aged ≥12 years with the same genotypes. Therefore, the clinical efficacy of IVA/TEZ/ELX in patients aged ≥12 years with F/Gating and F/RF genotypes were used to generate estimates of efficacy in patients aged 6-11 years with F/Gating and F/RF genotypes, respectively, by assuming the relative relationship observed in F/F and F/MF is applicable across genotypes.	B.3.3.6.1
Adverse events	The AE rates observed in the PBO arm of study 445-102 (7) in patients with F/MF genotype aged ≥12 years were applied to all patients across all genotypes aged ≥12 years receiving ECM alone.	This is a simplifying assumption.	B.3.3.8.1
	For patients initiating treatment at age 6-11, the AE rates observed in the PBO arm of the LUM/IVA pivotal trial in patients with F/F genotype aged 6-11 years, study 809-109 (159), were applied to all patients across all genotypes aged 6-11 years receiving ECM alone.	The PBO data from study 809-109 were selected over the ENVISION study for IVA (333) and study 445-116 for IVA/TEZ/ELX (175), which also included a PBO arm, due to the larger sample size (N=101 vs N=26 and N=61, respectively).	B.3.3.8.1
Treatment discontinuation	The acute discontinuation rate observed in patients with F/F genotype aged 6-11 years from study 445-106 (174) is assumed to be applicable to the populations with F/Gating and F/RF genotypes of the same age group.	In the absence of acute and post-acute discontinuation data for patients with F/Gating and F/RF genotypes aged 6-11 years treated with IVA/TEZ/ELX, this is considered a reasonable assumption.	B.3.3.9.1
	The post-acute discontinuation rate observed in patients with F/F and F/MF genotypes aged 6-11 years from OLE study 445-107 (202) is assumed to be applicable to the populations with F/Gating and F/RF genotypes of the same age group.		
Compliance over acute period	The IVA/TEZ/ELX pill count data from study 445-106 (174) in the combined population with F/F and F/MF genotypes aged 6-11 years is applied to patients with F/Gating and F/RF genotypes of the same age group.	In the absence of clinical trial data for IVA/TEZ/ELX in patients aged 6-11 years in the populations with F/Gating and F/RF genotypes, this is considered a reasonable assumption.	B.3.3.10.1

Parameter	Assumption	Justification	Section
Utility benefit of treatment	The economic model assumes that a patient treated with IVA/TEZ/ELX will have a utility score that is [redacted] units higher than that of a patient with the same $ppFEV_1$ value who is receiving ECM alone.	[redacted]	B.3.4.4
Caregiver utility	Patients who initiate IVA/TEZ/ELX treatment during ages 6-11 years are assumed to receive a [redacted]	Multiple studies have shown that caregiving for people with CF has a substantial impact on caregiver QoL, particularly for caregivers of paediatric patients and during PEx episodes (140, 248, 395). Recent studies [redacted] (408, 426).	B.3.4.4

Abbreviations: AE, adverse event; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; IA, interim analysis; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/ elexacaftor; MF, minimal function; MMRM, mixed-effect repeated measures; LUM/IVA, lumacaftor/ivacaftor; OLE, open-label extension; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; RF, residual function; WFAZ, weight-for-age z-score.

B.3.9.2.2 LUM/IVA

Assumptions exclusively related to the LUM/IVA model and their justification are summarised in Table 133.

Table 133. Assumptions applied to LUM/IVA model

Parameter	Assumption	Justification	Section
Baseline population	Baseline patient profiles for patients aged 2-5 years were derived by sampling patient-level baseline data (i.e., gender, $ppFEV_1$ and WFAZ) from the age 6-11 years clinical trial patient profiles and randomly assigning an integer baseline age of either 2, 3, 4, or 5 years.	$ppFEV_1$ is not available for patients aged 2-5 years, since it is not a reliable clinical measure in young children (331). The assigned $ppFEV_1$ is the lung function expected in the absence of a CFTRm when a patient turns age 6 in the model (the age at which the model starts tracking $ppFEV_1$).	B.3.3.1.1.1
Diabetes	Patients during age 2-5 are assumed to not be at risk of developing CFRD.	Incidence of diabetes is not considered before the age of 6 in the model. This is a simplifying assumption.	B.3.3.2
Acute $ppFEV_1$	Patients initiating LUM/IVA at age 2-5 are assumed to experience an acute increase in $ppFEV_1$ immediately upon turning age 6.	Age 6 is the point at which tracking of $ppFEV_1$ begins. The acute increase in $ppFEV_1$ of 2.4 percentage points upon turning age 6 is based on the statistically significant PBO-controlled results observed in patients aged 6-11 years in study 809-109 (159).	B.3.3.3.2

Parameter	Assumption	Justification	Section
Long-term ppFEV$_1$	Patients treated with LUM/IVA during age 2-5 are assumed to have avoided a proportion of lung function decline before age 6.	The proportion of lung function decline avoided during ages 2-5 for patients treated with LUM/IVA, relative to ECM alone, is assumed to be 42%, based on the LUM/IVA registry-matched analysis conducted in patients aged ≥12 years (155). The rate of ppFEV$_1$ decline in the absence of CFTRm treatment of 1.32 during age 6-8 derived from a retrospective cohort study of patients with F/F genotype in the US CFFPR from 2006 to 2014 (348) is assumed to be a proxy for the average decline experienced during age 2-5.	B.3.3.4.2
PEx	PEx are not estimated for patients aged 2-5 years.	This is a simplifying assumption, given PEx events are relatively infrequent in this age group.	B.3.3.5.2
Mortality	For patients aged 2-5 years 100% survival is assumed.	The key parameter needed to estimate survival, ppFEV$_1$, is not tracked in the model until the age of 6. Assuming 100% survival for patients aged 2-5 years is reasonable, as the UK mortality rate for this age group is negligible (372).	B.3.3.7
Lung transplantation	No lung transplantations occur for patients aged 2-5 years.	The model assumes that patients become eligible to receive a lung transplant once their ppFEV$_1$ drops below 30. No lung transplantation occurring for patients during age 2-5 is a simplifying assumption, given expected incidence is very low in this age group and because ppFEV$_1$ is not tracked in this age group.	B.3.3.11
Utilities	For patients aged 2-5 years, the utility value is assumed based on the ppFEV$_1$ expected upon turning age 6.	Utility values are stratified by ppFEV$_1$, and age 6 is the point at which tracking of ppFEV$_1$ begins.	B.3.4.4
Abbreviations: CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFRD, cystic fibrosis-related diabetes; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; LUM/IVA, lumacaftor/ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in one second; WFAZ, weight-for-age z-score.			

B.3.9.2.3 TEZ/IVA

Assumptions exclusively related to the TEZ/IVA model and their justification are summarised in Table 134.

Table 134. Assumptions applied to TEZ/IVA model

Parameter	Assumption	Justification	Section
Acute ppFEV$_1$	Patients with F/F and F/RF genotypes initiating TEZ/IVA treatment at age 6-11 are assumed to experience an acute increase in ppFEV$_1$ based on the mean within-group change from baseline for the TEZ/IVA arm of EMBRACE (326).	Given the small numbers of patients randomised to the control group (N = 10 PBO for F/F, N = 3 IVA for F/RF) of EMBRACE (326), the study was neither designed nor powered for between-group comparisons. Expert opinion was that the most appropriate model input for acute increase in ppFEV$_1$ is the mean within-group change observed across F/F and F/RF genotypes of EMBRACE, as it is consistent with the protocol-specified analysis and the interpretation of the genotype-specific comparator-controlled analyses would be limited due to the small sample size (347).	B.3.3.3.3

Parameter	Assumption	Justification	Section
Long-term ppFEV$_1$	Patients with F/RF genotype aged ≥12 treated with TEZ/IVA are assumed to experience a reduction in the ppFEV$_1$ decline rate relative to ECM alone based on the treatment effect observed in patients with F/F treated with TEZ/IVA compared with untreated patients with F/F in the US CFFPR (163).	Analysis assessing the reduction in the rate of ppFEV$_1$ decline for patients with F/RF genotype treated with TEZ/IVA relative to untreated controls was not feasible due to the limited number of untreated patients with F/RF genotype in the US CFFPR, which did not allow for robust propensity score matched analysis with sufficient power (163). Therefore, the results from the TEZ/IVA 12+ registry-matched analysis conducted in the population with F/F genotype was deemed the best available proxy.	B.3.3.4.3
Utility benefit of treatment	The economic model assumes that a patient with F/RF genotype treated with TEZ/IVA will have a utility score that is [redacted] units higher than that of a patient with the same ppFEV$_1$ value who is receiving ECM alone.	[redacted]	B.3.4.4
Abbreviations: CFFPR, Cystic Fibrosis Foundation Patient Registry; CFQ-R, Cystic Fibrosis Questionnaire-Revised; ECM, established clinical management; MMRM, mixed-effect repeated measures; ppFEV$_1$, percent predicted forced expiratory volume in one second; SE, standard error; TEZ/IVA, tezacaftor/ivacaftor.			

B.3.10 Base-case results

B.3.10.1 IVA/TEZ/ELX

Using base-case inputs and assumptions, the IVA/TEZ/ELX economic model projects that pwCF with at least one *F508del* allele treated with IVA/TEZ/ELX will experience a substantial survival gain of more than two decades ([redacted] LYs undiscounted) and HRQoL benefits ([redacted] additional undiscounted QALYs) compared to the SoC (Table 135). The substantial increases in both LYs and QALYs associated with IVA/TEZ/ELX are driven by the projected unprecedented benefits in expected median survival. Median predicted survival in IVA/TEZ/ELX-treated patients was estimated to be [redacted] years, a [redacted]-year increase compared with the median predicted survival for patients treated with SoC ([redacted] years) (Table 135). A comparison of the treatment-specific projected survival curves for pwCF with at least one *F508del* allele by genotype is shown in the figures below. In addition, the model predicted that pwCF receiving IVA/TEZ/ELX spent more time in higher lung function categories compared to those receiving SoC – [redacted] of residual LYs of patients treated with IVA/TEZ/ELX are spent with mild disease (i.e., ppFEV$_1$ ≥70% to <90%) vs only [redacted] for patients treated with SoC alone (Table 135).

Table 135. Deterministic base-case clinical outcomes from IVA/TEZ/ELX model

Treatment	Median survival (years)	LYs (undisc.)	QALYs (undisc.)	Proportion of undisc. LYs spent with $ppFEV_1$		
				≥70% to <90%	≥40% to <70%	<40%
Patients with at least one *F508del* allele (Weighted results)						
IVA/TEZ/ELX						
SoC						
IVA/TEZ/ELX vs SoC						
Population with F/F genotype (Genotype prevalence: 54.28%)						
IVA/TEZ/ELX						
ECM						
IVA/TEZ/ELX vs ECM						
Population with F/MF genotype (Genotype prevalence: 28.96%)						
IVA/TEZ/ELX						
ECM						
IVA/TEZ/ELX vs ECM						
Population with F/Gating genotype (Genotype prevalence: 10.57%)*						
IVA/TEZ/ELX						
IVA						
ECM						
IVA/TEZ/ELX vs IVA						
IVA/TEZ/ELX vs ECM						
Population with F/RF genotype (Genotype prevalence: 6.19%)						
IVA/TEZ/ELX						
ECM						
IVA/TEZ/ELX vs ECM						

Notes: *Market shares of comparators in F/Gating population: [redacted] IVA and [redacted] ECM.
Abbreviations: ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/ elexacaftor and ivacaftor; LYs, life years; $ppFEV_1$, percent predicted forced expiratory volume in one second; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 91. Predicted survival of cohorts of pwCF with F/F genotype eligible for IVA/TEZ/ELX treatment

Abbreviations: ECM, established clinical management; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; pwCF, people with cystic fibrosis.

Figure 92. Predicted survival of cohorts of pwCF with F/MF genotype eligible for IVA/TEZ/ELX treatment

Abbreviations: ECM, established clinical management; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; pwCF, people with cystic fibrosis.

Figure 93. Predicted survival of cohorts of pwCF with F/Gating genotype eligible for IVA/TEZ/ELX treatment

Abbreviations: ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; pwCF, people with cystic fibrosis.

Figure 94. Predicted survival of cohorts of pwCF with F/RF genotype eligible for IVA/TEZ/ELX treatment

Abbreviations: ECM, established clinical management; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; pwCF, people with cystic fibrosis.

Furthermore, the clinical outcomes and disaggregated results show reductions in disease management costs and use of healthcare resources including hospitalisations and lung transplants with IVA/TEZ/ELX treatment in the deterministic base-case analysis (see Appendix J).

The probabilistic base-case incremental cost-effectiveness results for IVA/TEZ/ELX treatment vs current SoC, which were calculated based on genotype prevalence and comparator market shares, are presented in Table 136. The IVA/TEZ/ELX economic model projects that patients with at least one *F508del* allele treated with IVA/TEZ/ELX will experience a health benefit of [redacted] LYs (discounted) and [redacted] QALYs (with severity weight of 1.7, discounted) compared to the SoC, with the incremental total costs being [redacted]. The resulting ICER was £109,280 per QALY gained, while the net health benefit (NHB) at the willingness to pay threshold (WTP) of £20,000 and £30,000 was [redacted] and [redacted], respectively.

Table 136. Probabilistic base-case incremental results from IVA/TEZ/ELX model

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients with at least one *F508del* allele (Weighted results)						
IVA/TEZ/ELX vs SoC	[redacted]	[redacted]	[redacted]	£109,280	[redacted]	[redacted]
Population with F/F genotype (Genotype prevalence: 54.28%)						

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£110,795	[redacted]	[redacted]
Population with F/MF genotype (Genotype prevalence: 28.96%)						
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£111,798	[redacted]	[redacted]
Population with F/Gating genotype (Genotype prevalence: 10.57%)**						
IVA/TEZ/ELX vs IVA	[redacted]	[redacted]	[redacted]	£50,938	[redacted]	[redacted]
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£112,352	[redacted]	[redacted]
Population with F/RF (Genotype prevalence: [redacted])						
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£143,182	[redacted]	[redacted]

Notes: *Severity weight of 1.7 applied;
** Market shares of comparators in F/Gating population: [redacted] IVA and [redacted] ECM.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

B.3.10.2 LUM/IVA

Using base-case inputs and assumptions, the LUM/IVA economic model projects that patients with F/F genotype treated with LUM/IVA will experience a substantial survival gain of [redacted] LYs (undiscounted) and HRQoL benefits ([redacted] additional undiscounted QALYs) compared to ECM (Table 137). The substantial increases in LYs and QALYs associated with LUM/IVA are driven by the projected benefits in expected median survival. Median predicted survival in the indicated population of LUM/IVA-treated patients was [redacted] years, a [redacted]-year increase compared with the median predicted survival of patients treated with ECM alone ([redacted] years) (Table 137). A comparison of the treatment-specific projected survival curves for patients aged ≥2 years with F/F genotype is presented in Figure 95. In addition, the model predicted that patients with F/F genotype receiving LUM/IVA spent more time in higher lung function categories compared to those receiving ECM – [redacted] of residual LYs for patients treated with LUM/IVA are spent with mild disease (i.e., $ppFEV_1$ ≥70% to <90%) vs [redacted] for patients treated with ECM alone (Table 137).

Table 137. Deterministic base-case clinical outcomes from LUM/IVA model

Treatment	Median survival (years)	LYs (undisc.)	QALYs (undisc.)	Proportion of undisc. LYs spent with $ppFEV_1$		
				≥70% to <90%	≥40% to <70%	<40%
Patients homozygous for *F508del* mutation						
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA vs ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; LUM/IVA, lumacaftor/ivacaftor; LYs, life years; $ppFEV_1$, percent predicted forced expiratory volume in one second; QALYs, quality-adjusted life years.

Figure 95. Predicted survival of cohorts of pwCF eligible for LUM/IVA treatment

Abbreviations: ECM, established clinical management; LUM/IVA, lumacaftor/ivacaftor; pwCF, people with cystic fibrosis.

Furthermore, the clinical outcomes and disaggregated results show reductions in disease management costs and use of healthcare resources including hospitalisations and lung transplants with LUM/IVA treatment in the deterministic base-case analysis (see Appendix J).

The probabilistic base-case incremental cost-effectiveness results for treatment with LUM/IVA vs ECM are presented in Table 138. The LUM/IVA economic model projects that patients with F/F genotype treated with LUM/IVA will experience a health benefit of [redacted] LYs (discounted) and [redacted] QALYs (with severity weight of 1.7, discounted) compared to ECM, with the incremental total costs being [redacted]. The resulting ICER was £144,411 per QALY gained, while the NHB at the WTP of £20,000 and £30,000 was [redacted] and [redacted], respectively.

Table 138. Probabilistic base-case incremental results from LUM/IVA model

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients homozygous for *F508del* mutation						
LUM/IVA vs ECM	[redacted]	[redacted]	[redacted]	£144,411	[redacted]	[redacted]

Note: *Severity weight of 1.7 applied.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.3.10.3 TEZ/IVA

Using base-case inputs and assumptions, the TEZ/IVA economic model projects that pwCF homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a RF mutation treated with TEZ/IVA will experience a substantial survival gain of [redacted] LYs (undiscounted) and HRQoL benefits ([redacted] additional undiscounted QALYs) compared to ECM (Table 139). The substantial increases in LYs and QALYs associated with TEZ/IVA are driven by the projected benefits in expected median survival. Median predicted survival in the indicated population of TEZ/IVA-treated patients was [redacted] years, a [redacted]-year increase vs the median predicted survival for patients treated with ECM alone ([redacted] years) (Table 139). Comparisons of the treatment-specific projected survival curves for pwCF with F/F and F/RF genotypes are presented in Figure 96 and Figure 97, respectively. The model also predicted that patients receiving TEZ/IVA spent more time in higher lung function categories compared to those receiving ECM – [redacted]% of residual LYs for patients treated with TEZ/IVA are spent with mild disease (i.e., ppFEV$_1$ ≥70% to <90%) vs only [redacted] for patients treated with ECM alone (Table 139).

Table 139. Deterministic base-case clinical outcomes from TEZ/IVA model

Treatment	Median survival (years)	LYs (undisc.)	QALYs (undisc.)	Proportion of undisc. LYs spent with ppFEV$_1$		
				≥70% to <90%	≥40% to <70%	<40%
Patients homozygous for *F508del* or heterozygous for *F508del* and RF (Weighted results)						
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population with F/F genotype (Genotype prevalence: 89.76%)						
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population with F/RF genotype (Genotype prevalence: 10.24%)						
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; LYs, life years; ppFEV$_1$, percent predicted forced expiratory volume in one second; QALYs, quality-adjusted life years; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

Figure 96. Predicted survival of cohorts of pwCF with F/F genotype eligible for TEZ/IVA treatment

Abbreviations: ECM, established clinical management; pwCF, people with cystic fibrosis; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

Figure 97. Predicted survival of cohorts of pwCF with F/RF genotype eligible for TEZ/IVA treatment

Abbreviations: ECM, established clinical management; pwCF, people with cystic fibrosis; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

Furthermore, the clinical outcomes and disaggregated results show reductions in disease management costs and use of healthcare resources including hospitalisations and lung transplants with TEZ/IVA treatment in the deterministic base-case analysis (see Appendix J).

The probabilistic base-case incremental cost-effectiveness results for treatment with TEZ/IVA vs ECM, calculated based on genotype prevalence, are presented in Table 140. The TEZ/IVA economic model projects that patients homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a RF mutation treated with TEZ/IVA will experience a health benefit of [redacted] LYs (discounted) and [redacted] QALYs (with severity weight of 1.7, discounted) compared to ECM, with the incremental total costs of [redacted]. The resulting ICER was £191,681 per QALY gained, while the NHB at the WTP of £20,000 and £30,000 was [redacted] and [redacted], respectively.

Table 140. Probabilistic base-case incremental results from TEZ/IVA model

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients homozygous for *F508del* or heterozygous for *F508del* and RF (Weighted results)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£191,681	[redacted]	[redacted]
Population with F/F genotype (Genotype prevalence: 89.76%)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£193,269	[redacted]	[redacted]
Population with F/RF genotype (Genotype prevalence: 10.24%)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£178,796	[redacted]	[redacted]

Note: *Severity weight of 1.7 applied.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

B.3.10.4 Companion analyses exploring impact of loss of exclusivity

As explained in B.3.5.1, the base-case excludes assumptions about generic pricing of CFTRms once patents expire and thus severely overestimates the true lifetime costs of these therapies. Patients treated with IVA/TEZ/ELX are projected to live into their [redacted] (see B.3.10.1), and hence remain on drug for an average of [redacted] years in the model. Small molecule products nearly always have generic competition once their patents expire and it is nearly certain that a generic drug would enter the market within the next [redacted] years. Reduction in the price of CFTRms following LoE should be considered in the cost-effectiveness analysis to adequately value the drugs, given the projected expiration of the European Union patents is well within the timeframe of the projected life expectancy of pwCF treated with a CFTRm. Therefore, a companion set of analyses considering reduction in the price of CFTRms following projected expiration of EU patents, based on published UK pricing trends (436), is presented in the tables below. This approach is consistent with the conclusions of the recent "HTA Troubleshooting" workshop of the National Centre for Pharmacoeconomics Annual Symposium, which highlighted the importance of accounting for future loss of market exclusivity with a case study based on the anticipated loss of exclusivity of eculizumab (446).

Table 141. Deterministic results from IVA/TEZ/ELX model incorporating LoE

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients with at least one *F508del* allele (Weighted results)						
IVA/TEZ/ELX vs SoC	[redacted]	[redacted]	[redacted]	£61,542	[redacted]	[redacted]
Population with F/F genotype (Genotype prevalence: 54.28%)						
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£61,477	[redacted]	[redacted]
Population with F/MF genotype (Genotype prevalence: 28.96%)						
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£62,581	[redacted]	[redacted]
Population with F/Gating genotype (Genotype prevalence: 10.57%)**						
IVA/TEZ/ELX vs IVA	[redacted]	[redacted]	[redacted]	£37,707	[redacted]	[redacted]
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£63,212	[redacted]	[redacted]
Population with F/RF (Genotype prevalence: 6.19%)						
IVA/TEZ/ELX vs ECM	[redacted]	[redacted]	[redacted]	£85,286	[redacted]	[redacted]

Notes: *Severity weight of 1.7 applied;
** Market shares of comparators in F/Gating population: [redacted] IVA and [redacted] ECM.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; LoE, loss of exclusivity; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

Table 142. Deterministic results from LUM/IVA model incorporating LoE

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients homozygous for *F508del* mutation						
LUM/IVA vs ECM	[redacted]	[redacted]	[redacted]	£80,458	[redacted]	[redacted]

Note: *Severity weight of 1.7 applied.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LoE, loss of exclusivity; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 143. Deterministic results from TEZ/IVA model incorporating LoE

Treatment	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Patients homozygous for *F508del* or heterozygous for *F508del* and RF (Weighted results)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£109,942	[redacted]	[redacted]
Population with F/F genotype (Genotype prevalence: 89.76%)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£110,601	[redacted]	[redacted]
Population with F/RF genotype (Genotype prevalence: 10.24%)						
TEZ/IVA vs ECM	[redacted]	[redacted]	[redacted]	£104,599	[redacted]	[redacted]

Note: *Severity weight of 1.7 applied.
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LoE, loss of exclusivity; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were conducted to account for multivariate and stochastic uncertainty in the models. The uncertainty in the individual parameters was characterised using probability distributions and analysed using Monte Carlo simulation (1,000 replications). A summary of the uncertainties around parameters for all three models in shown in Section B.3.9.1. For each PSA iteration, a new set of input parameter values was randomly sampled assuming the probability distributions specified. PSA results are displayed in incremental cost-effectiveness scatterplots,

which present the variability in incremental costs and incremental QALYs over 1,000 PSA iterations. Cost-effectiveness acceptability curves (CEACs) were also plotted, to determine the probability of CFTRms being cost-effective at varying cost-effectiveness thresholds. PSA results did not consider severity weight.

B.3.11.1.1 IVA/TEZ/ELX

PSA results are presented for patients with at least one *F5808del* allele treated with IVA/TEZ/ELX vs current SoC. [redacted] (Figure 98).

Figure 98. Cost-effectiveness scatterplot for IVA/TEZ/ELX vs SoC (weighted average)

[redacted]

Abbreviations: IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; QALY, quality-adjusted life year; SoC, standard of care.

The CEAC for IVA/TEZ/ELX vs SoC shows that IVA/TEZ/ELX is likely to be a cost-effective treatment at a WTP above [redacted] (at a WTP of [redacted] there is a [redacted] probability that IVA/TEZ/ELX is cost-effective). At a threshold of [redacted], IVA/TEZ/ELX has a [redacted] probability of being cost-effective vs SoC for pwCF with at least one *F5808del* allele (Figure 99).

Figure 99. Cost-effectiveness acceptability curve for IVA/TEZ/ELX vs SoC (weighted average)

B.3.11.1.2 LUM/IVA

PSA results are presented for patients aged ≥2 years homozygous for *F508del* mutation treated with LUM/IVA vs ECM. [redacted] (Figure 100).

Figure 100. Cost-effectiveness scatterplot for LUM/IVA vs ECM

Abbreviations: ECM, established clinical management; LUM/IVA, lumacaftor/ivacaftor; QALY, quality-adjusted life year.

The CEAC for LUM/IVA vs ECM shows that LUM/IVA is likely to be cost-effective at a WTP above [redacted] (at a WTP of [redacted] there is a [redacted] probability that LUM/IVA is cost-effective). LUM/IVA has a [redacted] probability of being cost-effective vs ECM for patients aged ≥2 years homozygous for *F508del* mutation at a WTP of [redacted], (Figure 101).

Figure 101. Cost-effectiveness acceptability curve for LUM/IVA vs ECM

B.3.11.1.3 TEZ/IVA

PSA results are presented for patients aged ≥6 years homozygous for *F508del* or heterozygous for *F508del* and RF treated with TEZ/IVA vs ECM. [redacted] (Figure 102).

Figure 102. Cost-effectiveness scatterplot for TEZ/IVA vs ECM (weighted average)

Abbreviations: ECM, established clinical management; QALY, quality-adjusted life year; TEZ/IVA, tezacaftor/ ivacaftor and ivacaftor.

The CEAC for TEZ/IVA vs ECM shows that TEZ/IVA is likely to be cost-effective at a WTP of above [redacted] (at a threshold of [redacted] there is a [redacted] probability that TEZ/IVA is cost-effective). TEZ/IVA has a [redacted] probability of being cost-effective vs ECM for patients aged ≥6 years homozygous for *F508del* or heterozygous for *F508del* and RF at a WTP of [redacted], (Figure 103).

Figure 103. Cost-effectiveness acceptability curve for TEZ/IVA vs ECM (weighted average)

B.3.11.2 Deterministic sensitivity analysis

For the deterministic sensitivity analyses (DSAs), the upper and lower bounds for the parameters considered were derived from descriptive statistics (e.g., 95% CIs). Where data were not available, the bounds for those parameters were derived from a 20% variation around mean value. DSA results for each CFTRm model are displayed in tornado diagrams, which demonstrate the model inputs that influence the ICER the most (discounted cost-per-QALY, without severity weight).

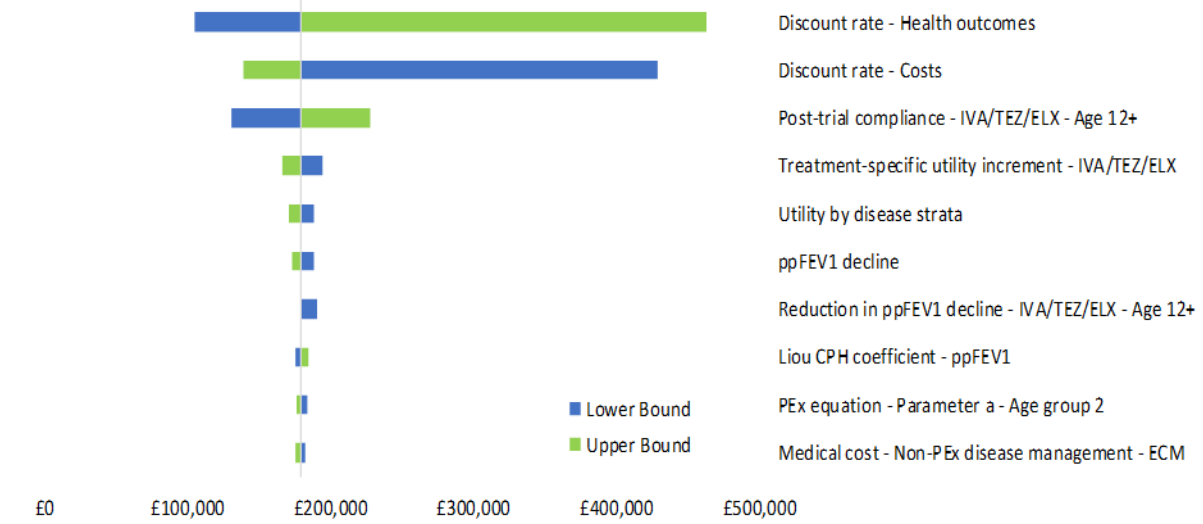
Across all three models, results are most sensitive to variation in the annual discount rates for health outcomes and costs (both varied from 0% to 5%). This effect is very particular to interventions like the CFTRm given that long-term projection of clinical benefits of CFTRms results in a significant extension of the median survival of pwCF receiving them such that survival benefits and costs are accrued far into the future, making them highly sensitive to the level of discounting. It is important to highlight that the discount rate, while it is the main driver of the analysis, it is not an outcome measure reflecting the clinical benefits of the CFTRm.

B.3.11.2.1 IVA/TEZ/ELX

DSA results for patients with at least one *F508del* allele treated with IVA/TEZ/ELX vs current SoC are displayed in Figure 104 and Table 144. Apart from sensitive to variation in the annual discount rates applied to health outcomes and costs, the IVA/TEZ/ELX model is also sensitive to variations in the post-trial compliance in

patients aged ≥12 years treated with IVA/TEZ/ELX and the utility benefit of treatment with IVA/TEZ/ELX.

Figure 104. Tornado diagram for IVA/TEZ/ELX vs SoC (weighted average)



Abbreviations: CPH, Cox Proportional Hazards; ECM, established clinical management; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; SoC, standard of care.

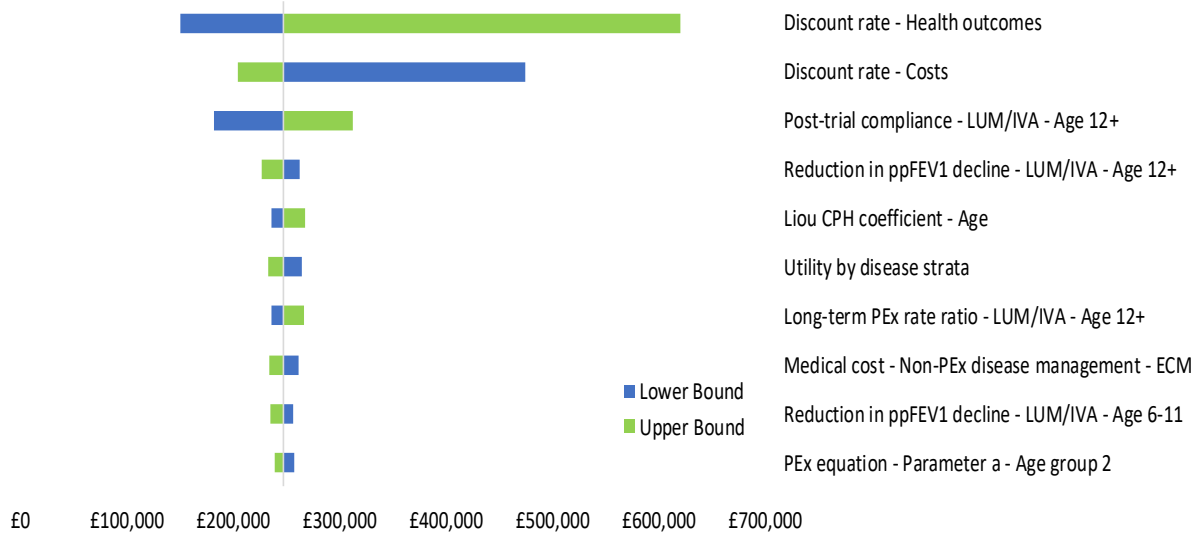
Table 144. DSA results for IVA/TEZ/ELX vs SoC (weighted average)

Variable	Base Case	Lower Bound	Upper Bound
Discount rate - Health outcomes	£179,288	£105,157	£463,116
Discount rate - Costs	£179,288	£429,059	£139,134
Post-trial compliance - IVA/TEZ/ELX - Age 12+	£179,288	£130,672	£227,903
Treatment-specific utility increment - IVA/TEZ/ELX	£179,288	£194,796	£166,067
Utility by disease strata	£179,288	£188,573	£170,874
$ppFEV_1$ decline	£179,288	£188,300	£173,553
Reduction in $ppFEV_1$ decline - IVA/TEZ/ELX - Age 12+	£179,288	£190,973	£179,288
Liou CPH coefficient - $ppFEV_1$	£179,288	£175,271	£184,991
PEx equation - Parameter a - Age group 2	£179,288	£183,871	£176,541
Medical cost - Non-PEx disease management - ECM	£179,288	£182,714	£175,861
Abbreviations: CPH, Cox Proportional Hazards; ECM, established clinical management; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second; SoC, standard of care.			

B.3.11.2.2 LUM/IVA

DSA results for patients aged ≥2 years homozygous for *F508del* mutation treated with LUM/IVA vs ECM are displayed in Figure 105 and Table 145. Apart from sensitive to variation in the annual discount rates for health outcomes and costs, the LUM/IVA model is also sensitive to variations in the post-trial compliance and the treatment effect on long-term $ppFEV_1$ in patients aged ≥12 years treated with LUM/IVA.

Figure 105. Tornado diagram for LUM/IVA vs ECM



Abbreviations: CPH, Cox Proportional Hazards; ECM, established clinical management; LUM/IVA, lumacaftor/ ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second.

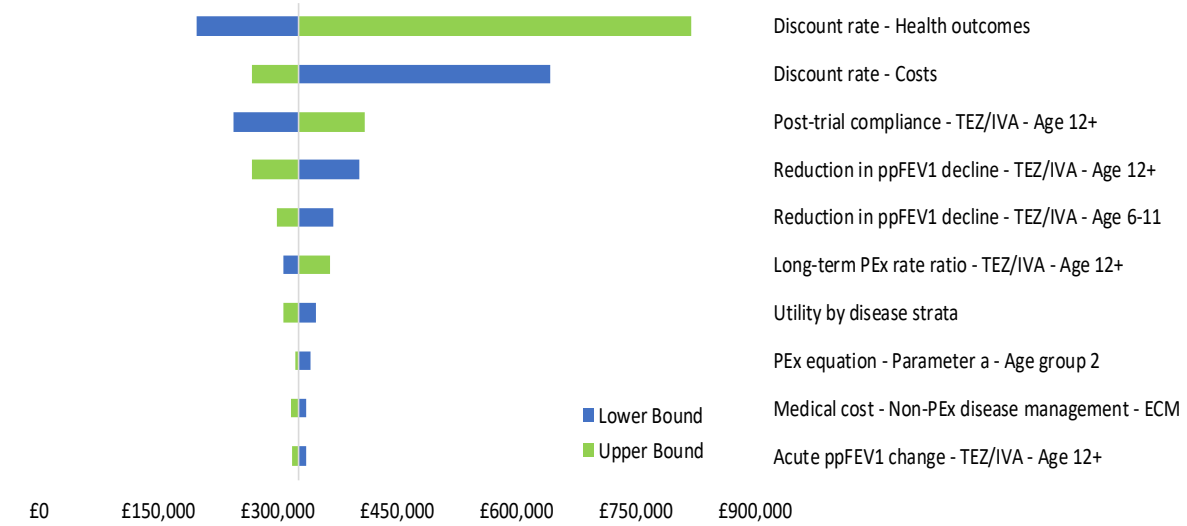
Table 145. DSA results for LUM/IVA vs ECM

Variable	Base Case	Lower Bound	Upper Bound
Discount rate - Health outcomes	£247,505	£150,519	£620,125
Discount rate - Costs	£247,505	£474,705	£204,074
Post-trial compliance - LUM/IVA - Age 12+	£247,505	£182,193	£312,818
Reduction in $ppFEV_1$ decline - LUM/IVA - Age 12+	£247,505	£262,672	£226,853
Liou CPH coefficient - Age	£247,505	£236,156	£267,883
Utility by disease strata	£247,505	£264,105	£232,869
Long-term PEx rate ratio - LUM/IVA - Age 12+	£247,505	£235,598	£266,498
Medical cost - Non-PEx disease management - ECM	£247,505	£261,394	£233,617
Reduction in $ppFEV_1$ decline - LUM/IVA - Age 6-11	£247,505	£256,131	£234,478
PEx equation - Parameter a - Age group 2	£247,505	£257,206	£239,120
Abbreviations: CPH, Cox Proportional Hazards; ECM, established clinical management; LUM/IVA, lumacaftor/ ivacaftor; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second.			

B.3.11.2.3 TEZ/IVA

DSA results for patients aged ≥6 years homozygous for *F508del* or heterozygous for *F508del* and RF treated with TEZ/IVA vs ECM are displayed in Figure 106 and Table 146. Apart from sensitive to variation in the annual discount rates for health outcomes and costs, the TEZ/IVA model is also sensitive to variations in the post-trial compliance and the treatment effect on long-term $ppFEV_1$ in patients aged ≥12 years treated with TEZ/IVA.

Figure 106. Tornado diagram for TEZ/IVA vs ECM (weighted average)



Abbreviations: ECM, established clinical management; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

Table 146. DSA results for TEZ/IVA vs ECM (weighted average)

Variable	Base Case	Lower Bound	Upper Bound
Discount rate - Health outcomes	£326,260	£197,725	£819,983
Discount rate - Costs	£326,260	£643,214	£266,918
Post-trial compliance - TEZ//IVA - Age 12+	£326,260	£243,619	£408,902
Reduction in $ppFEV_1$ decline - TEZ/IVA - Age 12+	£326,260	£402,361	£268,113
Reduction in $ppFEV_1$ decline - TEZ/IVA - Age 6-11	£326,260	£369,304	£298,955
Long-term PEx rate ratio - TEZ/IVA - Age 12+	£326,260	£306,500	£365,442
Utility by disease strata	£326,260	£347,828	£307,211
PEx equation - Parameter a - Age group 2	£326,260	£341,400	£321,530
Medical cost - Non-PEx disease management - ECM	£326,260	£335,735	£316,785
Acute $ppFEV_1$ change - TEZ/IVA - Age 12+	£326,260	£335,774	£318,330
Abbreviations: ECM, established clinical management; PEx, pulmonary exacerbation, $ppFEV_1$, percent predicted forced expiratory volume in one second; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.			

B.3.11.3 Scenario analyses

Scenario analyses were conducted to test how changes in model assumptions and input values derived from alternative data sources impact model outcomes from each CFTRm model. Scenarios explored the impact of alternative assumptions for model parameters including discount rates and health state utilities by $ppFEV_1$ strata across all three models, and caregiver utility applicable only to the IVA/TEZ/ELX model.

B.3.11.3.1 IVA/TEZ/ELX

Scenarios applied to the IVA/TEZ/ELX model and their justification are summarised in Table 147, with the corresponding results being presented in Table 148.

Table 147. Scenario analyses explored using the IVA/TEZ/ELX model

Parameter	Justification
Scenario 1: Uniform discount rate of 3.5% for health outcomes and costs	This scenario is aligned with the NICE reference case of 3.5% discounting for utilities and costs (10).
Scenario 2: Uniform discount rate of 3.5% for health outcomes and costs; and EQ-5D utility values by $ppFEV_1$ from Acaster et al. (403)	This scenario is aligned with the NICE reference case for discounting, and uses the most recent UK EQ-5D data stratified by $ppFEV_1$.

Parameter	Justification
Scenario 3: Uniform discount rate of 3.5% for health outcomes and costs; and exclusion of caregiver utility increment	This scenario is aligned with the NICE reference case for discounting, and explores the impact of excluding caregiver utility in patients treated with IVA/TEZ/ELX.
Abbreviations: EQ-5D, EuroQol-Five Dimension; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor; NICE, National Institute for Health and Care Excellence; $ppFEV_1$, percent predicted forced expiratory volume in one second.	

Table 148. Scenario analyses results for IVA/TEZ/ELX vs SoC (weighted average)

Scenario	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Base case	[redacted]	[redacted]	[redacted]	£109,280	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]	£268,836	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	£271,312	[redacted]	[redacted]
Scenario 3	[redacted]	[redacted]	[redacted]	£269,435	[redacted]	[redacted]
Notes: *Severity weight of 1.7 and 1.2 applied to base case and scenario analyses, respectively; Abbreviations: ICER, incremental cost-effectiveness ratio; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.						

B.3.11.3.2 LUM/IVA

Scenarios applied to the LUM/IVA model and their justification are summarised in Table 149, with the corresponding results being presented in Table 150.

Table 149. Scenario analyses explored using the LUM/IVA model

Parameter	Justification
Scenario 1: Uniform discount rate of 3.5% for health outcomes and costs	This scenario is aligned with the NICE reference case of 3.5% discounting for utilities and costs (10).
Scenario 2: Uniform discount rate of 3.5% for health outcomes and costs; and EQ-5D utility values by $ppFEV_1$ from Acaster et al. (403)	This scenario is aligned with the NICE reference case for discounting, and uses the most recent UK EQ-5D data stratified by $ppFEV_1$.
Abbreviations: EQ-5D, EuroQol-Five Dimension; LUM/IVA, lumacaftor/ivacaftor; NICE, National Institute for Health and Care Excellence; $ppFEV_1$, percent predicted forced expiratory volume in one second.	

Table 150. Scenario analyses results for LUM/IVA vs ECM

Scenario	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Base case	[redacted]	[redacted]	[redacted]	£144,411	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]	£361,423	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	£372,889	[redacted]	[redacted]
Notes: *Severity weight of 1.7 and 1.2 applied to base case and scenario analyses, respectively; Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.						

B.3.11.3.3 TEZ/IVA

Scenarios applied to the TEZ/IVA model and their justification are summarised in Table 151, with the corresponding results being presented in Table 152.

Table 151. Scenario analyses explored using the TEZ/IVA model

Parameter	Justification
Scenario 1: Uniform discount rate of 3.5% for health outcomes and costs	This scenario is aligned with the NICE reference case of 3.5% discounting for utilities and costs (10).
Scenario 2: Uniform discount rate of 3.5% for health outcomes and costs; and EQ-5D utility values by $ppFEV_1$ from Acaster et al. (403)	This scenario is aligned with the NICE reference case for discounting, and uses the most recent UK EQ-5D data stratified by $ppFEV_1$.
Abbreviations: EQ-5D, EuroQol-Five Dimension; NICE, National Institute for Health and Care Excellence; $ppFEV_1$, percent predicted forced expiratory volume in one second; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.	

Table 152. Scenario analyses results for TEZ/IVA vs ECM (weighted average)

Scenario	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Base case	[redacted]	[redacted]	[redacted]	£191,681	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]	£477,674	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	£485,194	[redacted]	[redacted]

Notes: * Severity weight of 1.7 and 1.2 applied to base case and scenario analyses, respectively;
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TEZ/IVA, tezacaftor/ivacaftor and ivacaftor.

B.3.12 Subgroup analysis

No subgroup analyses were conducted.

B.3.13 Benefits not captured in the QALY calculation

As described in Section B.3.4, caring for children with CF represents a major challenge for parents and caregivers, especially with increasing child age and treatment burden (115, 144, 394, 395). Day-to-day care of pwCF imposes a considerable burden on their caregivers and families. Multiple studies have demonstrated that caregiving for pwCF has a substantial impact on caregiver QoL, particularly for caregivers of paediatric patients and during PEx episodes (140, 248, 395). 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 methodologies have confirmed the positive impact that CFTRm treatment has had on caregivers of pwCF, including reduced worrying and stress, improved outlook on patient health, and reduced time spent caregiving (408, 426).

[redacted]

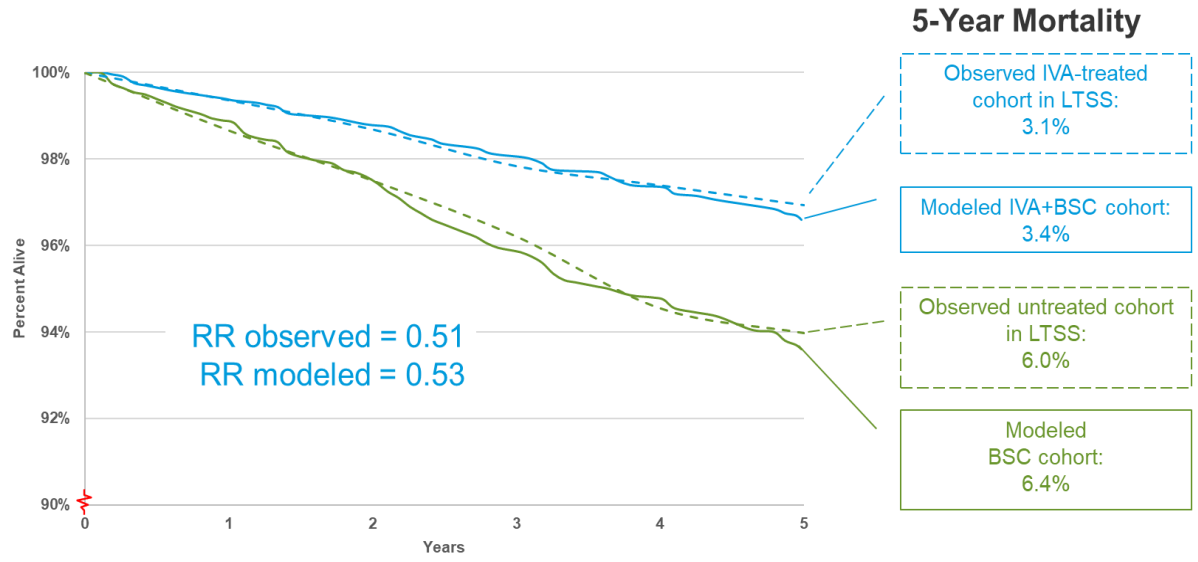
B.3.14 Validation

An exercise to validate Vertex's CFTRm survival model methodology and survival projections was performed by comparing 5-year model-projected mortality to observed

5-year mortality from the IVA LTSS, which followed patients treated with IVA and untreated matched comparators in the US CFFPR for five years (2012-2016) (338). Baseline characteristics of the LTSS participants from the US CFFPR were entered into the model and outcomes were simulated over a 5-year model horizon. The 5-year model-projected mortality with bootstrapped credible intervals (CrI) was then compared to mortality observed in the LTSS.

The modelled 5-year mortality projections very closely approximated real-world LTSS outcomes in both the untreated (6.4% [95% CrI: 5.3%-7.6%] modelled vs 6.0% observed) and IVA-treated (3.4% [95% CrI 2.7%-4.4%] modelled vs 3.1% observed) CF populations (Figure 107). The model also predicts that over 5 years, IVA-treated patients have a relative risk of mortality of 0.53 ([95% CrI 0.47-0.60] modelled vs 0.51 observed) vs untreated patients (373).

Figure 107. US LTSS 5-year survival (2012 cohort entry)



Abbreviations: BSC, best supportive care; IVA, ivacaftor; LTSS, long-term safety study; RR, relative risk; US, United states.

Modelled 5-year survival projections tracked closely the observed registry data. These findings support the validity of the CFTRm models based on the CPH equation from Liou et al. in predicting long-term survival and estimating the clinical and economic outcomes of CFTRms (64, 373). Considering the similarity in the mechanism of action of CFTRms and efficacy as shown in Section B.3.3, it is considered that the validation using patients treated with IVA is comparable to the model outcomes for IVA/TEZ/ELX, LUM/IVA and TEZ/IVA.

In addition, the model has been reviewed by numerous HTA bodies, including NICE (TA398) (301). Areas of critique from HTA feedback, such as the calibration of PEx, have been addressed. The underlying survival calculation approach is consistent with several published survival analyses for pwCF in the UK and the US treated with IVA/TEZ/ELX (315-319), LUM/IVA (320) and TEZ/IVA (321-323). Slight modifications to these published models have been made to improve efficiency and external validity.

B.3.15 Interpretation and conclusions of economic evidence

A patient-level state-transition model was developed to evaluate the cost-effectiveness of CFTRms as add-on to ECM for the treatment of pwCF with at least one *F508del* mutation in the *CFTR* gene, consistent with the model appraised in TA398 (301) and documented in published literature (318). The clinical inputs of the model are based on extensive clinical trial programmes and real-world evidence which have demonstrated that IVA/TEZ/ELX, LUM/IVA and TEZ/IVA are highly effective treatments for the indicated populations of pwCF, resulting in clinically meaningful improvements in key predictors of morbidity and mortality, such as lung function measured by $ppFEV_1$, PEx and nutritional status (Section B.2.11).

The model predicts unprecedented prolongation of survival as well as improvement in HRQoL alongside reductions in healthcare resource use in patients treated with CFTRm compared to ECM. It also predicts that patients treated with a CFTRm spend a greater proportion of their lifetime with better lung function and consequently, with improved HRQoL relative to ECM. The interim real-world outcomes collected through the Data Collection Agreement help to reduce the uncertainty associated with long-term extrapolation of clinical outcomes in the model. The fact that the magnitude and the duration of lung function benefits in the UKCFR study are highly consistent with the results of RCTs/rollover studies and are also sustained over an extended follow-up period of two years, suggests that IVA/TEZ/ELX can modify the trajectory of CF lung disease, thereby alleviating clinical uncertainties previously identified by NICE. In addition, real-world data collected on the quality of life of patients and caregiver emphasizes the quality-of-life improvements these therapies provide, as well as real-world data on mortality and lung transplantation confirming substantial improvements in both outcomes.

Specifically, pwCF with at least one *F508del* allele aged ≥6 years treated with IVA/TEZ/ELX are projected to experience a substantial survival gain of 25.72 LYs (undiscounted), with a 31.57-year increase in median predicted survival, as well as HRQoL benefits ([redacted] additional discounted QALYs with severity weight of 1.7) compared to pwCF treated with SoC, resulting in an ICER of £109,280 per QALY gained. When generic pricing is considered to account for patent expiration within the model time horizon, the ICER is reduced to £61,542 per QALY gained.

Patients homozygous for *F508del* mutation aged ≥2 years treated with LUM/IVA are projected to experience a substantial survival gain of [redacted] LYs (undiscounted), with a [redacted]-year increase in median predicted survival, as well as HRQoL benefits ([redacted] additional discounted QALYs with severity weight of 1.7) compared to patients treated with ECM alone, yielding an ICER of £144,411 per QALY gained. When generic pricing is considered to account for known patent expiration within the model time horizon, the ICER is reduced to £80,458 per QALY gained.

Patients homozygous for *F508del* mutation or heterozygous for *F508del* and RF aged ≥6 years treated with TEZ/IVA are projected to experience a substantial survival gain of [redacted] LYs (undiscounted), with a [redacted]-year increase in medial predicted survival, as well as HRQoL benefits ([redacted] additional discounted QALYs with severity weight of 1.7) compared to patients treated with ECM alone, yielding an ICER of £191,681 per QALY gained. When generic pricing is considered to account for patent expiration within the model time horizon, the ICER is reduced to £109,942 per QALY gained.

The results of the cost-effectiveness analyses are generalisable to the indicated CF populations in England for each CFTRm, given UK-specific inputs where possible.

The model validation was undertaken by testing its predictive value on a set of patients treated with IVA in the real-world (373). The results of the validation, performed by comparing the 5-year model-projected mortality to observed 5-year mortality from the IVA LTSS, which followed IVA-treated patients and matched comparators in the US CFFPR (338), indicate that the microsimulation accurately reproduces the real-world impact of CFTRms, thereby bolstering its credibility (373).

Sensitivity analysis found the model results to be most sensitive to the variation in the annual discount rates for health outcomes and costs; this is expected given that

survival benefits are expected to be achieved for many years into the future and are thus sensitive to the level of discounting. As with all models, assumptions were made and there are limitations to predicting long-term outcomes. However, the sensitivity and scenario analyses for IVA/TEZ/ELX suggest the model results are robust with regards to parameter uncertainty or alternative assumptions.

In conclusion, IVA/TEZ/ELX, LUM/IVA and TEZ/IVA offer unprecedented and sustainable clinical and HRQoL benefits to patients. By targeting the underlying cause of disease and improving multiple clinically meaningful outcomes, CFTRms are anticipated to lead to substantial improvements in long-term survival and HRQoL accompanied by reductions in healthcare resource utilisation (hospitalisations and lung transplants, in particular). Importantly, initiating IVA/TEZ/ELX treatment during ages 6-11, at an early stage of disease, could prevent serious long-term complications and is projected to add upwards of three to four decades of survival benefit vs ECM alone, allowing pwCF and at least one *F508del* mutation to achieve near normal life expectancy. The survival benefit of this magnitude suggests that IVA/TEZ/ELX could have the potential to transform health outcomes for many people living with CF.

The modelling assumptions of base case analysis regarding the discounting and the use of a disease-specific utility instrument, depart from the NICE reference case. However, flexibility in modelling assumptions when appraising lifelong treatments for rare, chronic diseases, may be necessary to fully reflect the value of life-extending therapies more accurately and equitably, to continue to encourage the development of innovative treatments for rare diseases, and to ensure appropriate access for patients.

References

1. Vertex. Kaftrio 75 mg 50 mg 100 mg film-coated tablets Summary of Product Characteristics 2022 [updated 18/02/2022. Available from: https://products.mhra.gov.uk/ Accessed 25 March 2022].
2. Vertex. Orkambi 100 mg/125 mg granules in sachet Summary of Product Characteristics 2021 [Available from: https://products.mhra.gov.uk/ Accessed 25 March 2022].
3. Vertex. Orkambi 200 mg/125 mg film coated tablets Summary of Product Characteristics 2021 [Available from: https://products.mhra.gov.uk/ Accessed 11 April 2022].
4. Vertex. Symkevi 100 mg/150 mg film coated tablets Summary of Product Characteristics 2021 [Available from: https://products.mhra.gov.uk/ Accessed 25 March 2022].
5. National institute for Health and Care Excellence (NICE). Data collection agreement 2022 [Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement 06 April 2022].
6. NHS England. Updated Commissioning Statement: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations. 2022.
7. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. New England Journal of Medicine. 2019;381(19):1809-19.
8. Vertex. An Observational Study of Users of Kaftrio, Orkambi and Symkevi in the UK Cystic Fibrosis Registry to Satisfy Data Collection Agreement in the UK: Second Interim Analysis (IA2). 2023.
9. Southern KW, Castellani C, Lammertyn E, Smyth A, VanDevanter D, van Koningsbruggen-Rietschel S, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. Journal of Cystic Fibrosis. 2022.
10. NICE. NICE health technology evaluations: the manual [PMG36]. 2022.
11. Zorginstituut Nederland. Guideline for economic evaluations in healthcare 2016.
12. The Agency for Health Technology Assessment and Tariff System. Health Technology Assessment Guidelines Version 3.0. Warsaw; 2016.
13. Sharma D, Aggarwal AK, Downey LE, Prinja S. National Healthcare Economic Evaluation Guidelines: A Cross-Country Comparison. Pharmacoecon Open. 2021;5(3):349-64.
14. Cleemput I, Neyt M, Van De Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. Health Technology Assessment (HTA). Brussels. Belgian Health Care Knowledge Centre (KCE); 2012. Contract No.: KCE Reports 183C. DOI : 10.57598/R183C.
15. Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health Econ. 2011;20(1):2-15.
16. Gravelle H, Smith D. Discounting for health effects in cost-benefit and cost-effectiveness analysis. Health economics. 2001;10(7):587-99.

17. Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. Value in Health. 2004;7(4):397-401.
18. Saint-Criq V, Gray MA. Role of CFTR in epithelial physiology. Cell Mol Life Sci. 2017;74(1):93-115.
19. Clancy JP. Rapid therapeutic advances in CFTR modulator science. Pediatric Pulmonology. 2018;53(S3):S4-S11.
20. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373(9678):1891-904.
21. Ratjen F, Grasemann H. New therapies in cystic fibrosis. Current pharmaceutical design. 2012;18(5):614-27.
22. Patel SD, Bono TR, Rowe SM, Solomon GM. CFTR targeted therapies: recent advances in cystic fibrosis and possibilities in other diseases of the airways. European Respiratory Review. 2020;29(156):190068.
23. Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. Sci Rep. 2019;9(1):7234.
24. Fiedorczuk K, Chen J. Mechanism of CFTR correction by type I folding correctors. Cell. 2022;185(1):158-68.e11.
25. Ensinck MM, De Keersmaecker L, Ramalho AS, Cuyx S, Van Biervliet S, Dupont L, et al. Novel CFTR modulator combinations maximise rescue of G85E and N1303K in rectal organoids. ERJ Open Research. 2022;8(2):00716-2021.
26. Laselva O, Bartlett C, Gunawardena TNA, Ouyang H, Eckford PDW, Moraes TJ, et al. Rescue of multiple class II CFTR mutations by elexacaftor+tezacaftor+ivacaftor mediated in part by the dual activities of elexacaftor as both corrector and potentiator. European Respiratory Journal. 2021;57(6):2002774.
27. US FDA. TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) product label. Last Revised: October 2019. 2019.
28. Eckford PDW, Li C, Ramjeesingh M, Bear CE. Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiator VX-770 (Ivacaftor) Opens the Defective Channel Gate of Mutant CFTR in a Phosphorylation-dependent but ATP-independent Manner*♦. Journal of Biological Chemistry. 2012;287(44):36639-49.
29. European Medicines Agency. Orkambi: Assessment report. Procedure No. EMEA/H/C/003954/0000 2015 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/orkambi-epar-public-assessment-report_en.pdf Accessed 11 January 2023].
30. Parliament U. Research Briefing: Access to Orkambi and other drugs for people with cystic fibrosis 2019 [Available from: https://commonslibrary.parliament.uk/research-briefings/cdp-2019-0145/ Accessed 27 January 2023].
31. European Medicines Agency. Symkevi Publication Details [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/symkevi accessed 08 May 2022].
32. European Medicines Agency. Symkevi: Assessment report. Procedure No. EMEA/H/C/004682/0000 2018 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/symkevi-epar-public-assessment-report_en.pdf Accessed 11 January 2023].
33. Cystic Fibrosis Trust. Symkevi 2022 [Available from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/treatments-and-medication/kaftrio Accessed 27 January 2023].

34. European Medicines Agency. Kaftrio Publication Details [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio.
35. Cystic Fibrosis Trust. Kaftrio 2022 [Available from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/treatments-and-medication/kaftrio Accessed 27 January 2023].
36. British National Formulary. LUMACAFTOR WITH IVACAFTOR [Available from: https://bnf.nice.org.uk/medicinal-forms/lumacaftor-with-ivacaftor.html Accessed 25 March 2022].
37. BNF for children. LUMACAFTOR WITH IVACAFTOR 2022 [Available from: https://bnfc.nice.org.uk/medicinal-forms/lumacaftor-with-ivacaftor.html Accessed 25 March 2022].
38. British National Formulary. TEZACAFTOR WITH IVACAFTOR 2022 [Available from: https://bnf.nice.org.uk/medicinal-forms/tezacaftor-with-ivacaftor.html Accessed 25 March 2022].
39. British National Formulary. IVACAFTOR 2022 [Available from: https://bnf.nice.org.uk/medicinal-forms/ivacaftor.html Accessed 25 March 2022].
40. British National Formulary. TEZACAFTOR WITH IVACAFTOR AND ELEXACAFTOR 2022 [Available from: https://bnf.nice.org.uk/medicinal-forms/tezacaftor-with-ivacaftor-and-elexacaftor.html Accessed 25 March 2022].
41. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science (New York, NY). 1989;245(4922):1066-73.
42. Dechecchi MC, Tamanini A, Cabrini G. Molecular basis of cystic fibrosis: from bench to bedside. Ann Transl Med. 2018;6(17):334-.
43. Paranjape SM, Mogayzel Jr PJ. Cystic fibrosis in the era of precision medicine. Paediatric respiratory reviews. 2018;25:64-72.
44. Teach Me Paediatrics. Cystic Fibrosis: Teach Me Paediatrics; [Available from: https://teachmepaediatrics.com/respiratory/lower-respiratory-tract/cystic-fibrosis/ accessed 21 June 2022].
45. CFTR2. Clinical and Functional Translation of CFTR (CFTR2). Accessed June 10, 2019. Available at: https://cftr2.org/ 2019 [Available from: http://cftr2.org.
46. Koch C, Cuppens H, Rainisio M, Madessani U, Harms H, Hodson M, et al. European Epidemiologic Registry of Cystic Fibrosis (ERCF): comparison of major disease manifestations between patients with different classes of mutations. Pediatr Pulmonol. 2001;31(1):1-12.
47. Jennings MT, Flume PA. Cystic Fibrosis: Translating Molecular Mechanisms into Effective Therapies. Ann Am Thorac Soc. 2018;15(8):897-902.
48. Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. Mol Biol Cell. 2016;27(3):424-33.
49. Harman K, Dobra R, Davies JC. Disease-modifying drug therapy in cystic fibrosis. Paediatr Respir Rev. 2018;26:7-9.
50. Cheng SH, Gregory RJ, Marshall J, Paul S, Souza DW, White GA, et al. Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. Cell. 1990;63(4):827-34.
51. Wang XR, Li C. Decoding F508del misfolding in cystic fibrosis. Biomolecules. 2014;4(2):498-509.
52. Martins RdS, Campos Junior M, Dos Santos Moreira A, Marques Zembrzuski V, da Fonseca ACP, Abreu GdM, et al. Identification of a novel large deletion and other

copy number variations in the CFTR gene in patients with Cystic Fibrosis from a multiethnic population. Mol Genet Genomic Med. 2019;7(7):e00645-e.
53. Taylor-Cousar JL, Mall MA, Ramsey BW, McKone EF, Tullis E, Marigowda G, et al. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. ERJ Open Res. 2019;5(2).
54. Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson JP, Jr., et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2012;11(3):237-45.
55. Castellani C, Assael BM. Cystic fibrosis: a clinical view. Cell Mol Life Sci. 2017;74(1):129-40.
56. Cleveland Clinic. Cystic Fibrosis 2021 [Available from: https://my.clevelandclinic.org/health/diseases/9358-cystic-fibrosis accessed: 10 January 2023].
57. Shteinberg M, Downey DG, Beattie D, McCaughan J, Reid A, Stein N, et al. Lung function and disease severity in cystic fibrosis patients heterozygous for p.Arg117His. ERJ Open Research. 2017;3(1):00056-2016.
58. NHS. Overview-Cystic fibrosis 2021 [Available from: https://www.nhs.uk/conditions/cystic-fibrosis/ accessed 18 August 2022].
59. UK Cystic Fibrosis Registry. 2021 Annual Data Report. 2022.
60. Scotet V, Gutierrez H, Farrell PM. Newborn Screening for CF across the Globe—Where Is It Worthwhile? International Journal of Neonatal Screening. 2020;6(1):18.
61. Cystic Fibrosis News Today. Cystic Fibrosis Statistics 2022 [Available from: https://cysticfibrosisnewstoday.com/cystic-fibrosis-statistics/ accessed 22 August 2022].
62. UK Cystic Fibrosis Registry. 2011 Annual Data Report 2013 [Available from: https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/2011%20Registry%20Annual%20Data%20Report.pdf accessed 05 January 2023].
63. NHS Commissioning Board. Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis: Reference NHSCB/A01/P/b. 2012. Contract No.: 05 January 2023.
64. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. American journal of epidemiology. 2001;153(4):345-52.
65. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. European Respiratory Journal. 2015;45(3):670.
66. Nkam L, Lambert J, Latouche A, Bellis G, Burgel PR, Hocine MN. A 3-year prognostic score for adults with cystic fibrosis. Journal of Cystic Fibrosis. 2017;16(6):702-8.
67. Mall MA. Unplugging Mucus in Cystic Fibrosis and Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2016;13 Suppl 2:S177-85.
68. Wielpütz MO, Eichinger M, Zhou Z, Leotta K, Hirtz S, Bartling SH, et al. Monitoring of cystic fibrosis-like lung disease in mice by volumetric computed tomography. European Respiratory Journal. 2011;38(5):1060.
69. Kuo W, de Bruijne M, Petersen J, Nasserinejad K, Ozturk H, Chen Y, et al. Diagnosis of bronchiectasis and airway wall thickening in children with cystic fibrosis: Objective airway-artery quantification. Eur Radiol. 2017;27(11):4680-9.

70. King PT. The pathophysiology of bronchiectasis. Int J Chron Obstruct Pulmon Dis. 2009;4:411-9.
71. Cystic Fibrosis Trust. Additional symptoms of cystic fibrosis [Available from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/symptoms-of-cystic-fibrosis/additional-complications accessed 21 June 2022].
72. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2016;15(2):147-57.
73. Mayo Clinic. Pneumothorax 2021 [Available from: https://www.mayoclinic.org/diseases-conditions/pneumothorax/symptoms-causes/syc-20350367 accessed 21 June 2022].
74. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA. Early Lung Disease in Infants and Preschool Children with Cystic Fibrosis. What Have We Learned and What Should We Do about It? American Journal of Respiratory and Critical Care Medicine. 2017;195(12):1567-75.
75. Tepper LA, Caudri D, Rovira AP, Tiddens HA, de Bruijne M. The development of bronchiectasis on chest computed tomography in children with cystic fibrosis: can pre-stages be identified? Eur Radiol. 2016;26(12):4563-9.
76. Terheggen-Lagro SW, Arets HG, van der Laag J, van der Ent CK. Radiological and functional changes over 3 years in young children with cystic fibrosis. Eur Respir J. 2007;30(2):279-85.
77. Walsh AC, Rault G, Li Z, Scotet V, Dugueperoux I, Ferec C, et al. Pulmonary outcome differences in U.S. and French cystic fibrosis cohorts diagnosed through newborn screening. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2010;9(1):44-50.
78. Tiddens HAWM, Puderbach M, Venegas JG, Ratjen F, Donaldson SH, Davis SD, et al. Novel outcome measures for clinical trials in cystic fibrosis. Pediatr Pulmonol. 2015;50(3):302-15.
79. Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV_1 decline in both adults and children with cystic fibrosis. Pediatr Pulmonol. 2011;46(4):393-400.
80. Turkovic L, Caudri D, Rosenow T, Ranganathan S, Hall GL, Stick SM. Structural determinants of long term functional outcomes in children with cystic fibrosis. Am J Respir Crit Care Med. 2017;195:A4845.
81. O'Sullivan AK, Kahle JS, VanDevanter DR, Sikirica S, Hodgkins P. 186 Manifestation and progression of illness in young children with cystic fibrosis: A targeted literature review. Journal of Cystic Fibrosis. 2015;14:S105.
82. D'Auria JP, Christian BJ, Henderson ZG, Haynes B. The company they keep: The influence of peer relationships on adjustment to cystic fibrosis during adolescence. Journal of Pediatric Nursing. 2000;15(3):175-82.
83. American Lung Association. Cystic Fibrosis Symptoms, Causes & Risk Factors. 2022 [Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/cystic-fibrosis/symptoms-diagnosis accessed 04 July 2022].
84. VanDevanter DR, Morris NJ, Konstan MW. IV-treated pulmonary exacerbations in the prior year: An important independent risk factor for future pulmonary exacerbation in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2016;15(3):372-9.

85. Stenbit AE, Flume PA. Pulmonary exacerbations in cystic fibrosis. Curr Opin Pulm Med. 2011;17(6):442-7.
86. Bhatt JM. Treatment of pulmonary exacerbations in cystic fibrosis. European Respiratory Review. 2013;22(129):205-16.
87. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax. 2007;62(4):360-7.
88. Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. European Respiratory Journal. 2012;40(1):61.
89. Wagener JS, Rasouliyan L, VanDevanter DR, Pasta DJ, Regelmann WE, Morgan WJ, et al. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2013;48(7):666-73.
90. Rubin JL, Thayer S, Watkins A, Wagener JS, Hodgkins PS, Schechter MS. Frequency and costs of pulmonary exacerbations in patients with cystic fibrosis in the United States. Current medical research and opinion. 2017;33(4):667-74.
91. Flume PA, Suthoff ED, Kosinski M, Marigowda G, Quittner AL. Measuring recovery in health-related quality of life during and after pulmonary exacerbations in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2019;18(5):737-42.
92. Hassan M, Bonafede M, Limone B, Hodgkins P, Sawicki G. The burden of cystic fibrosis in the Medicaid population. Clinicoecon Outcomes Res. 2018;10:423-31.
93. de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax. 2011;66(8):680-5.
94. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report 2014;2015; Focus Theme: Early Graft Failure. The Journal of Heart and Lung Transplantation. 2015;34(10):1264-77.
95. UK Cystic Fibrosis Registry. 2020 Annual Data Report 2021 [Available from: https://www.cysticfibrosis.org.uk/sites/default/files/2022-03/2020%20Annual%20data%20report%20-%20Version%203.pdf accessed 09 May 2022].
96. Adler FR, Aurora P, Barker DH, Barr ML, Blackwell LS, Bosma OH, et al. Lung transplantation for cystic fibrosis. Proc Am Thorac Soc. 2009;6(8):619-33.
97. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th Adult Lung and Heart-Lung Transplant Report. The Journal of Heart and Lung Transplantation. 2012;31(10):1073-86.
98. Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: Pathophysiology, screening and diagnosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2019;18 Suppl 2:S3-s9.
99. CFC. Cystic Fibrosis Canada (CFC). The Canadian Cystic Fibrosis Registry. 2017 Annual Data Report. December 2018. Available at: https://www.cysticfibrosis.ca/uploads/Registry%20Report%202017/2017%20Registry%20Annual%20Data%20Report.pdf. 2018.
100. Litvin M, Nwachukwu S. Cystic Fibrosis Related Diabetes: a Unique Challenge in Diabetes Care. Mo Med. 2016;113(5):384-9.

101. Adler AI, Shine BSF, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. Diabetes Care. 2008;31(9):1789-94.
102. De Lisle RC, Borowitz D. The cystic fibrosis intestine. Cold Spring Harb Perspect Med. 2013;3(9):a009753-a.
103. Panagopoulou P, Fotoulaki M, Tsitouridis I, Nousia-Arvanitakis S. Soft tissue inflammation: Presenting feature of Crohn's disease in a cystic fibrosis adolescent. Journal of Cystic Fibrosis. 2007;6(5):366-8.
104. Maiuri L, Villella VR, Raia V, Kroemer G. The gliadin-CFTR connection: new perspectives for the treatment of celiac disease. Italian Journal of Pediatrics. 2019;45(1):40.
105. Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis: a review. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2013;28(6):676-83.
106. Derichs N. Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. European respiratory review : an official journal of the European Respiratory Society. 2013;22(127):58-65.
107. Peterson ML, Jacobs DR, Milla CE. Longitudinal Changes in Growth Parameters Are Correlated With Changes in Pulmonary Function in Children With Cystic Fibrosis. Pediatrics. 2003;112(3):588-92.
108. Zemel BS, Jawad AF, FitzSimmons S, Stallings VA. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. J Pediatr. 2000;137(3):374-80.
109. van Mourik IDM. Liver disease in cystic fibrosis. Paediatrics and Child Health. 2017;27(12):552-5.
110. Ciuca IM, Pop L, Tamas L, Taban S. Cystic fibrosis liver disease - from diagnosis to risk factors. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie. 2014;55(1):91-5.
111. Boëlle P-Y, Debray D, Guillot L, Clement A, Corvol H, Investigators obotFCMGS. Cystic Fibrosis Liver Disease: Outcomes and Risk Factors in a Large Cohort of French Patients. Hepatology. 2019;69(4):1648-56.
112. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of Mortality in Patients with Cystic Fibrosis. New England Journal of Medicine. 1992;326(18):1187-91.
113. ICER. Cystic Fibrosis: Public Comments. Available at: https://icer-review.org/material/cystic-fibrosis-public-comments/. 2018.
114. Exchange Rates UK. Euro to British Pound Spot Exchange Rates for 2015 2015 [Available from: https://www.exchangerates.org.uk/EUR-GBP-spot-exchange-rates-history-2015.html#:~:text=This%20is%20the%20Euro%20(EUR,rate%20in%202015%3A%200.7263%20GBP. accessed 22 August 2022].
115. Angelis A, Kanavos P, López-Bastida J, Linertová R, Nicod E, Serrano-Aguilar P. 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(1):428.
116. Ramagopalan S, Lambrelli D, Rubin J, Cox A, MacLachlan S. Predictors of Healthcare Costs for Cystic Fibrosis Patients in the United Kingdom. 15th Biennial

European Meeting at the Society for Medical Decision Making; 2014, June 8-10; Antwerp, Belgium2014.
117. Lieu TA, Ray GT, Farmer G, Shay GF. The Cost of Medical Care for Patients With Cystic Fibrosis in a Health Maintenance Organization. Pediatrics. 1999;103(6):e72-e.
118. Levy JF, Rosenberg MA, Farrell PM. Innovative assessment of inpatient and pulmonary drug costs for children with cystic fibrosis. Pediatr Pulmonol. 2016;51(12):1295-303.
119. British Lung Foundation. Cystic fibrosis statistics 2012 [Available from: https://statistics.blf.org.uk/cystic-fibrosis#:~:text=Emergency%20hospital%20admissions,-How%20do%20rates&text=Cystic%20fibrosis%20accounts%20for%209%2C500,patient%20than%20most%20lung%20diseases accessed 22 August 2022].
120. Dewitt EM, Grussemeyer CA, Friedman JY, Dinan MA, Lin L, Schulman KA, et al. Resource use, costs, and utility estimates for patients with cystic fibrosis with mild impairment in lung function: analysis of data collected alongside a 48-week multicenter clinical trial. Value Health. 2012;15(2):277-83.
121. ClinicalTrials.gov. NCT00446680: Long Term Administration of Inhaled Dry Powder Mannitol In Cystic Fibrosis - A Safety and Efficacy Study 2010 [Available from: https://clinicaltrials.gov/ct2/show/NCT00446680 accessed 06 October 2022].
122. ClinicalTrials.gov. NCT00630812: Long Term Administration of Inhaled Mannitol in Cystic Fibrosis 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT00630812 accessed 06 October 2022].
123. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (STA) Mannitol dry powder for inhalation for the treatment of cystic fibrosis. 2011.
124. Mitchell RM, Jones AM, Stocking K, Foden P, Barry PJ. Longitudinal effects of ivacaftor and medicine possession ratio in people with the Gly551Asp mutation: a 5-year study. Thorax. 2021;76(9):874-9.
125. Ruban C, Saunders W, Marino J. Cross-sectional analysis of cystic fibrosis related diabetes inpatient admissions in the United States. Value in Health. 2017;20(5):A346.
126. Hodgkins P, Ayyagari R, Guo J, Wagener J, O'Sullivan AK. Inpatient Burden Among Patients With Cystic Fibrosis Who Are Homozygous for The F508del Mutation. Value in Health. 2015;18(7):A672.
127. Vertex. Cost-Effectiveness Analyses for Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor (ELX/TEZ/IVA) for the Treatment of Patients Aged 6 Years and Older with Cystic Fibrosis and At Least One F508del-CFTR Mutation. Technical Report. Version: 2.0. Date: September 27, 2021 [Data on file]. 2021.
128. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technology Assessment. 2014;18(18):1-106.
129. Chevreul K, Michel M, Brigham KB, Lopez-Bastida J, Linertova R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with cystic fibrosis in Europe. The European journal of health economics : HEPAC : health economics in prevention and care. 2016;17 Suppl 1:7-18.
130. Exchange Rates UK. Euro to British Pound Spot Exchange Rates for 2016 2016 [Available from: https://www.exchangerates.org.uk/EUR-GBP-spot-exchange-rates-

history-2016.html#:~:text=Average%20exchange%20rate%20in%202016,GBP%20on%2005%20Jan%202016. accessed 22 August 2022].
131. Martin A. Evidence map of costs studies in cystic fibrosis since 2000. Value in Health. 2017;20(9):A643.
132. Targett KB, S; Nash, E; Murphy, E; Ayres, J; Devereux, G. Employment in adults with cystic fibrosis Occupational Medicines. 2014;64(2):87-94.
133. Vertex. Caregiver burden in cystic fibrosis: A systematic literature review. 2020.
134. Patel LG, C., Dixon C, Dyer K, Southern KW. Does administering a parent reported outcome measure during the annual review process improve the self efficacy of the carer of a child with CF? Pediatric Pulmonology. 2010;45:441.
135. Wyatt H, Ingram A, Wasiak R, Lambrelli D, Davies J, Bilton D, et al., editors. Genotype, disease severity, and healthcare resource use by patients with CF in the UK National Health Service. 36th European Cystic Fibrosis Conference; 2013; Lisbon, Portugal.
136. Chevreul K, Berg Brigham K, Michel M, Rault G. Costs and health-related quality of life of patients with cystic fibrosis and their carers in France. Journal of Cystic Fibrosis. 2015;14(3):384-91.
137. Szentpetery SEF, K., Christon LM. Relationship of caregiver depression and anxiety to pediatric cystic fibrosis health outcomes. Pediatric Pulmonology. 2018;53 432-3.
138. Castellani C, Duff AJ, Bell SC, Heijerman HG, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. Journal of cystic fibrosis. 2018;17(2):153-78.
139. Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, et al. International committee on mental health in cystic fibrosis: Cystic Fibrosis Foundation and European cystic fibrosis society consensus statements for screening and treating depression and anxiety. Thorax. 2016;71(1):26-34.
140. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. Journal of cystic fibrosis. 2009;8(2):91-6.
141. Sawicki GS, Tiddens H. Managing treatment complexity in cystic fibrosis: challenges and opportunities. Pediatr Pulmonol. 2012;47(6):523-33.
142. Jamieson N, Fitzgerald D, Singh-Grewal D, Hanson CS, Craig JC, Tong A. Children's experiences of cystic fibrosis: a systematic review of qualitative studies. Pediatrics. 2014;133(6):e1683-97.
143. Habib AR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. Annals of the American Thoracic Society. 2015;12(3):420-8.
144. Fitzgerald C, George S, Somerville R, Linnane B, Fitzpatrick P. Caregiver burden of parents of young children with cystic fibrosis. Journal of Cystic Fibrosis. 2018;17(1):125-31.
145. CFC. The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Available at: https://www.cysticfibrosis.ca/registry/2019AnnualDataReport.pdf. 2020.
146. CFF. About Cystic Fibrosis 2022 [Available from: https://www.cff.org/intro-cf/about-cystic-fibrosis accessed 04 July 2022].
147. Proesmans M. Best practices in the treatment of early cystic fibrosis lung disease. Ther Adv Respir Dis. 2017;11(2):97-104.

148. Hoo AF, Thia LP, Nguyen TT, Bush A, Chudleigh J, Lum S, et al. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. Thorax. 2012;67(10):874-81.
149. Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med. 2009;180(2):146-52.
150. National institute for Health and Care Excellence (NICE). Cystic fibrosis: diagnosis and management NICE guideline [NG78] 2017 [Available from: https://www.nice.org.uk/guidance/ng78 Accessed 14 April 2022].
151. NHS. Treatment-Cystic fibrosis 2021 [Available from: https://www.nhs.uk/conditions/cystic-fibrosis/treatment/ Accessed 13 April 2022].
152. Wallis C. Mucolytic therapy in cystic fibrosis. Journal of the Royal Society of Medicine. 2001;94 Suppl 40:17-24.
153. Merjaneh L, Hasan S, Kasim N, Ode KL. The role of modulators in cystic fibrosis related diabetes. J Clin Transl Endocrinol. 2021;27:100286-.
154. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013;1(8):630-8.
155. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017;5(2):107-18.
156. Chilvers MA, Davies JC, Milla C, Tian S, Han Z, Cornell AG, et al. Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study. The Lancet Respiratory Medicine. 2021;9(7):721-32.
157. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med. 2017;377(21):2013-23.
158. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. New England Journal of Medicine. 2015;373(3):220-31.
159. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2017;5(7):557-67.
160. Vertex. DOF Orkambi PASS IA3 2020.
161. Hoppe JE, Chilvers M, Ratjen F, McNamara JJ, Owen CA, Tian S, et al. Long-term safety of lumacaftor-ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. Lancet Respir Med. 2021;9(9):977-88.
162. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. Lancet Respir Med. 2019;7(4):325-35.
163. Flume P, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al., editors. An open-label extension study of tezacaftor/ivacaftor in patients aged ≥ 12 years with

cystic fibrosis homozygous for *F508del-CFTR* or heterozygous for *F508del-CFTR* and a residual function mutation. North American Cystic Fibrosis Conference; 2019 31 October-2 November 2019; Nashville, TN.
164. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. N Engl J Med. 2017;377(21):2024-35.
165. Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021;20(1):68-77.
166. Vertex. Data on File. REF-9272. 2021.
167. Vertex. Study 809-116: Clinical Study Report: A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 1.0, Protocol Number: VX16-809-116. 11 December 2019. 2019.
168. Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes. N Engl J Med. 2021;385(9):815-25.
169. Fajac I, Brunt K, Daines C, Durieu I, Goralski J, Heijerman H, et al. P221 Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508del and a minimal function mutation: results from a Phase 3 clinical study. Journal of Cystic Fibrosis. 2020;19:S118-S9.
170. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019;394(10212):1940-8.
171. Majoor C VBK, Daines C, et al. . Impact of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) triple combination therapy on health-related quality of life (HRQoL) in people with cystic fibrosis (pwCF) homozygous for F508del (F/F): results from a Phase 3 clinical study. . Journal of Cystic Fibrosis. 2020;19.
172. Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. The Lancet Respiratory Medicine. 2022;10(3):267-77.
173. Vertex. AURORA 6-11 OLE (Study 107): Clinical Study Protocol: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older. Version 2.0. Vertex Study Number: VX19-445-107. June 10, 2021. 2019.
174. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A Phase 3 Open-Label Study of ELX/TEZ/IVA in Children 6 Through 11 Years of Age With CF and at Least One *F508del* Allele. American Journal of Respiratory and Critical Care Medicine. 2021(12):1522-32.
175. Vertex. GALILEO (Study 445-116): Clinical Study Report: A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of

Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 1.0, Protocol Number VX19-445-116. 27 August 2021. 2021.
176. Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. Thorax. 2014;69(12):1090-7.
177. Majoor C, Brunt K, Daines C, Durieu I, Fajac I, Goralski J, et al. S66 Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis homozygous for F508del (F/F): results from a Phase 3 clinical study2021. A41-A2 p.
178. Kym PR, Wang X, Pizzonero M, Van der Plas SE. Chapter Four - Recent Progress in the Discovery and Development of Small-Molecule Modulators of CFTR. In: Witty DR, Cox B, editors. Progress in Medicinal Chemistry. 57: Elsevier; 2018. p. 235-76.
179. Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021;20(2):243-9.
180. UK Cystic Fibrosis Registry. Annual data report 2015 2016 [Available from: https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/2015%20Registry%20Annual%20Data%20Report%20v3.pdf accessed 09 May 2022].
181. Office for National Statistics. National life tables – life expectancy in the UK: 2018 to 2020 2021 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020 Accessed 12 January 2023].
182. Konstan MW, Wagener JS, Vandevanter DR, Pasta DJ, Yegin A, Rasouliyan L, et al. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2012;11(5):405-11.
183. Modi AC, Driscoll KA, Montag-Leifling K, Acton JD. Screening for symptoms of depression and anxiety in adolescents and young adults with cystic fibrosis. Pediatr Pulmonol. 2011;46(2):153-9.
184. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. The Lancet Respiratory Medicine. 2020;8(1):65-124.
185. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. Ann Am Thorac Soc. 2018;15(3):271-80.
186. Vertex. AURORA F/F (Study 103): Clinical Study Report: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del Mutation (F/F). Version 1.0, Protocol Number: VX17-445-103. 2019.
187. ClinicalTrials.gov. NCT03525574 (Study 105): A Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03525574.

188. Vertex. AURORA OLE (Study 445-105): Clinical Study Report: Week 144 Interim CSR: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation. Protocol Number: VX17-445-105. 27 June 2022. 2022.
189. ClinicalTrials.gov. NCT04058366: Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy 2023 [Available from: https://clinicaltrials.gov/ct2/show/NCT04058366 accessed 08 July 2022].
190. Chmiel J, Barry PJ, Colombo C, Wachter E, Fajac I, Mall MA, et al. P185 Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating or residual function mutation. Poster presented at the 36th Annual North American Cystic Fibrosis Conference; November 20222022.
191. Vertex. AURORA F/RF F/G OLE (Study 110): Clinical Study Report - Part A: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 1.0, Protocol Number: VX18-445-110. 31 August 2022. 2022.
192. NCT03525444. A Phase 3 Study of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF) 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT03525444?term=NCT03525444&draw=2&rank=1 [Accessed 29 April 2022].
193. Vertex. AURORA F/MF (Study 102): Clinical Study Protocol: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 3.0, Vertex Study Number: VX17-445-102. 19 July 2019 2018 [Available from: https://clinicaltrials.gov/ProvidedDocs/44/NCT03525444/Prot_000.pdf [Accessed 29 April 2022].
194. Vertex. AURORA F/MF (Study 445-102): Clinical Study Report: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 1.0, Protocol Number: VX17-445-102. 02 July 2019. 2019.
195. Vertex. AURORA F/F (Study 103): Clinical Study Protocol: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del Mutation (F/F). Version 3.0, Vertex Study Number: VX17-445-103. 19 July 2018 2018 [Available from: https://clinicaltrials.gov/ProvidedDocs/48/NCT03525548/Prot_000.pdf [Accessed 06 June 2022].
196. Vertex. AURORA F/RF F/G (Study 104): Clinical Study Protocol: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 2.0, Vertex Study Number: VX18-445-104. 02 December 2019 2019 [Available from:

https://clinicaltrials.gov/ProvidedDocs/53/NCT04058353/Prot_000.pdf [Accessed 04 May 2022].
197. Vertex. AURORA F/RF F/G OLE (Study 110): Clinical Study Protocol: A Phase 3, Open-label Study Evaluating the Long term Safety and Efficacy of VX 445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 1.1, Vertex Study Number: VX18-445-110. 2019.
198. (EMA) EMA. Assessment report - Kaftrio, EMA/385871/2020 Rev.1, Procedure No. EMEA/H/C/005269/0000. 10 July 2020 2020 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/kaftrio-epar-public-assessment-report_en.pdf [Accessed 13 July 2022].
199. Vertex. AURORA 6-11 (Study 445-106): Clinical Study Report: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age. Version 1.0, Protocol Number: VX18-445-106. 11 November 2020. 2020.
200. NCT03691779. Evaluation of VX 445/TEZ/IVA in Cystic Fibrosis Subjects 6 Through 11 Years of Age (AURORA 6-11 Part B) 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03691779 [accessed 18 May 2022].
201. Wainwright C, McColley SA, McNally P, Powers MR, Ratjen F, Rayment JH, et al. P163 Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in children 6 years and older with cystic fibrosis and at least one F508del allele: 96-week interim results from an open-label extension study. Poster presented at the 36th Annual North American Cystic Fibrosis Conference; November 20222022.
202. Vertex. AURORA 6-11 OLE (Study 445-107): Clinical Study Report: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of ELX/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who are 6 Years of Age and Older. Version 1.0, Protocol Number: VX19-445-107. 30 September 2022. 2022.
203. NCT04183790. Evaluation of Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04183790 accessed 08 July 2022].
204. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3B, Randomized, Placebo-Controlled Study. Am J Respir Crit Care Med. 2022.
205. Vertex. AURORA 6-11 (Study 106): Clinical Study Protocol: Evaluation of VX 445/TEZ/IVA in Cystic Fibrosis Subjects 6 Through 11 Years of Age (AURORA 6-11 Part B). Version 3.0, Vertex Study Number: VX18-445-106. 18 December 2019 2019 [Available from: https://clinicaltrials.gov/ProvidedDocs/79/NCT03691779/Prot_000.pdf [Accessed 18 May 2022].
206. Vertex. AURORA 6-11 OLE (Study 445-107): Statistical Analysis Plan (Methods): A Phase 3, Open label Study Evaluating the Long term Safety and Efficacy of ELX/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older. Version 1.0, Protocol Number: VX19-445-107. 18 December 2020. 2020.
207. ClinicalTrials.gov. NCT04353817 (Study 116): A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 Through 11 Years of Age With

Cystic Fibrosis and F/MF Genotypes 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04353817?term=NCT04353817&draw=2&rank=1 [Accessed 04 August 2022].
208. Vertex. GALILEO (Study 116): Clinical Study Protocol: A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 1.0, Vertex Study Number: VX19-445-116. 18 December 2019 2019 [Available from: https://clinicaltrials.gov/ProvidedDocs/17/NCT04353817/Prot_000.pdf [Accessed 04 August 2022].
209. ClinicalTrials.gov. NCT01807923: A Study of Lumacaftor in Combination With Ivacaftor in Cystic Fibrosis Subjects Aged 12 Years and Older Who Are Homozygous for the F508del-CFTR Mutation (TRAFFIC) 2015 [Available from: https://clinicaltrials.gov/ct2/show/NCT01807923 accessed 25 May 2022].
210. NCT01807949. A Study of Lumacaftor in Combination With Ivacaftor in Cystic Fibrosis Subjects Aged 12 Years and Older Who Are Homozygous for the F508del-CFTR Mutation (TRANSPORT) 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT01807949 Accessed 25 May 2022].
211. NCT01931839. A Phase 3 Rollover Study of Lumacaftor in Combination With Ivacaftor in Subjects 12 Years and Older With Cystic Fibrosis 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT01931839 accessed 31 May 2022].
212. European Medicines Agency. Orkambi Publication Details [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi accessed 08 May 2022].
213. NCT02514473. A Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects With CF, Homozygous for the F508del-CFTR Mutation 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT02514473 accessed 01 Septmeber 2022].
214. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR. American journal of respiratory and critical care medicine. 2017;195(7):912-20.
215. Vertex. Study 809-110: Clinical Study Report - Treatment Periods 1 and 2: A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 1.0, Protocol Number: VX15-809-110. 24 August 2020. 2020.
216. ClinicalTrials.gov. Study 809-110. NCT02544451. Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT02544451 accessed 23 September 2022].
217. NCT02797132. Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del 2018 [Available from: https://clinicaltrials.gov/ct2/show/NCT02797132 accessed 01 September 2022].
218. NCT03125395. A Rollover Safety Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR

Mutation 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT03125395 accessed 01 September 2022].
219. Vertex. Clinical Study Protocol VX15-809-115: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the 508del-CFTR Mutation 2017.
220. Vertex. Study 809-116 Clinical Study Protocol: A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 1.1 10 October 2016. 2016.
221. Vertex. EVOLVE (Study 661-106): Clinical Study Protocol: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 4.0, Vertex Study Number: VX14-661-106. 06 May 2016 [Available from: https://clinicaltrials.gov/ProvidedDocs/57/NCT02347657/Prot_000.pdf [Accessed 31 August 2022].
222. Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. Lancet Respir Med. 2021;9(7):733-46.
223. Vertex. EXTEND OLE (Study 661-110): Clinical Study Protocol: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation. Version 2.0, Vertex Study Number: VX14-661-110. 27 May 2016 [Available from: https://clinicaltrials.gov/ProvidedDocs/14/NCT02565914/Prot_000.pdf [Accessed 05 September 2022].
224. Vertex. EXTEND OLE (Study 661-110): Clinical Study Report - Interim Analysis 1: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long term Treatment With VX 661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation. Version 1.0, Protocol VX14 661 110. 02 June 2017. 2017.
225. NCT02392234. EXPAND (Study 108): Statistical Analysis Plan Methods: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function. Version 1.1, Protocol Number: VX14-661-108. 24 February 2017 2017 [Available from: https://clinicaltrials.gov/ProvidedDocs/34/NCT02392234/SAP_001.pdf [Accessed 02 September 2022].
226. NCT02347657. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor 2018 [Available from: https://clinicaltrials.gov/ct2/show/NCT02347657?term=NCT02347657&draw=2&rank=1 [Accessed 01 September 2022].
227. NCT02392234. EXPAND (Study 108): Clinical Study Protocol: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the

Efficacy and Safety of Ivacaftor and VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function. Version 3.0, Vertex Study Number: VX14-661-108. 10 June 2016 2016 [Available from: https://clinicaltrials.gov/ProvidedDocs/34/NCT02392234/Prot_000.pdf [Accessed 02 September 2022].
228. NCT02565914. A Study to Evaluate the Safety and Efficacy of Long Term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an F508del-CFTR Mutation 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT02565914?term=NCT02565914&draw=2&rank=1 [Accessed 05 September 2022].
229. Vertex. EMBRACE (Study 115): Clinical Study Protocol: A Phase 3, double-Blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination with Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous fpr the F508del-CFTR Mutation. Version 1.0, Vertex Study Number: VX16-661-115. 17 November 2017 [Available from: https://clinicaltrials.gov/ProvidedDocs/62/NCT03559062/Prot_000.pdf [Accessed 05 September 2022].
230. Vertex. MAGNIFY: Quality of Life for Cystic Fibrosis Patients Treated With OrkambiTM, SymkeviTM, or KaftrioTM and for Primary Caregivers in the United Kingdom (Interim Clinical Study Report). 27 October 2022. v 1.0. 2022.
231. Vertex. TRAJECTORY INTERIM CSR (Protocol VX20-CFD-005) A Longitudinal Study on the Impact of ELX/TEZ/IVA Treatment in Patients With Cystic Fibrosis in the Real WorldA Longitudinal Study on the Impact of ELX/TEZ/IVA Treatment in Patients With Cystic Fibrosis in the Real World. v 1.0. 2022.
232. Liou TG, Kartsonaki C, Keogh RH, Adler FR. Evaluation of a five-year predicted survival model for cystic fibrosis in later time periods. Scientific reports. 2020;10(1):1-11.
233. (EMA) EMA. Report of the workshop on endpoints for cystic fibrosis clinical trials. Last revised: November 29, 2012 2012 [Available from: https://www.ema.europa.eu/en/documents/report/report-workshop-endpoints-cystic-fibrosis-clinical-trials_en.pdf [Accessed 22 July 2022].
234. Liou TG, Elkin EP, Pasta DJ, Jacobs JR, Konstan MW, Morgan WJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2010;9(4):250-6.
235. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest. 2009;135(6):1610-8.
236. Griese M, Tullis E, Chilvers MA, Fabrizzi B, Raksha J, Legg J, et al. P170 Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One F508del Allele: 144-Week Interim Results From an Open-Label Extension Study. Poster presented at the 36th Annual North American Cystic Fibrosis Conference; November 20222022.
237. Vertex. AURORA F/RF F/G (Study 445-104): Clinical Study Report: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of Elexacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Are

Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 1.0, Protocol Number: VX18-445-104. 21 August 2020. 2020.
238. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, et al. Progression of Lung Disease in Preschool Patients with Cystic Fibrosis. Am J Respir Crit Care Med. 2017;195(9):1216-25.
239. Frauchiger BS, Binggeli S, Yammine S, Spycher B, Krüger L, Ramsey KA, et al. Longitudinal course of clinical lung clearance index in children with cystic fibrosis. Eur Respir J. 2021;58(1).
240. Kurz JM, Ramsey K, Kraemer R, Spycher B, Fischer Biner R, Latzin P, et al. Association of lung clearance index with survival in patients with cystic fibrosis. European Respiratory Journal. 2021.
241. Vertex. PROGRESS- Clinical Study Report: Protocol VX12-809-105 A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation v1.0 [data on file]. 2016.
242. Vertex. TRANSPORT: Clinical Study Report. Protocol VX12-809-104. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2014.
243. Vertex. TRAFFIC Clinical Study Report: Protocol VX12-809-103. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. V.1. 08 September 2014. 2014.
244. Vertex. Clinical Study Report: Protocol VX14-809-109: A Phase 3, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, homozygous for the F508del-CFTR Mutation. Version 1.0. 18 January 2017. 2017.
245. Vertex. Study 809-115: Clinical Study Report: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the 508del-CFTR Mutation. Version 1.0, Protocol Number: VX15-809-115. 05 January 2018. 2018.
246. Vertex. EVOLVE (Study 661-106): Clinical Study Report: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 1.0, Protocol VX14-661-106. 26 May 2017. 2017.
247. Vertex. EXPAND (Study 108): Clinical Study Report: A Phase 3, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function. Version 1.0, Protocol VX14-661-108. 09 June 2017. 2017.

248. Daly C, Ruane P, O'Reilly K, Longworth L, Vega-Hernandez G. Caregiver burden in cystic fibrosis: a systematic literature review. Ther Adv Respir Dis. 2022;16.
249. Vertex. Vertex Data on File – HEOR – CFQ-R-8D utilities derived from TRAJECTORY (VX20-CFD-005) IA1 REF-18262. 2022.
250. Vertex. NICE Interim Access Oversight committee VERTEX update 2022.
251. Vertex. VERTEX COMPLIANCE RATE REPORT: A report on the compliance rate of Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies. 2022.
252. Vertex. AURORA F/MF (Study 102): Statistical Analysis Plan (Methods): A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF). Version 1.0, Protocol Number: VX17-445-102. 25 September 2018 2018 [Available from: https://clinicaltrials.gov/ProvidedDocs/44/NCT03525444/SAP_001.pdf [Accessed 02 May 2022].
253. Vertex. AURORA F/F (Study 103): Statistical Analysis Plan (Methods): A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del Mutation (F/F). Version 1.0, Protocol Number: VX17-445-103. 25 September 2018 2018 [Available from: https://clinicaltrials.gov/ProvidedDocs/48/NCT03525548/SAP_001.pdf [Accessed 06 June 2022].
254. Vertex. AURORA F/RF F/G (Study 445-104): Statistical Analysis Plan (Methods): A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 2.0, Protocol Number: VX18-445-104. 22 June 2020 2020 [Available from: https://clinicaltrials.gov/ProvidedDocs/53/NCT04058353/SAP_001.pdf [Accessed 05 May 2022].
255. Vertex. EVOLVE (Study 661-106): Statistical Analysis Plan Methods: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of tezacaftor in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. Version 2.0, Vertex Study Number: VX14-661-106. 09 February 2017 [Available from: https://clinicaltrials.gov/ProvidedDocs/57/NCT02347657/SAP_001.pdf [Accessed 29 Aug 2022].
256. Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2014;13 Suppl 1:S23-42.
257. CFT. United Kingdom Cystic Fibrosis Trust (CFT). Nutritional Management of Cystic Fibrosis. September 2016. Available at: https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/consensus-documents. 2016.
258. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
259. Stanojevic S, Stocks J, Bountziouka V, Aurora P, Kirkby J, Bourke S, et al. The impact of switching to the new global lung function initiative equations on spirometry results in the UK CF registry. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2014;13(3):319-27.

260. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993;15(2):75-88.
261. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87.
262. Centers for Disease Control and Prevention NCfHS. CDC Growth Charts - Percentile Data Files with LMS Values 2009 [updated August 4, 2009. Available from: https://www.cdc.gov/growthcharts/percentile_data_files.htm [Accessed 09 September 2022].
263. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest. 2005;128(4):2347-54.
264. NCT04545515. A Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis (CF) Subjects 6 Years and Older and F/MF Genotypes 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04545515 accessed 08 July 2022].
265. NCT04362761. A Study Evaluating the Long-Term Safety of Elexacaftor Combination Therapy 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04362761 accessed 08 July 2022].
266. NCT04043806. A Study Evaluating the Long-term Safety of VX-445 Combination Therapy 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04043806 accessed 08 July 2022].
267. Lee S, Morton J, Chapman S, Hopkins E, Yeo A, Bussell L, editors. IS IMPULSE OSCILLOMETRY (IOS) BETTER THAN SPIROMETRY FOR MONITORING TREATMENT OUTCOMES IN CYSTIC FIBROSIS (CF) ADULTS ON ORKAMBI? A PILOT STUDY. RESPIROLOGY; 2020: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
268. Sawicki GS, Chilvers M, McNamara J, Naehrlich L, Saunders C, Sermet-Gaudelus I, et al. A Phase 3, open-label, 96-week trial to study the safety, tolerability, and efficacy of tezacaftor/ivacaftor in children ≥ 6 years of age homozygous for F508del or heterozygous for F508del and a residual function CFTR variant. Journal of Cystic Fibrosis. 2022;21(4):675-83.
269. NCT03537651. A Study to Evaluate the Safety and Efficacy of Long-term Treatment With TEZ/IVA in CF Subjects With an F508del CFTR Mutation 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03537651?term=NCT03537651&draw=2&rank=1 [Accessed 08 September 2022].
270. Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2016;15(4):416-23.
271. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med. 2018;379(17):1612-20.
272. Gustafsson PM, De Jong PA, Tiddens HAWM, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008;63(2):129.
273. Daines CL, Tullis E, Costa S, Linnemann RW, Mall MA, McKone EF, et al. Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One F508del Allele: 96-Week Interim Results From an Open-

Label Extension Study. Poster presented at the 35th Annual North American Cystic Fibrosis Conference (virtual)2021.
274. (EMA) EMA. Reflection paper on the use of extrapolation in the development of medicines for paediatrics 2018 [updated Last Revised: October, 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf [Accessed 20 October 2022].
275. Ollivier C, Mulugeta Y, Ruggieri L, Saint-Raymond A, Yao L. Paediatric extrapolation: A necessary paradigm shift. British Journal of Clinical Pharmacology. 2019;85(4):675-9.
276. (FDA) UFaDA. Clinical Investigation of Medicinal Products in the Pediatric Population 2000 [updated December 2000. Available from: https://www.fda.gov/media/71355/download [Accessed 20 October 2022].
277. Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. Lancet Respir Med. 2016;4(8):617-26.
278. McColley SA, Konstan MW, Ramsey BW, Stuart Elborn J, Boyle MP, Wainwright CE, et al. Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV(1). Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2019;18(1):94-101.
279. Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax. 2001;56(10):746-50.
280. Stahl M, Roehmel J, Eichinger M, Doellinger F, Nährlich L, Kopp M, et al. WS12.1 An exploratory study to determine the impact of lumacaftor/ivacaftor (LUM/IVA) on disease progression in children 2 through 5 years of age with cystic fibrosis homozygous for F508del-CFTR (F/F). Journal of Cystic Fibrosis. 2021;20:S22-S3.
281. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med. 2016;4(2):107-15.
282. Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med. 2018;6(7):545-53.
283. Schwarz C, Sutharsan S, Epaud R, Klingsberg RC, Fischer R, Rowe SM, et al. Tezacaftor/ivacaftor in people with cystic fibrosis who stopped lumacaftor/ivacaftor due to respiratory adverse events. Journal of Cystic Fibrosis. 2021;20(2):228-33.
284. Christopher F, Chase D, Stein K, Milne R. rhDNase therapy for the treatment of cystic fibrosis patients with mild to moderate lung disease. Journal of clinical pharmacy and therapeutics. 1999;24(6):415-26.
285. Suri R, Grieve R, Normand C, Metcalfe C, Thompson S, Wallis C, et al. Effects of hypertonic saline, alternate day and daily rhDNase on healthcare use, costs and outcomes in children with cystic fibrosis. Thorax. 2002;57(10):841-6.
286. Grieve R, Thompson S, Normand C, Suri R, Bush A, Wallis C. A cost-effectiveness analysis of rhDNase in children with cystic fibrosis. International journal of technology assessment in health care. 2003;19(1):71-9.

287. Iles R, Legh-Smith J, Drummond M, Prevost A, Vowler S. Economic evaluation of Tobramycin nebuliser solution in cystic fibrosis. Journal of Cystic Fibrosis. 2003;2(3):120-8.
288. Groen H, Van Der Bij W, Koeter GH, TenVergert EM. Cost-Effectiveness of Lung Transplantation in Relation to Type of End-Stage Pulmonary Disease. American Journal of Transplantation. 2004;4(7):1155-62.
289. Thornton J, Elliott R, Tully M, Dodd M, Webb A. Clinical and economic choices in the treatment of respiratory infections in cystic fibrosis: comparing hospital and home care. Journal of Cystic Fibrosis. 2005;4(4):239-47.
290. Woodward TC, Brown R, Sacco P, Zhang J. Budget impact model of tobramycin inhalation solution for treatment of Pseudomonas aeruginosa in cystic fibrosis patients. Journal of medical economics. 2010;13(3):492-9.
291. NICE. Mannitol dry powder for inhalation for treating cystic fibrosis [TA266] 2012 [Available from: https://www.nice.org.uk/guidance/ta266.
292. Tappenden P, Harnan S, Uttley L, Mildred M, Carroll C, Cantrell A. Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis: systematic review and economic model. Health technology assessment (Winchester, England). 2013;17(56):v-xvii.
293. Tappenden P, Harnan S, Uttley L, Mildred M, Walshaw M, Taylor C, et al. The cost effectiveness of dry powder antibiotics for the treatment of Pseudomonas aeruginosa in patients with cystic fibrosis. Pharmacoeconomics. 2014;32(2):159-72.
294. Sole A, Poveda J, Giron R, Prados M, De GJ, Casado M. Economic Impact Linked To the Reduction of Exacerbations When A Treatment Regime With Inhaled Antibiotics Is Switched To Aztreonam Lysine In Patients With Cystic Fibrosis and Chronic Pulmonary Infection Caused By Pseudomonas Aeruginosa. Value in Health. 2014;17(7):A526.
295. Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam lysine versus inhaled tobramycin in cystic fibrosis. An economic evaluation. Annals of the American Thoracic Society. 2015;12(7):1030-8.
296. Schultz NM, Daines CL, Malone DC. A Cost-Effectiveness Analysis Of Ivacaftor (Kalydeco®) For Treatment Of Cystic Fibrosis. B102 NOVEL APPROACHES TO UNDERSTAND AND IMPROVE HEALTH OUTCOMES: American Thoracic Society; 2015. p. A3713-A.
297. Schwenkglenks M, Toward T, Dooley B, Burns R, Adams E, Van Stiphout J. 133 Cost-effectiveness of dry-powder mannitol for inhalation as an add-on to best supportive care (BSC) in the treatment of adult cystic fibrosis (CF) patients in Ireland. Journal of Cystic Fibrosis. 2015;14:S91.
298. Dilokthornsakul P, Hansen RN, Campbell JD. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. European Respiratory Journal. 2016;47(6):1697-705.
299. Medic G, Westen M, Wille M, Hemels M. Cost-Effectiveness Of Levofloxacin Inhalation Solution Vs. Aztreonam Inhalation Solution In Cystic Fibrosis Patients In Belgium. Value in Health. 2016;19(7):A432.
300. Medic G, Franck-Larsson K, Wille M, Rodahl S, Hemels M. Cost-Effectiveness Of Levofloxacin Inhalation Solution Vs. Aztreonam Inhalation Solution And Tobramycin Dry Powder For Inhalation In Cystic Fibrosis Patients In Sweden. Value in Health. 2016;19(7):A431.

301. NICE. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [TA398] 2016 [Available from: https://www.nice.org.uk/guidance/ta398.
302. All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Ivacaftor (Kalydeco®) 150 mg film-coated tablets. Reference number:2680. 2017.
303. Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the long-term clinical and economic outcomes of lumacaftor/ivacaftor in cystic fibrosis patients with homozygous phe508del mutation. Value in Health. 2017;20(10):1329-35.
304. Graz M, Walker S, Alderson D, Morris J, Graz H, editors. EXPLORING ECONOMIC VALUE IN TREATING PSEUDOMONAS AERUGINOSA INFECTIONS IN CYSTIC FIBROSIS-EARLY MODELLING TO INFORM PRODUCT DEVELOPMENT2017: ELSEVIER SCIENCE INC 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.
305. Panguluri S, Gunda P, Debonnett L, Hamed K. Economic evaluation of tobramycin inhalation powder for the treatment of chronic pulmonary pseudomonas aeruginosa infection in patients with cystic fibrosis. Clinical Drug Investigation. 2017;37(8):795-805.
306. Sharma D, Xing S, Hung Y-T, Caskey RN, Dowell ML, Touchette DR. Cost-effectiveness analysis of lumacaftor and ivacaftor combination for the treatment of patients with cystic fibrosis in the United States. Orphanet journal of rare diseases. 2018;13(1):1-12.
307. Vadagam P, Kamal KM, Covvey JR, Giannetti V, Mukherjee K. Cost-effectiveness and budget impact of lumacaftor/ivacaftor in the treatment of cystic fibrosis. Journal of Managed Care & Specialty Pharmacy. 2018;24(10):987-97.
308. Lopez A, Rubin JL, Chandler C, Jena AB. PRO13 LIMITATIONS OF COST-EFFECTIVENESS METHODS WHEN ANALYZING LIFE-EXTENDING TREATMENTS FOR RARE, CHRONIC, GENETIC DISEASES: A CYSTIC FIBROSIS CASE STUDY. Value in Health. 2019;22:S337.
309. Rezaei S, Taheri S, Yousefi N, Peiravian F. PRS22 THE COST EFFECTIVENESS OF DORNASE ALFA VERSUS INHALED TOBRAMYCIN IN THE MANAGEMENT OF PATIENTS WITH CYSTIC FIBROSIS. Value in Health. 2019;22:S876.
310. Warren E, Morgan K, Toward TJ, Schwenkglenks M, Leadbetter J. Cost effectiveness of inhaled mannitol (Bronchitol®) in patients with cystic fibrosis. PharmacoEconomics. 2019;37(3):435-46.
311. Wherry K, Williamson I, Chapman RH, Kuntz KM. Cost-Effectiveness of Ivacaftor Therapy for Treatment of Cystic Fibrosis Patients With the G551D Gating Mutation. Value in Health. 2020;23(10):1332-9.
312. Langton Hewer SC, Smyth AR, Brown M, Jones AP, Hickey H, Kenna D, et al. Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and Pseudomonas aeruginosa infection: the TORPEDO-CF RCT. Health Technology Assessment. 2021;25(65).
313. Yang Y, Lopez A, Sawicki G, Van Brunt K, Ghizzi Pedra G, Rubin J, editors. J14 PROJECTED FIVE-YEAR CLINICAL OUTCOMES AND COST SAVINGS ASSOCIATED WITH USE OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR AND IVACAFTOR FOR THE TREATMENT OF PEOPLE WITH CYSTIC FIBROSIS AGED ≥6 YEARS IN THE US. Academy of Managed Care Pharmacy NEXUS; 2021.

314. Rubin JL, Lopez A, Booth J, Gunther P, Jena AB. Limitations of standard cost-effectiveness methods for health technology assessment of treatments for rare, chronic diseases: a case study of treatment for cystic fibrosis. Journal of Medical Economics. 2022(just-accepted):1-30.
315. Vega-Hernandez G, MacGregor G, Lopez A, Daly C, Rubin J. PRS2 Modelling Survival of People with Cystic Fibrosis (PWCF) Aged≥ 12 YEARS Heterozygous for the F508DEL Mutation with a Minimal Function Mutation Treated with Ivacaftor/Tezacaftor/Elexacaftor and Ivacaftor (IVA/TEZ/ELX). Value in Health. 2021;24:S213.
316. Vega-Hernandez G, MacGregor G, Lopez A, Daly C, Rubin J. PRS31 Modelling Survival of People with Cystic Fibrosis (PWCF) Aged≥ 12 YEARS Homozygous for the F508DEL Mutation Treated with Ivacaftor/Tezacaftor/Elexacaftor and Ivacaftor (IVA/TEZ/ELX). Value in Health. 2021;24:S218.
317. Lopez A, Ghizzi Pedra G, Sawicki G, Van Brunt K, Yang Y, Rubin J, editors. J15 MODELED SURVIVAL GAINS FOR PEOPLE WITH CYSTIC FIBROSIS AGED ≥6 YEARS HETEROZYGOUS FOR THE F508DEL MUTATION WITH A MINIMAL FUNCTION MUTATION IN THE US TREATED WITH ELEXACAFTOR/TEZACAFTOR/IVACAFTOR AND IVACAFTOR. Academy of Managed Care Pharmacy NEXUS; 2021.
318. Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. Journal of Cystic Fibrosis. 2023.
319. Lopez A, Booth J, Bailey E, Ektare V, Rubin-Cahill J, editors. J16 Modeled Survival Gains and Cost-Effectiveness of Trikafta (Elexacaftor/Tezacaftor/Ivacaftor) in the Treatment of Patients with Cystic Fibrosis in the US. Academy of Managed Care Pharmacy; 2020.
320. Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. Ther Adv Respir Dis. 2019;13.
321. Lopez A, Suthoff E, Chandler C, Liou T, Konstan M, Pelligra C, et al. Modeled Survival Gains of Patients with Cystic Fibrosis (CF) Aged≥ 12 Years Homozygous for the F508dEL Mutation Treated with the CF Transmembrane Conductance Regulator Modulator (CFTRM) Tezacaftor/Ivacaftor (TEZ/IVA). Value in Health. 2018;21:S205.
322. Lopez A, Yang Y, Loop B, Chandler C, Liou T, Konstan M, et al. PRS16-MODELED SURVIVAL GAINS OF PATIENTS WITH CYSTIC FIBROSIS (CF) AGED≥ 12 YEARS HETEROZYGOUS FOR F508DEL-CFTR AND A RESIDUAL FUNCTION MUTATION (F508DEL/RF) TREATED WITH THE CF TRANSMEMBRANE CONDUCTANCE REGULATOR MODULATOR (CFTRM) TEZACAFTOR/IVACAFTOR (TEZ/IVA). Value in Health. 2018;21:S406.
323. Hu X, Yang Y, Konstan M, Tichy E, Gani R, Rubin-Cahill J, editors. J15 Modeling Survival and Long-Term Health Outcomes of Patients with Cystic Fibrosis Aged ≥6 Years Homozygous for the F508del-CFTR Mutation Treated with Tezacaftor/Ivacaftor. Academy of Managed Care Pharmacy; 2020.
324. Vertex. Data on File. REF-9828. 2021.
325. Vertex. Study 661-110: Clinical Study Report - Part A: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation. Version 1.0, Protocol Number: VX14-661-110. 24 October 2019. 2019.

326. Vertex. Study 661-115: Clinical Study Report: A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation. Version 1.0, Protocol Number: VX14-661-115. 15 May 2019. 2019.
327. Bessonova L, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. Thorax. 2018;73(8):731-40.
328. Volkova N, Evans J, Higgins M, Campbell D, Tian S, Simard C, et al. IPD2.02 Real-world outcomes in patients with CF treated with ivacaftor: 2016 US and UK CF Registry analyses. Journal of Cystic Fibrosis. 2018;17:S54.
329. Walker S, Flume P, McNamara J, Solomon M, Chilvers M, Chmiel J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. Journal of Cystic Fibrosis. 2019;18(5):708-13.
330. UK CF Registry Trust. 2018 Genotype Data by Nation and Age: Number of individuals eligible by genotype for CFTR modulating therapy in each nation of the UK, defined by centre attended. 2020.
331. Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. European Respiratory Journal. 2014;43(1):125-33.
332. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. New England Journal of Medicine. 2011;365(18):1663-72.
333. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. American journal of respiratory and critical care medicine. 2013;187(11):1219-25.
334. De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis. 2014;13(6):674-80.
335. Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, et al. Efficacy and safety of ivacaftor treatment: randomized trial in subjects with cystic fibrosis who have an R117H-CFTR mutation. The Lancet Respiratory Medicine. 2015;3(7):524-33.
336. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. The Lancet. 2003;361(9370):1671-6.
337. Sawicki GS, McKone EF, Millar SJ, Pasta DJ, Konstan MW, Lubarsky B, et al. Patients with cystic fibrosis and a G551D or homozygous F508del mutation: similar lung function decline. American journal of respiratory and critical care medicine. 2017;195(12):1673-6.
338. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. Journal of Cystic Fibrosis. 2020;19(1):68-79.
339. Knox C, Han Z, Wu R, Wang LT, Elbert A, Tian S. WS12-3 Real-world outcomes among patients with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA) in 2017: an interim analysis of data from the US CF Foundation Patient Registry (CFFPR). Journal of Cystic Fibrosis. 2019;18:S22-S3.
340. Vertex. Data on File. REF-0656. 2018.

341. Gaines H, Jones KR, Lim J, Medhi NF, Chen S, Scofield RH. Effect of CFTR modulator therapy on cystic fibrosis-related diabetes. Journal of Diabetes and its Complications. 2021;35(6).
342. Vertex. Data on File. REF-7071. 2020.
343. Vertex. Data on File. REF-7152. 2020.
344. Vertex. Data on File. REF-7153. 2020.
345. Vertex. Indirect Treatment Comparisons in F/F patients aged 6 through 11 years. 2021.
346. Vertex. Data on File. REF-10409. 2021.
347. Vertex. Data on File. REF-6058. 2020.
348. Sawicki GS, Konstan MW, McKone EF, Moss RB, Lubarsky B, Suthoff E, et al. Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation. Pulmonary Therapy. 2022:1-11.
349. Sawicki GS, Van Brunt K, Booth J, Bailey E, Millar S, Konstan M, et al. Burden of Illness in People ≥12 Years of Age With Cystic Fibrosis Heterozygous for the F508del Mutation and a Minimal Function Mutation. 33rd Annual North American Cystic Fibrosis Conference; 2019, October 31-November 2 Nashville, TN.2019.
350. Harun SN, Wainwright C, Klein K, Hennig S. A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. Paediatric respiratory reviews. 2016;20:55-66.
351. Leung GJ, Cho TJ, Kovesi T, Hamid JS, Radhakrishnan D. Variation in lung function and nutritional decline in cystic fibrosis by genotype: An analysis of the Canadian cystic fibrosis registry. Journal of Cystic Fibrosis. 2020;19(2):255-61.
352. Lee T, Sawicki GS, Altenburg J, Millar SJ, Geiger JM, Jennings MT, et al. Effect of Elexacaftor/Tezacaftor/Ivacaftor on Annual Rate of Lung Function Decline in People With Cystic Fibrosis. Journal of Cystic Fibrosis. 2022.
353. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. American journal of respiratory and critical care medicine. 2015;192(7):836-42.
354. Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, et al. Real-world outcomes of ivacaftor treatment in people with cystic fibrosis: a systematic review. Journal of clinical medicine. 2021;10(7):1527.
355. Bower JK, Tian S, Zahigian R, Sewall A, Wu R, Elbert A. WS13. 1 Disease progression in F508del homozygous (F/F) persons with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA): interim results of a long-term safety study using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Journal of Cystic Fibrosis. 2020;19:S21.
356. Bourgani E, Stagaki E, Gioka M, Nakou A, Antonogiannaki E-M, Papadopoulos D, et al. P267 Two years' experience of lumacaftor/ivacaftor treatment at an adult cystic fibrosis centre in Athens, Greece. Journal of Cystic Fibrosis. 2019;18:S132.
357. Collet C, Bui S, Mittaine M, Bremont F, Galode F, Fayon M. P025 Lumacaftor/ivacaftor in real life for Phe508del homozygous, adolescents with severe and normal lung function. Journal of Cystic Fibrosis. 2018;17:S66.
358. Ejiofor LCK, Mathiesen IHM, Jensen-Fangel S, Olesen HV, Skov M, Philipsen LKD, et al. Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment. Pediatric Pulmonology. 2020;55(12):3364-70.

359. Loukou I, Moustaki M, Plyta M, Douros K. Longitudinal changes in lung function following initiation of lumacaftor/ivacaftor combination. Journal of Cystic Fibrosis. 2020;19(4):534-9.
360. Muilwijk D, Zomer DD, Gulmans VAM, van der Ent CK. P055 Real-world trends in long-term clinical outcomes of lumacaftor/ivacaftor. Journal of Cystic Fibrosis. 2020;19:S70-S1.
361. Tong K, Barker D, France M, Burr L, Greville H, Visser S, et al. Lumacaftor/ivacaftor reduces exacerbations in adults homozygous for Phe508del mutation with severe lung disease. Journal of Cystic Fibrosis. 2020;19(3):415-20.
362. Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. The Journal of pediatrics. 2007;151(2):134-9.
363. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). The lancet Respiratory medicine. 2014;2(11):902-10.
364. Vertex. Real-World Effects and Utilisation Patterns of Elexacaftor, Tezacaftor, and Ivacaftor Combination Therapy (ELX/TEZ/IVA) in Patients with Cystic Fibrosis (CF). Interim Study Report 1. 2021.
365. Dwight M, Marshall B. CFTR modulators: transformative therapies for cystic fibrosis. Journal of Managed Care & Specialty Pharmacy. 2021;27(2):281-4.
366. Vertex. Study 770-103: Clinical Study Report: A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551D Mutation. Version 2.0, Protocol Number: VX08-770-103. 29 March 2012. 2012.
367. Vertex. Data on File. REF-4977. 2020.
368. Vertex. Data on File. REF-11003. 2021.
369. Vertex. Data on File. VXR-CA-02-00267. 2015.
370. Vertex. Data on File. REF-4983. 2018.
371. ONS. Office for National Statistics. National life tables: England and Wales 2021 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables.
372. UK CF Registry Trust. 2008 Annual Data Report. 2009.
373. McGarry L, Lopez A, Chandler C, Pelligra C, Alkhateeb Z, Rubin JL, et al. MS1 Validation of modeled 5-year survival outcomes among patients with cystic fibrosis (CF) treated with the CF transmembrane conductance regulator modulator (CFTRM) ivacaftor using US CF Foundation Patient Registry (USCFFPR) data. Value in Health. 2020;23:S8.
374. Ishak KJ, Kreif N, Benedict A, Muszbek N. Overview of parametric survival analysis for health-economic applications. Pharmacoeconomics. 2013;31(8):663-75.
375. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8(1):1-16.
376. Vertex. Data on File. REF-5028. 2017.
377. Liou TG, Adler FR. WS18. 4 Five-year survivorship in cystic fibrosis: Outcomes improve but the disease remains the same. Journal of Cystic Fibrosis. 2015;14:S33.

378. Ooi CY, Dupuis A, Ellis L, Jarvi K, Martin S, Gonska T, et al. Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language? Thorax. 2012;67(7):618-24.
379. Buzzetti R, Alicandro G, Minicucci L, Notarnicola S, Furnari ML, Giordano G, et al. Validation of a predictive survival model in Italian patients with cystic fibrosis. Journal of Cystic Fibrosis. 2012;11(1):24-9.
380. Aaron SD, Stephenson AL, Cameron DW, Whitmore GA. A statistical model to predict one-year risk of death in patients with cystic fibrosis. Journal of clinical epidemiology. 2015;68(11):1336-45.
381. Fleurence RL, Hollenbeak CS. Rates and Probabilities in Economic Modelling. Pharmacoeconomics. 2007;25(1):3-6.
382. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American statistical association. 1958;53(282):457-81.
383. Vertex. Study 445-109: Clinical Study Report: A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del. Version 1.0, Protocol Number: VX18-445-109. 16 October 2020. 2020.
384. Vertex. Study 770-102: Clinical Study Report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects with Cystic Fibrosis and the G551D Mutation. Version 2.0, Protocol Number: VX08-770-102. 17 August 2011. 2011.
385. Vertex. Data on File. VXR-HQ-88-00032. 2016.
386. Vertex. Data on File. REF-8667. 2021.
387. Suthoff ED, Bonafede M, Limone B, O'Callaghan L, Sawicki GS, Wagener JS. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. Journal of Medical Economics. 2016;19(9):845-51.
388. Sutton S, Hayden J, Howlett M, Davies J, Fleming A, Elnazir B, et al. ePS6. 10 A real-world study evaluating the impact of elexacaftor/tezacaftor/ivacaftor treatment on medication adherence in cystic fibrosis. Journal of Cystic Fibrosis. 2022;21:S60.
389. Witt E, Broadus A, McElya B, Hira N, Kirkham H. 232: Cystic fibrosis transmembrane conductance regulator modulator adherence across age groups in pharmacy data. Journal of Cystic Fibrosis. 2021;20:S112.
390. Vertex. Data on File. VXR-HQ-88-00029. 2016.
391. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. Transplantation. 1998;66(7):951-6.
392. Royal Brompton Hospital. Clinical Guidelines: Care of Children with Cystic Fibrosis 2017; 7th Edition. 2017.
393. ISHLT. Adult Lung Transplantation Statistics 2019 [Available from: https://ishltregistries.org/registries/slides.asp?yearToDisplay=2019.
394. Wojtaszczyk A, Glajchen M, Portenoy RK, Berdella M, Walker P, Barrett M, et al. Trajectories of caregiver burden in families of adult cystic fibrosis patients. Palliative & Supportive Care. 2018;16(6):732-40.
395. Suthoff E, Mainz JG, Cox DW, Thorat T, Grossoehme DH, Fridman M, et al. Caregiver Burden Due to Pulmonary Exacerbations in Patients with Cystic Fibrosis. The Journal of Pediatrics. 2019;215:164-71.
396. Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997:1095-108.

397. Solem CT, Vera-Llonch M, Tai M, O'Callaghan L. Pulmonary Exacerbations, Lung Dysfunction, And Eq-5d Measures In Adolescents And Adults With Cystic Fibrosis And Homozygous For The F508del-Cftr Mutation. Value in Health. 2016;19(3):A116-A7.
398. Solem CT, Vera-Llonch M, Liu S, Botteman M, Lin FJ, Castiglione B. Impact of pulmonary exacerbations on Eq-5d measures in patients with cystic fibrosis. Value in Health. 2014;17(7):A535.
399. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health and quality of life outcomes. 2016;14(1):1-9.
400. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. 2014.
401. Vertex. Data on File. REF-5026. 2018.
402. Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. Quality of Life Research. 2012;21(7):1267-78.
403. Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. Health and quality of life outcomes. 2015;13(1):1-11.
404. Rees J, Clarke MG, Waldron D, O'Boyle C, Ewings P, MacDonagh RP. The measurement of response shift in patients with advanced prostate cancer and their partners. Health and Quality of Life Outcomes. 2005;3(1):1-8.
405. Wahl AK, Rustøen T, Hanestad BR, Gjengedal E, Moum T. Living with cystic fibrosis: impact on global quality of life. Heart & Lung. 2005;34(5):324-31.
406. Acaster S, Mukuria C, Rowen D, Brazier J, Wainwright C, Quon B, et al. Development of the cystic fibrosis questionnaire-revised preference based scoring algorithm. Pediatric Pulmonology. 2019;54(S2):S443-S.
407. Vertex. Clinical Study Report IA1: Protocol VX20-CFD-005. 2022.
408. Vertex. Clinical Study Report IA1: Protocol VX20-CFD-004. 2022.
409. Vertex. Key Results Memo: RWE Study of Users of ELX/TEZ/IVA, LUM/IVA and TEZ/IVA in the UK Using UKCFR Data - IA2 (NICE Data Collection Agreement). 2022.
410. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. Journal of clinical epidemiology. 1998;51(11):1115-28.
411. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.
412. Brazier J, Czoski-Murray C, Roberts J, Brown M, Symonds T, Kelleher C. Estimation of a preference-based index from a condition-specific measure: the King's Health Questionnaire. Medical Decision Making. 2008;28(1):113-26.
413. Yang Y, Brazier J, Tsuchiya A, Coyne K. Estimating a preference-based single index from the Overactive Bladder Questionnaire. Value in Health. 2009;12(1):159-66.
414. Rowen D, Brazier J, Young T, Gaugris S, Craig BM, King MT, et al. Deriving a preference-based measure for cancer using the EORTC QLQ-C30. Value in Health. 2011;14(5):721-31.
415. Mulhern B, Labeit A, Rowen D, Knowles E, Meadows K, Elliott J, et al. Developing preference-based measures for diabetes: DHP-3D and DHP-5D. Diabetic Medicine. 2017;34(9):1264-75.

416. Mukuria C, Rowen D, Brazier JE, Young TA, Nafees B. Deriving a preference-based measure for myelofibrosis from the EORTC QLQ-C30 and the MF-SAF. Value in Health. 2015;18(6):846-55.
417. Brazier J, Rowen D. NICE DSU Technical Support Document 11: Alternatives to EQ-5D for Generating Health State Utility Values [Internet]. 2011.
418. Acaster S, Mukuria C, Rowen D, Brazier JE, Wainwright CE, Quon BS, et al. Development of the CFQ-R-8D: Estimating Utilities From the Cystic Fibrosis Questionnaire-Revised. Value in Health. 2022.
419. Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. European Respiratory Journal. 2013;41(3):571-7.
420. Tappenden P, Sadler S, Wildman M. An early health economic analysis of the potential cost effectiveness of an adherence intervention to improve outcomes for patients with cystic fibrosis. Pharmacoeconomics. 2017;35(6):647-59.
421. Gee L, Abbott J, Conway SP, Etherington C, Webb AK. Validation of the SF-36 for the assessment of quality of life in adolescents and adults with cystic fibrosis. Journal of Cystic Fibrosis. 2002;1(3):137-45.
422. Solem C, LLonch MV, Liu S, Botteman M, Lasch K, Rodriguez S, et al. Responsiveness of the Eq-5D index and visual analog scale to changes in lung function in patients with cystic fibrosis. Value in Health. 2014;17(3):A178.
423. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. An economic evaluation of lung transplantation. The Journal of thoracic and cardiovascular surgery. 2002;123(3):411-20.
424. Vertex. Data on File. REF-19105. HEOR – CFQ-R-8D treatment-specific utility increment for ELX/TEZ/IVA (F/MF). 2023.
425. Vertex. Data on File. REF-19112. HEOR – CFQ-R-8D treatment-specific utility increment for TEZ/IVA (F/RF). 2023.
426. Van Brunt K, Gwaltney C, Kaley D, Krupnick R, Phinney M, Bailey E, et al. 285: Impact of treatment with elexacaftor/tezacaftor/ivacaftor and ivacaftor in people with cystic fibrosis and caregivers in the United States: A qualitative study. Journal of Cystic Fibrosis. 2021;20:S137-S8.
427. Lambrelli D, Wasiak R, Ingram A, Harrow B, Becker C, Eriksson D, et al. PRS46 Health Care Resource Use of Patients With Cystic Fibrosis (CF) in the UK. Value in Health. 2012;15(7):A567-A8.
428. Simmonds NJ, van der Ent CK, Colombo C, Kinnman N, DeSouza C, Thorat T, et al. VOCAL: An observational study of ivacaftor for people with cystic fibrosis and selected non–G551D-CFTR gating mutations. Journal of Cystic Fibrosis. 2022.
429. NHS. National Cost Collection for the NHS. 2020/21 National Cost Collection data [
430. PSSRU. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021 2021 [
431. ONS. Office for National Statistics. Consumer price inflation time series [Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/datasets/consumerpriceindices.
432. BNF. British National Formulary [Available from: https://bnf.nice.org.uk.
433. Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The impact of patent expiry on drug prices: a systematic literature review. Applied health economics and health policy. 2018;16:653-60.

434. Mycka JM, Dellamano R, Kolassa EM, Wonder M, Ghosh S, Hay JW, et al. Good research practices for measuring drug costs in cost effectiveness analyses: an industry perspective: the ISPOR drug cost task force report—Part V. Value in Health. 2010;13(1):25-7.
435. Neumann PJ, Podolsky MI, Basu A, Ollendorf DA, Cohen JT. Do cost-effectiveness analyses account for drug genericization? A literature review and assessment of implications. Value in Health. 2022;25(1):59-68.
436. Kanavos P. Measuring performance in off-patent drug markets: a methodological framework and empirical evidence from twelve EU Member States. Health Policy. 2014;118(2):229-41.
437. Bessonova L, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, et al. 411 Disease progression in patients (pts) with cystic fibrosis (CF) treated with ivacaftor (IVA): analysis of real-world data from the UK CF Registry. Journal of Cystic Fibrosis. 2017;1(16):S167.
438. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU report.; 2022.
439. VanDevanter DR, Konstan MW. Outcome measures for clinical trials assessing treatment of cystic fibrosis lung disease. Clinical investigation. 2012;2(2):163.
440. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. Thorax. 2016;71(5):454-61.
441. Sanders DB, Chmiel JF. Drug development for cystic fibrosis. Pediatric Pulmonology. 2021;56:S10-S22.
442. Davies JC, Drevinek P, Elborn JS, Kerem E, Lee T, Amaral MD, et al. Speeding up access to new drugs for CF: Considerations for clinical trial design and delivery. Journal of Cystic Fibrosis. 2019;18(5):677-84.
443. De Boeck K, Lee T, Amaral M, Drevinek P, Elborn JS, Fajac I, et al. Cystic fibrosis drug trial design in the era of CFTR modulators associated with substantial clinical benefit: stakeholders' consensus view. Journal of Cystic Fibrosis. 2020;19(5):688-95.
444. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, et al. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. American journal of respiratory and critical care medicine. 2011;183(6):752-8.
445. Vermeulen F, Proesmans M, Boon M, Havermans T, De Boeck K. Lung clearance index predicts pulmonary exacerbations in young patients with cystic fibrosis. Thorax. 2014;69(1):39-45.
446. Pharmacoeconomics NCf. NCPE Pharmacoeconomic Annual Symposium, October 21st 2022, Morning Session, HTA Troubleshooting, Case Study 1, Slide 108. 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Clarification questions

PART 1

March 2023

File name	Version	Contains confidential information	Date
ID3834 EAG Clarification Questions	1.0	Yes	April to June 2023

Clarification Questions

Section A: Clarification on effectiveness data

Requests for further data/publications

A1. A press release published on the Vertex website suggested two posters were presented at the 2022 North American Cystic Fibrosis Conference. The EAG was unable to find these abstracts, despite searching the conference abstract book. Please provide the following abstracts, and please also provide any others reports or CSRs associated with these studies.

a. #693: Data from an investigational Phase 3 open-label study designed to evaluate the safety, pharmacokinetics and efficacy of TRIKAFTA in children 2 through 5 years of age with CF and at least one F508del allele

b. #694: A pooled analysis from multiple Phase 3 studies with CFTR modulators evaluating how the restoration of CFTR-mediated chloride transport, as reflected by changes in sweat chloride concentration, impacts clinical outcomes in people with CF treated with CFTR modulators

The posters referred to were submitted as late breakers to the 2022 North American Cystic Fibrosis Conference and were therefore not included in the conference booklet. Study 445-111 manuscript has now been published and is attached in the references folder.

A2. The EAG included the following study from its SLR: VX20-445-111 / NCT04537793. Data from this study are published on the EU Clinical Trials Register, but several clinical outcomes that were reported as collected on the NCT04537793 recorded were not reported, including absolute change in sweat chloride and $LCI_{2.5}$. Please provide these outcome data, and any CSR associated with the study.

Study 445-111 manuscript has now been published and is attached in the references folder. The CSR for study VX20-445-111 is attached in NICE Docs and is to be treated commercially confidential.

A3. The EAG notes that only limited baseline characteristics were reported for the F/Gating subgroup of studies considered for evidence synthesis in F/Gating population aged ≥12 years (AURORA, STRIVE, KONNECTION, KONDUCT). Please provide an updated Table 39 of Appendix D of these baseline characteristics, including: geographic region, prior treatment history data and *Pseudomonas aeruginosa*-positive within previous 2 years for these subgroups.

Unfortunately, the requested baseline characteristics by genotype (i.e., comparator cohort) in study 445-104, or by subgroups defined by age and genotype (F/G551 in STRIVE; patients aged ≥12 years old at screening with F/non-G551D gating genotype in KONNECTION; and patients aged ≥12 years old at screening with F/R117H genotype in KONDUCT) could not be obtained within the time frame of these clarification questions.

Results of subgroup analyses suggest that geographic region and P. aeruginosa infection at baseline are not likely to be strong modifiers of the treatment effect on ppFEV1. For example, the post-hoc subgroup analysis of between-group treatment differences in ppFEV1 through Week 8 with IVA/TEZ/ELX vs active control (IVA or TEZ-IVA) yielded the LS mean difference (95% confidence interval) of 3.3 (1.6 to 5.1) and 3.5 (1.8 to 5.3) in North America and Europe, respectively (1). Similarly, the efficacy of IVA with respect to the change from baseline through Week 48 in ppFEV1 in STRIVE (770-102) was statistically significant and similar in magnitude across the geographic regions [9.0 ($p<0.001$), 9.9 ($p<0.001$) and 11.9 ($p=0.008$)] in North America, Europe and Australia, respectively (2). The treatment effect of IVA vs PBO on ppFEV1 in KONDUCT (770-110) was very similar in Europe and North America [4.81 (-0.071 to 9.69) in North America and 4.51 (-3.67 to 12.7) in Europe] and was also consistent across patients who were positive [4.32 (-1.25 to 9.88)] or negative [5.73 (0.27 to 11.20)] for P. aeruginosa at baseline (3). The only exception was the subgroup analyses of primary and secondary endpoints in KONNECTION (770-111), which revealed that subjects in Europe generally had larger treatment differences than subjects in North America (11.76 vs 6.13 for ppFEV1) with both responses statistically significant ($p <0.05$). Subjects who had P. aeruginosa infection at baseline had larger treatment differences in favour of IVA in BMI (approximately 2-fold increase in

treatment difference vs PBO), BMI-for-age z-score (approximately 4-fold increase in treatment difference vs PBO), and CFQ-R respiratory domain score (approximately 3-fold increase in treatment difference versus PBO) than subjects who were negative for P. aeruginosa at baseline (4).

A4. It is unclear which file: “345. Vertex. Indirect Treatment Comparisons in F/F patients aged 6 through 11 years. 2021”, is referring to in the CS references, and the EAG has been unable to locate the file. Please provide the name of this file in the reference pack, or, if it is missing, please provide the file.

Reference 345 refers to the file “Vertex_2021_ITC_FF 6-11” in the reference pack.

A5. Please provide the CSRs for the following studies: VX16-809-122, VX20-445-111, Study 770-110 and Study 770-111.

Please see the accompanying reference file.

Decision problem and treatment pathway

A6. Table 1 of the CS contains the draft scope issued by NICE, rather than the final scope. Please update Table 1 to include the final scope issued by NICE. Please also provide any updates to the two remaining columns that follow from this change.

Table 1 of the CS has been revised per Table 1 below. There were two additional outcomes in the final scope versus the draft scope i.e. forced vital capacity and sweat chloride.

Table 1. Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	• Ivacaftor, tezacaftor and elexacaftor combination therapy (Kaftrio) • Tezacaftor and ivacaftor combination therapy (Symkevi) • Lumacaftor and ivacaftor combination therapy (Orkambi)	Same	
Population	PwCF with at least one *F508del* mutation	Same	
Subgroups	People who are • homozygous for the *F508del* mutation, or • heterozygous for the *F508del* mutation and a residual function mutation	PwCF with at least one *F508del* mutation in the *CFTR* gene are in scope.	It is not relevant or appropriate to consider subgroups within CF since all CF patients within the licensed indications will benefit clinically from the indicated CFTR modulator (as demonstrated for example for IVA/TEZ/ELX in Middleton et al., 2019) (5).
Comparator(s)	• Established clinical management (ECM) including o best supportive care o mannitol dry powder for inhalation o inhaled mucolytics o nebulised hypertonic saline o anti-inflammatory agents o bronchodilators o vitamin supplements o pancreatic enzymes • The interventions will be compared to each other	**Relevant comparators for IVA/TEZ/ELX:** **In pwCF aged 6 years or older who are homozygous for the *F508del* mutation:** • ECM without IVA/TEZ/ELX **In pwCF aged 6 years or older who are heterozygous for the *F508del* mutation:** • ECM without IVA/TEZ/ELX for those heterozygous for the *F508del* mutation with one of the specified licensed minimal function mutations (F/MF) or one of the specified licensed residual function mutations (F/RF) (*P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*) • IVA monotherapy in combination with ECM for those heterozygous for the *F508del* mutation with one of the	• IVA monotherapy is a relevant comparator in PwCF who are heterozygous for the F508del mutation and a gating mutation, and should therefore be added to the list of comparators • It is not necessary or appropriate to compare the interventions to one another: o The current uptake figures for pwCF aged 6+ years with at least one *F508del* mutation show that [redacted] in England. Data collected through the Data collection agreement [redacted] of the UK CF Registry

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		specified licensed gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H*) • ECM without IVA/TEZ/ELX for all remaining indicated mutations **<u>Relevant comparators for LUM/IVA</u>** • ECM without LUM/IVA **<u>Relevant comparators for TEZ/IVA</u>** **PwCF aged 6 years or older who are homozygous for the *F508del* mutation:** • ECM without TEZ/IVA **PwCF aged 6 years or older who are heterozygous for the *F508del* mutation with one of the specified licensed residual function mutations (F/RF)** *(P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T)*: • ECM without TEZ/IVA	Study in July 2022. [redacted] due to LUM/IVA's licence in 2-5 year old population which is not at present covered by the IVA/TEZ/ELX licence. In the same period, [redacted] 6). o The ECFS consensus statement on standards of care for CFTR variant-specific therapy stipulates that pwCF "aged six years or older, with one or two F508del variants, should have daily treatment with triple modulator therapy (IVA/TEZ/ELX)" (7). The market share data in conjunction with ECFS statement suggest that IVA/TEZ/ELX is standard of care for the vast majority of eligible pwCF in the UK while alternatives are only suitable if IVA/TEZ/ELX is not indicated or tolerated. o It is inappropriate to compare the interventions to one another given that the NICE methods clearly state technologies recommended in managed access agreements are not considered suitable comparators, and LUM/IVA and TEZ/IVA fall into this category (8).
Outcomes	The outcome measures to be considered include: • Mortality • Change in the percentage of predicted forced expiratory volume • Forced vital capacity • Lung function, including transplantation • Body mass index • Respiratory symptoms • Pulmonary exacerbations including frequency and severity of acute infections	The outcome measures to be considered include: • Mortality • Lung function o Change in the percentage of predicted forced expiratory volume o Lung clearance index 2.5 ($LCI_{2.5}$) o Lung transplantation • Body mass index • Respiratory symptoms • Pulmonary exacerbations including frequency and	Forced vital capacity is the maximum amount of air one can forcibly exhale from the lungs after fully inhaling. Change in forced vital capacity from baseline was collected in a number of trials relevant to this appraisal. However, this is a spirometry parameter and thus it would be duplicative to include it in the appraisal given changes in another spirometry outcome i.e. the percentage of predicted forced expiratory volume have already been

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Sweat chloride • $LCI_{2.5}$ • Pulmonary bacterial colonisation • Need for hospitalisation and other treatments including antibiotics • Adverse effects of treatment • Health-related quality of life	severity of acute infections • Need for hospitalisation & other treatments including antibiotics • Adverse effects of treatments • Health-related quality of life	included. Consequently, this outcome was not deemed necessary for this appraisal. Absolute change in sweat chloride concentration from baseline was collected in all trials and reports of this endpoint are available in the publications and CSRs of the relevant trials if required. However, this parameter is a biomarker of the functional capacity of the CFTR ion channel and is therefore a surrogate outcome for the efficacy of CFTRms at the molecular level but not a clinically relevant outcome. SwCl also does not feature in the cost-effectiveness model.. Therefore, to keep the submission concise this endpoint was not included in the submission. Pulmonary bacterial colonisation – was not a routinely collected outcome in Vertex trials and thus has not been included in this submission.
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. 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 and cost of biosimilar and generic products should be taken into account.	• Cost-effectiveness results are expressed in terms of ICER • A lifetime horizon is used in the model • Costs are considered from a National Health Service and Personal Social Services perspective • A differential annual discount rate of 1.5% for health outcomes and 3.5% for costs is applied in the base case • QALY shortfall analyses has been conducted to reflect the high degree of the severity of CF • The impact of loss of exclusivity on cost-effectiveness is considered in a scenario analysis	Uniform discounting of costs and benefits, although recommended by majority of national HTA guidelines, leads to prioritisation of treatments with immediate health benefits and works against preventative health programmes and other interventions characterised by early investment and late accrual of health benefits. The national HTA guidelines of Belgium, Poland and the Netherlands, recommend using a lower discount rate for outcomes (1.5%, 1.5% and 3.5%, respectively) compared with costs (3%, 4% and 5%, respectively), arguing that this is a normative decision taken to "avoid too strong penalisation of interventions such as screening or vaccination programmes" where uniform discounting could lead to perpetual deferral of investment (9-12). It has been shown that equal discount rate for costs and outcomes is appropriate for decision making in a society maximising the present value of health under the conditions of a fixed NHS budget and a constant willingness-to-pay threshold (13). However, it is likely that the value of health over time will increase due to

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			rising social expectations regarding maintaining good health and income growth (14). The increase in the threshold would mean that future additional costs will displace less health; a lower discount rate for health outcomes vs costs would account for such future increase in the value of health benefits (13, 15).
Equality and other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.	An appraisal approach of subgrouping the indicated populations according to *CFTR* genotype or baseline lung function may raise equality concerns.	

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator gene protein; *CFTR*, cystic fibrosis transmembrane conductance regulator gene; ECFS, European Cystic Fibrosis Society; ECM, established care management; ELX, elexacaftor; FEV, forced expiratory volume; F/F, homozygous for the *F508del-CFTR* 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 activity ('residual function'); HRQoL, health related quality of life; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; LUM, lumacaftor; $LCI_{2.5}$, lung clearance index 2.5; NHS, National Health Service; pwCF, people with CF; TEZ, tezacaftor.

A7. Please provide a subgroup analysis of EMBRACE, including baseline characteristics and clinical outcomes, by genotype.

Subgroup analyses of Study 661-115 (EMBRACE), by genotype, are provided in Appendix E (Table 9) for the following outcomes: absolute change in $LCI_{2.5}$ from baseline at Week 8, absolute change from baseline in CFQ-R RD score at Week 8 (child version), absolute change from baseline in CFQ-R RD score at Week 8 (adult version) and absolute change from baseline in $ppFEV_1$ at Week 8. The referred table – including the additional endpoints absolute change from baseline in BMI at Week 8 and absolute change from baseline in BMI z score at Week 8 – is presented below.

Table 2. Post-hoc subgroup analysis of primary and a selection of secondary endpoints by genotype – EMBRACE (Study 661-115)

Endpoint[a,b] (16)	Subgroups by genotype			
	F/F		F/RF	
	TEZ/IVA	Placebo	TEZ/IVA	IVA
$LCI_{2.5}$ (units)				
Absolute change in $LCI_{2.5}$ from baseline at Week 8, mean (SD), n – baseline	9.84 (2.17), n=42	9.67 (1.65), n=10	8.60 (1.30), n=12	8.60 (1.40), n=3
Absolute change in $LCI_{2.5}$ from baseline at Week 8, mean (SD), n – within-group change	−0.56 (1.14), n=38	0.10 (1.16), n=8	−1.12 (1.07), n=11	-0.61 (0.88), n=3
CFQ-R respiratory domain score (points)				
Absolute change from baseline in CFQ-R RD score at Week 8 (child version), mean (SD), n – baseline	85.3 (9.7), n=42	80.0 (21.2), n=10	81.9 (16.2), n=12	75.0 (22.0), n=3
Absolute change from baseline in CFQ-R RD score at Week 8 (child version), mean (SD), n – within-group change	2.0 (12.0), n=42	9.2 (23.1), n=10	1.5 (24.9), n=1	2.8 (9.6), n=3
Absolute change from baseline in CFQ-R RD score at Week 8 (adult version), mean (SD), n – baseline	87.1 (13.0), n=40	NR	86.6 (19.3), n=12	NR
Absolute change from baseline in CFQ-R RD score at Week 8 (adult version), mean (SD), n – within-group change	−0.5 (14.6), n=40	NR	0.0 (29.6), n = 11	NR
$ppFEV_1$ (percentage points)				
Absolute change from baseline in $ppFEV_1$ at Week 8, percentage point - mean (SD), n – baseline	85.1 (12.9), n=42	89.6 (10.1), n=10	91.2 (12.4), n=12	89.1 (5.7), n=3
Absolute change from baseline in $ppFEV_1$ at Week 8, percentage point - mean (SD), n – within group change	3.2 (8.9), n=4	-3.7 (6.1), n=9	2.9 (7.1), n=9	-0.4 (6.0), n=3
BMI (kg/m^2)				
Absolute change from baseline in BMI at Week 8, kg/m^2 - mean (SD), n – baseline	15.96 (1.53), n=42	16.17 (1.02), n=10	16.74 (2.00), n=12	15.98 (1.58), n=3
Absolute change from baseline in BMI at Week 8, kg/m^2 - mean (SD), n – within group change	−0.06 (0.41), n=42	0.02 (0.41), n=10	0.05 (0.49), n=11	0.11 (0.53), n=3
BMI z-score				
Absolute change from baseline in BMI z-score at Week 8 - mean (SD), n – baseline	−0.33 (0.88), n=42	-0.24 (0.37), n=10	0.02 (0.70), n=12	-0.35 (0.54), n=3
Absolute change from baseline in BMI z-score at Week 8 - mean (SD), n – within group change	−0.09 (0.26), n=42	-0.05 (0.22), n=10	−0.01 (0.29), n=11	0.08 (0.37), n=3

Endpoint[a,b] (16)	Subgroups by genotype			
	F/F		F/RF	
	TEZ/IVA	Placebo	TEZ/IVA	IVA
Weight z-score				
Absolute change from baseline in weight z-score at Week 8 - mean (SD), n – baseline	−0.36 (0.73), n=42	-0.19 (0.62), n=10	0.03 (0.62), n=12	0.28 (0.56), n=3
Absolute change from baseline in weight z-score at Week 8 - mean (SD), n – within group change	−0.06 (0.16), n=42	-0.02 (0.15), n=10	0.04 (0.19), n=11	0.03 (0.23), n=3

[a]54 participants were in the TEZ/IVA group: 42 had the F/F genotype and 12 had an F /RF genotype. 13 participants were in the blinding group: 10 had the F/F genotype and received PBO treatment; 3 had an F/RF genotype and received IVA treatment.; [b]Baseline was the most recent non-missing measurement before the first dose of the study drug.
Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; IVA, ivacaftor; $LCI_{2.5}$, lung clearance index 2.5; NR, not reported; RD, respiratory domain; SD, standard deviation; TEZ, tezacaftor.

Real world evidence

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

Indirect and mixed treatment comparisons

[redacted]

Study 445-104 included an IVA Run-in Period prior to baseline, while patients from STRIVE, KONNECTION, and KONDUCT were treatment-naïve at baseline. [redacted]

[redacted]

[redacted]

Study 809-109 was included in the ITC as it met pre-specified criteria for study inclusion (population, intervention and comparator of interest, phase III design and study duration of at least 24 weeks). Phase 3 studies were chosen over observational studies as they provide the most robust evidence and ensure homogeneity in the distribution of effect modifiers across the evidence base. The use of observational data in the analysis (e.g., using real-world data for a PBO comparator) could introduce heterogeneity, especially with regards to the population characteristics and outcome measurement since spirometry measurements may not be standardised in clinical practice.

[redacted]

Table 3. IVA/TEZ/ELX model inputs for acute increase in ppFEV$_1$ by genotype and CFTRm for patients initiating treatment at age 6-11

CFTRm	BASE CASE INPUTS			ALTERNATIVE EFFICACY INPUTS
	PBO-adjusted ppFEV$_1$ increment (95% CI)	Acute period duration (weeks)	Source	PBO-adjusted ppFEV$_1$ increment (derived assuming annual decline of -0.66 percentage points with PBO)
F/F				
IVA/TEZ/ELX	[redacted]	24	ITC (B.2.8.2)	[redacted]
F/MF				
IVA/TEZ/ELX	11.0 (6.9 to15.1)	24	Study 445-116	Unchanged
F/Gating				
IVA/TEZ/ELX	[redacted]	8	Assumption	[redacted]
IVA	10.0 (4.5 to 15.5)	48	ENVISION	Unchanged
[redacted]				
IVA/TEZ/ELX	[redacted]	8	Assumption	[redacted]

CFTRm	BASE CASE INPUTS			ALTERNATIVE EFFICACY INPUTS
	PBO-adjusted $ppFEV_1$ increment (95% CI)	Acute period duration (weeks)	Source	PBO-adjusted $ppFEV_1$ increment (derived assuming annual decline of -0.66 percentage points with PBO)
Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CI, confidence interval; ITC, indirect treatment comparison; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in one second.				

[redacted]

A15. Priority: The NICE final scope states that: "the interventions will be compared to each other", and as such, the EAG will seek to compare the clinical efficacy and safety of each intervention compared to each other. While the EAG notes that the company considers it "neither necessary or appropriate to compare the interventions to one another", [redacted] **. Please present the results of**

ITC analyses conducted between IVA/TEZ/ELX, TEZ/IVA and LUM/IVA for all populations where these have been performed, for both the 6-11 and 12+ age groups.

Vertex does not believe it is clinically relevant to compare the three CFTR modulators under consideration in this appraisal to one another.

16. Priority: For the 12+ F/F population, please provide network meta-analyses comparing ELX/TEZ/IVA, TEZ/IVA, LUM/IVA and ECM for ppFEV$_1$, weight-for-age z score, BMI score and CFQ-R RD through 24 weeks, providing a league table of the NMA results comparing each treatment with each other.

Vertex does not believe it is clinically relevant to compare the three CFTR modulators under consideration in this appraisal to one another.

[redacted]

Study 661-115 was designed with the PBO group intended for blinding purposes and was not powered for a between-group comparison. The 4:1 randomization to TEZ/IVA or to the blinding arm (PBO for F/F, IVA for F/RF) was performed to maximize evaluation of treatment efficacy, limit bias in both efficacy and safety outcomes, and minimize the number of subjects required to be treated with PBO or IVA monotherapy. The within-treatment group analysis was conducted with approximately 40 patients required in the TEZ/IVA arm to achieve at least 90% power to demonstrate treatment effect of TEZ/IVA (compared to a pre-specified maximum PBO effect, which was the lower bound of the 90% CI for the within-group change from baseline for the PBO arm of study 809-109) (16). During the conduct of Study 661-115, many eligible F/F patients aged 6 -11 years were anticipated to have already begun treatment with LUM/IVA, as it was expected to become commercially available during that time, resulting in a smaller number of eligible paediatric patients for TEZ/IVA trial

recruitment. Therefore, it was important that Study 661-115 was designed to minimize the number of patients required to be treated with PBO or IVA to ensure the study could be enrolled.

[redacted]

a. [redacted]

The ITC included data from all Phase 3 clinical trials with the relevant population, intervention, and comparators. The inclusion criteria were: study design is a Phase 3 trial; population includes F/F patients aged 6 through 11 years; interventions include IVA/TEZ/ELX, TEZ/IVA, or LUM/IVA; comparators include TEZ/IVA, LUM/IVA, or Placebo; study duration of 24 weeks.

[redacted]

[redacted]

Moss et al. (20) enrolled a population of patients aged 6 years or older, and as such, we included a subset of patients aged 12 years or older with the F/R117H genotype, as it was an indication for this specific age group.

According to the Moss et al. study, there were 14 patients aged 6 to 11 years with the F/R117H mutation. Therefore, the total number of patients in the study with this mutation would be 39 plus 14, equating to a total of 53 patients.

A20. The EAG notes that the [redacted]. Please comment on why this might be the case, including whether genotype is a treatment effect modifier. Please also comment on the rationale for combining these data in a fixed-effects meta-analysis, and provide an ITC analysis for:

a. F/R117H patients only.

b. F/Gating, not including F/R117H, patients only.

Although R117H patients can be phenotypically dissimilar from other gating patients, patients were grouped by their approved comparator group (all patients approved for IVA), as was done in the trial. Additionally, patient genotype can impact the effect of treatment.

A21. The UK Cystic Fibrosis Registry 2021 Annual Data Report shows that in England the F/R117H genotype is more common (4.6% of CF patients) than the F/G551D genotype (4.4% of CF patients). However, for the F/Gating and F/R117H comparisons between IVA/TEZ/ELX, IVA and ECM, [redacted]. Please comment on the representativeness of the AURORA gating mutation population, and the combined STRIVE, KONDUCT and KONNECTION population, to UK clinical practice.

The study 445-104 protocol states that ‘in the IVA comparator group, up to 20% of subjects may be enrolled with an R117H mutation (approximately 20 subjects)’ which explains why only 17% of patients with the F/R117H mutation were enrolled in this arm. This was a multicentre, global study. The percentage of R117H varies across the

globe; in the US, which represents the largest population of people with CF, the R117H accounts for 3.3% of people with CF, while G551D genotype is more common and accounts for 4.2%. The proportion of each genotype included in the 445-104 study was determined to reflect the representativeness of each genotype across the globe (21).

AURORA F/RF F/G locations were US, Canada, EU, Australia and UK (8 out of 93 locations) and around 38% of patients were from the North American region (37.1% in ELX/TEZ/IVA, 38.1% in control).

STRIVE (*G511D-CFTR*), KONDUCT (*R117H-CFTR*) and KONNECTION (*non-G511D*) recruited most patients in the US, which may explain different proportions in mutations compared to the UKCFR study. STRIVE recruited patients in the UK in 2 out of 65 locations, and KONDUCT in 2 out of 31 locations. KONNECTION did not include any UK locations.

The available trial evidence for the ITC of IVA/TEZ/ELX versus PBO in the F/Gating (including F/R117H) population comprised four studies: study 445-105, STRIVE, KONDUCT and KONNECTION. Study 445-104 compared the efficacy of IVA/TEZ/ELX with both IVA and TEZ/IVA whereas STRIVE, KONDUCT and KONNECTION compared the efficacy of IVA to PBO. The results of the latter three trials were pooled to conduct the ITC.

Only the patient-level data for the subset of patients in the IVA comparator group of study 445-104 were considered for this ITC. F/Gating and F/R117H genotypes were represented in this group. This distribution of genotypes was accounted for in the ITC by including only the subset of patients with the F/gating or F/R117H genotype from STRIVE, KONDUCT and KONNECTION. The following specific subsets of trial data from the studies were considered: the subset of STRIVE patients with an F508del-CFTR mutation on the second allele (F/G551D), the subset of KONDUCT patients who had an F508del-CFTR mutation on the second allele (F/R117H) and the subset of KONNECTION patients who had an F508del-CFTR mutation on the second allele (F/non-G551D gating).

A22. Priority: In Appendix D, it is stated that for the unanchored MMRM ITC: [redacted]

[redacted] **For an unanchored comparison, all treatment effect modifiers and prognostic variables should be adjusted for. The EAG is does not consider the decisions regarding which covariates to include in the MMRM analyses to be appropriately justified, nor the selection process for covariates to be transparently reported. Please:**

a. **Provide full details on the process used to select covariates for inclusion in the MMRM analysis, or the MMRM models used to produces estimates for the Bucher's comparisons, including stating whether any such selection process was pre-specified or post-hoc.**

b. **Provide justification for each of the prognostic baseline variables that were available but not included as covariates not being included in the models.**

c. **Provide sensitivity analyses using additional covariates in the MMRM models to explore the sensitivity of the MMRM estimates to the decision to include or exclude certain covariates.**

The ITC MMRM analysis is aligned with the original 445-106 MMRM analysis, which pre-specified inclusion of the corresponding baseline variable as a covariate. [redacted] Given the small number of TRI-treated F/F patients available for analysis in this ITC (n=29), there were a limited number of covariates that could realistically be included to keep the risk of overfitting low. Standard approaches for model selection are inefficient, and acknowledged to have selection uncertainty problem with such small sample sizes. Covariate selection for the MMRM analyses in the pivotal clinical trials have also been informed by experience across over 50 CFTRm clinical trials since 2010, and those analyses have provided confidence in our understanding of the key prognostic variables and effect modifiers in CF for these outcome.

[redacted]

Sweat chloride was a stratification factor in study 445-104 and as such, it was included as a covariate in the CSR MMRM model. It was not a stratification factor in study 661-108 and thus was not in the 661-108 CSR MMRM model. The requested sensitivity ITC analysis is currently not available.

A24. MMRMs are used throughout the clinical analyses. Please comment on:

a. The clinical plausibility of the missing-at-random assumption of the MMRMs used, and the magnitude of any biases expected when this assumption is violated;

b. The rate of missing data across studies;

c. The consistency between data analysed using MMRM analyses and analyses using multiple imputation, where these have been performed.

Multiple imputation analyses have been conducted for a number of studies including 445-102/103/104/106/109 and in all of these studies, the multiple imputation results and findings are consistent with the findings from the primary MMRM analysis. The rate of discontinuation due to AE (reason for missing not at random) was very low in all studies, and the main reasons for missingness were assessments rejected/invalid due to not meeting standard criteria or missed visits. Given this and the consistency of the multiple imputation results with the primary MMRM analyses, we are confident that the missing-at-random assumption holds in all studies.

A25. Please can the company clarify further what is meant by “[Appendix D] To ensure that trials included in pairwise ITCs have comparable baseline distributions of effect modifiers and prognostic variables [369], a population adjustment was undertaken using individual patient data (IPD) from the relevant treatment groups of included studies in the mixed effects model for repeated measures (MMRM) (Section D.5.7).”

It is currently unclear which aspect of the company's ITCs this section is referring to, and the linked Section D.5.7 appears to be the incorrect section.

We apologise for the incorrect cross-reference in this paragraph. The correct cross-reference is that to Section to D.5.1, which describes the features of MMRM models used to derive estimates of pairwise relative effects for each of the outcomes of interest ($ppFEV_1$, weight-for-age z score, BMI-for-age z score, CFQ-R RD score, and $LCI_{2.5}$).

[redacted]

Subgroup analyses

A26. Priority: The NICE final scope states that: "If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.". In addition, the EAG considers that exploring the relationship between baseline lung function and clinical effectiveness is important to consider when interpreting the results of ITCs between studies where participants' baseline lung function differs between studies. Please provide an analysis of the relationship between baseline lung function and clinical effectiveness.

Vertex is exploring this post-hoc analysis of clinical trial data internally and will share with NICE once this is available. In addition, a sub-group analysis of UK DCA real-world outcomes by baseline $ppFEV_1$ (<40% and ≥40%) showed improvements in $ppFEV_1$ post initiation of a CFTRm irrespective of baseline $ppFEV_1$ group up to a 1-year follow up.

COVID-19 and long-term data

A27. Priority: The EAG is concerned that the company has not adequately addressed the potential confounding effects of the COVID-19 pandemic in the

analysis of real world evidence and clinical trials, nor has the company outlined which studies are most likely to have been affected by these confounds. Please:

a. **Provide a complete list of studies used to inform the cost-effectiveness analysis, detailing whether the study dates overlap with the COVID-19 pandemic;**

b. **Assess the likely direction and magnitude of any bias introduced by the COVID-19 pandemic for each efficacy and safety outcome used in the cost effectiveness modelling, including but not limited to:**

    a. **The effects of shielding and social distancing on the rate of pulmonary exacerbations, including pulmonary exacerbations requiring IV antibiotics and/or hospitalisation;**

    b. **The effects of shielding and social distancing on $ppFEV_1$ and $LCI_{2.5}$, and discuss how changes to spirometry measurements might affect the magnitude of treatment effects on $ppFEV_1$ or $LCI_{2.5}$, or the reliability of and the amount of missing $ppFEV_1$ or $LCI_{2.5}$ measurements.**

Clinical studies and real-world analyses conducted prior to the onset of the COVID-19 pandemic (e.g., 445-102, 445-103) showed that treatment with IVA/TEZ/ELX resulted in robust reductions in PEx and unprecedented improvements in lung function, demonstrating a clear benefit of IVA/TEZ/ELX on these outcomes outside of any pandemic-related impact.

Studies 445-106, part of 445-107 and 445-105, 445-116 (included in the submission dossier) overlapped with COVID-19 pandemic.

Results from the final analysis of study 445-105, which completed on January 9, 2023 and includes an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, demonstrated that participants treated with IVA/TEZ/ELX had on average no loss of lung function which is consistent with the results seen in IA3 of 445-105 (22). We will also aim to address the impact of COVID-19 final DCA report to be submitted in June.

Miscellaneous

A28. The company appear internally inconsistent between their own documents on between genotype differences in long-term FEV_1 decline. In IA2 of the UKCFR Study, the company states: [redacted] whereas in the CS, the long-term rate of decline observed in homozygous patients is applied to F/MF and F/Gating: “In the absence of genotype-specific rates for the populations with F/MF and F/Gating genotypes, the rates of $ppFEV_1$ decline reported for the population with F/F genotype in the Sawicki et al. (2022) study were applied (Table 90) (348). This is a reasonable assumption given the similar burden of disease and disease progression seen among patients with F/F and other F508del-containing genotypes, such as F/MF (349) and F/Gating (336, 337)”. Please comment on this.

To clarify, the UKCFR report refers to the F/F genotypes declining more rapidly than other genotypes which include patients with a residual functional mutation. The statement was in reference to F/RF genotypes only. Based on literature, patients with an F/F genotype have a similar disease burden to those with an F/Gating or F/MF genotype.

A29. Please comment on whether the company expects the crossover design of Study 661-108 to lead to an overestimation or underestimation of the treatment effect of TEZ/IVA compared to placebo at 8 weeks, compared to a hypothetical parallel group RCT. If available, please provide the efficacy results of Study 661-108 for Treatment Period 1 only.

Vertex does not expect that the crossover design of Study 661-108 will lead to an overestimation or underestimation of the treatment effect of TEZ/IVA compared to placebo at 8 weeks, compared to a hypothetical parallel group RCT. Carryover effect for the primary analysis was assumed to be negligible, if any, due to the adequately long washout period of 8 weeks. To support this assumption, Vertex compared Period 1 and Period 2 baseline $ppFEV_1$ according to the Period 1 treatment assignment. For example, to assess carryover effects for TEZ/IVA, we pooled the 2 sequences in which TEZ/IVA was assigned in Period 1 (TEZ/IVA-PBO, TEZ/IVA-IVA sequences). The Period 2 treatment assignment does not affect the Period 2 baseline, because Period

2 baseline was measured before the first dose in Period 2. Mean baseline values at the start of Periods 1 and 2 are provided in Table 38 in CHMP D120 Q181 by treatment assignment in Period 1. Subjects receiving TEZ/IVA in Period 1 had similar baseline mean ppFEV1 in Period 1 and Period 2.

A30. Priority. Following the EAG's systematic literature review, the EAG notes that data on change from baseline weight-for-age z-scores are often not available in the study CSRs provided, despite informing the economic models. When weight-for-age z-score data are reported in CSRs, this is often only for the <21 years subgroup. For each study in the 12+ age group that is used to inform the CEM, either directly or indirectly via ITCs, please provide, by arm, the absolute change from baseline in weight-for-age z-score at Week 24 (or the primary endpoint). Where applicable, please provide this separately for the <21 years subgroup and for the full trial population. Please also provide these separately for TRAFFIC and TRANSPORT (rather than pooled), and for each arm (IVA and PBO) of the F/Gating subgroups of STRIVE, KONNECTION and KONDUCT.

Weight-for-age z-scores (WFAZ) were found to be associated with survival of CF patients as observed by Liou *et al*. (2001), therefore, the model tracks WFAZ across all patients. However, WFAZ is not a key driver of survival in our model. Please see submitted DOFs.

A31. Please provide further justification around the decision to assume growth statistics of 20-year-olds for all patients aged >20 years in the change in weight-for-age z-score analyses. Please comment on whether this is likely to lead to an overestimation of any CFTR modulator treatment effect.

Growth statistics are only available up until age 20, and assumptions made are consistent with those in the original Liou et al (2001) publication. Further, weight-for-age z-score has negligible impact in the model results.

A32. Please clarify which doses were used in Study VX20-445-111 for Part A and for Part B.

The following IVA/TEZ/ELX doses were administered in Study 445-111:

- Part A: Weight at Day 1 ≥14 kg: ELX 100 mg once daily + TEZ 50 mg once daily +IVA 75 mg twice daily
- Part B:
    - Weight at Day 1 ≥10 to <14 kg: ELX 80 mg once daily +TEZ 40 mg once daily + IVA 60 mg once daily am and IVA 59.5 mg once daily pm
    - Day 1 weight ≥14 kg ELX 100 mg once daily + TEZ 50 mg once daily + IVA 75 mg twice daily

A33. Please clarify the difference in the participant disposition data reported in Rayment et al. 2022 and on NCT03601637. In the primary publication, Figure 1 states that only one child discontinued (due to an AE) and 45 children completed the study drug. In contrast, on the NCT record it is reported that three children did not complete the study (1 discontinuation due to AE, 1 withdrawal of consent and 1 other discontinuation).

In study 809-122 the publication refers to treatment discontinuation, but the NCT refers to study discontinuation hence the discrepancy.

A34. If possible, please provide adverse event data separately for each of the F/RF and F/Gating subgroups of Study 445-104, including any data on pulmonary exacerbations. If this is not possible, please provide any data on pulmonary exacerbations for each of the F/RF and F/Gating subgroups.

Safety across mutation groups has generally been seen to be genotype-agnostic.

A35. If possible, please provide tables of prior medication use and participant disposition for the F/Gating and F/RF subgroups of Study 445-104.

Prior medication can be found in table 10.4 of the CSR and patient disposition for the F/Gating and F/RF subgroups are in table 10.5.

A36. For STRIVE, KONNECTION and KONDUCT, please provide adverse event data for the F/Gating subgroups.

Safety across different genotypes has generally been seen to be genotype-agnostic.

A37. For TRAFFIC and TRANSPORT, please provide baseline EQ-5D-3L data by arm for each study, separately.

CSRs (previously submitted) for both TRAFFIC and TRANSPORT studies report absolute change to EQ-5D-3L and not baseline data.

A38.Priority. Section 14 of the following CSRs are missing blank: 661-106; 661-108; 809-109; 809-115; 661-110; 661-115; 445-104; 445-109; 445-116; 445-105; 445-107; 445-110; 661-110; 809-103 (provided in document A reference pack); 809-104 (provided in document A reference pack); 809-105; 809-110; 809-116; 809-115 (provided in document A reference pack). As Section 14 provides the most comprehensive tables of outcomes, including missing data and sensitivity analyses, please provide updated CSRs with Section 14 fully reported.

These have been submitted.

A39. Please provide the CSR for study VX15-809-112.

This has been submitted.

A40. The MMRM analyses of weight-for-age z-scores are inconsistently presented in the submission, sometimes in Section 2 with other clinical data and other times, e.g., Study 445-102 only in Section 3 with a reference to Data on File. Please confirm that all MMRM analyses of weight-for-age z-scores that have been performed have been provided as part of the submission.

Clarification will follow as soon as possible.

A41. Vertex Data On File REF-9272, reference 166 in the company submission, states that there were [redacted] CF patients aged 6 to <12 years in Wales in 2021. However, it also states that [redacted] CF patients aged 6 to <12 years in Wales had genotype data available. Could the company clarify if one of these numbers are incorrect, and provide updated figures if so? The EAG also notes that the genotype prevalence data from REF-9272 are marked as AIC in Table 82, but not in Table 9. Could the company clarify whether the data from REF-9272 are AIC?

The number of patients with genotype data should be [redacted] and not [redacted]. Data from REF-9272 are AIC.

A42. Please provide Section 14 of the CSRs for VX16-809-122, and for the following OLE studies (VX17-445-105, VX17-661-116, VX12-809-105)

Work in progress. Will respond separately.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

Baseline patient characteristics

B1. The model randomly selects a user defined number of patients from the “patient data”. These patients are defined by the patient characteristics, one of which is genotype. However, the models runs patients with each genotype and then weights results by the UK population. Do the selected patients genotype’s factor into the model calculations?

The genotypes included on the "Patient Data" worksheet indicate which patient profiles are eligible for random selection when running each genotype. For example, the model will only select among the F/F profiles when running the F/F genotype analysis. Genotype-specific model inputs are applied to these patients in the simulation.

The model inputs for clinical effectiveness are derived from trials of CFTR modulators conducted in populations of pwCF with a specific *CFTR* genotype. Selection of a given genotype on the “Dashboard” worksheet of the model ensures that the clinical inputs, such as annual decline of $ppFEV_1$ in the absence of a CFTR modulator treatment, CFTR modulator efficacy, discontinuation, and compliance rates, specific to that genotype are applied in the model calculations. If all four genotypes are selected, and the number of the patient profiles to be used in the simulation is set to 2000, then the model runs 2000 patients with *each of the four genotype*s, using genotype specific clinical inputs. Outcomes are then aggregated by genotype and also weighted by the

proportion of each genotype in the UK pwCF population, as inputted on the “Dashboard” worksheet.

B2. Some patient age data appears to be very specific to a patient’s age but there are also a large number of patients who are listed as exactly the round number of age in years:

a. How was the imputation issue with rounded ages addressed?

b. Some patients appeared to have oddly specific ages; patient 20 for example was 6.029 years old. This equates to 6 years and 10.67 days (if it was 6.030 years old it would be 11 days and if it was 6.027 years it would be 10 days). Given this doesn’t appear to be a rounding issue how were these exact ages derived?

The age of the patient profiles included in the model are consistent with how age was collected and calculated in each of the contributing Vertex-sponsored clinical trials. Some trials (e.g., IVA/TEZ/ELX clinical trials) collected age by year and month and made assumptions to calculate a study baseline age (e.g., age = (years*365.25) + (months*30.4375) + 15). This may lead to the appearance of “oddly specific ages” in patient profiles. Older trials (e.g., IVA clinical trials) collected and reported only an integer age at baseline.

B3. **Priority: During the walkthrough call the company stated that they investigated/considered using model generated patients over their current approach of randomly selected real patients. Can the company elaborate on how this would have worked if implemented?**

For analyses to support the Lopez 2023 manuscript (23), authors created a "UK Registry-like cohort", in which 5000 F/F patient profiles were created based on the age, $ppFEV_1$ and weight-for-age z-score distribution from the UK CF registry. To preserve the correlation between age, $ppFEV_1$ and weight-for-age z-score, a multivariate normal distribution was used with a vector of sample means representing the observed mean of each variable and a covariance matrix representing the interrelationship between each pair of variables. Authors found that the baseline characteristics of the "UK Registry-like cohort" was very similar to the F/F patient

profiles derived from the clinical trials, and thus, the projected survival benefits were of similar magnitude. This is noted in the manuscript, though the survival results for the UK Registry-like cohort were not included.

B4. **Priority: In sheet 'Parameters', please clarify what the values in cells "AK10:13" represent. If this is the average values from the model for the simulated patients characteristics, please clarify why mean age, proportion female and weight for age z score differs so much from the values in cells "AJ10:13", representing the trial averages. This question also applies to the other genotypes represented in columns AN, AP and AS**

Cells AK10:13 represent the average characteristics of the 2,000 sampled patient profiles used in the simulation. Cells AJ10:13 represent the average baseline characteristics of the available pool of patients to be sampled in the model (which is also displayed on the Results worksheet).

There is a slight issue in the way the VBA code is copying the characteristics of the recently run simulated cohort (cells BA9:BA13) over to the hard-copy results for each genotype (cells AK9:AK13 for F/F, cells AO9:AO13 for F/MF, etc.). For this reason, the patient characteristics for the simulated F/RF patients are being copied/pasted under F/F. The issue is only in the display of average characteristics of simulated cohort on the "Parameters" worksheet, and not in the selection of patients, the model run functionality, or any of the output presented on the "Results" worksheet.

To address this change, the VBA code on lines 198 to 214 (which copy/pastes the patient characteristics from the recently run output) to above line 407 (after the genotype-specific run is complete) of the module "RunModel". When this is addressed, the displayed characteristics are very similar between the pool of available profiles and the 2,000 profiles selected for the simulation. For example, the average age of the simulated F/F cohort in the IVA/TEZ/ELX model is 22.8 years which is comparable to 22.4 years, the average age of the clinical trial patient profiles.

Treatment effectiveness within the model

B5. **Priority: Attempting to use the model as a Markov by applying averages to all baseline patient values results in significant deviations in cost-effectiveness. What are the primary drivers of this?**

The individual state-transition patient simulation model structure is well-suited for modelling pwCF as it captures the heterogeneity of the disease and tracks specific time-dependent patient characteristics and treatment effects that influence survival. Applying averages to all baseline patient values does not capture the heterogeneity observed in pwCF.

However, when running a single patient profile with the average patient characteristics through the model 2000 times, simulation results are largely consistent with the submitted base case are obtained.

If the intention is to run the model once (one simulated patient) with a single average patient profile, some changes to the model structure would be required. For example, all random variation should be removed (e.g., death or PEx occurrence in a cycle would need to change from 0/1 to a probability/rate/expected value).

Vertex cannot further comment on the results of the ERG's attempted Markov model without seeing the model structure and calculation changes.

B6. Please clarify if the model assumes that patients on best supportive care do not achieve any increase in weight for age z score at any point in the model time horizon. If so, how was this assumption clinically validated?

All efficacy inputs in the model are placebo-adjusted and informed by the indirect treatment comparisons described in section B2.8 of the main dossier. Since only a relative treatment effect on each of the endpoints (absolute change in $ppFEV_1$ from baseline, PEx rate ratio, and absolute change in weight-for-age-z-score from baseline) are used in the model, patients treated with ECM alone experience no absolute change in $ppFEV_1$ or weight-for-age-z-score over the acute period which reflects the duration of the data collection period in the studies included in the ITC. Following the period of acute change, a patient's WFAZ is assumed to be constant for the remainder of the model simulation.

Assuming weight-for-age z-score is held constant was considered a reasonable simplifying assumption by clinical CF specialists who were involved with model development, including Ted Liou and Mike Konstan who were involved with the Rubin 2019 publication of LUM/IVA survival projections (24) and more recently by Gordon MacGregor who was involved with the Lopez 2023 (23) publication of TRI survival projections.

B7. When the model is run with a single patient, results are still produced for all four mutations and the weighted results are a combination of all four genotypes. Please can the company explain why the model does not seem to be informed by the baseline patient data (which includes patient genotype)?

A) If the company has done this to ensure that the CFRD status matched UK CF registry data why was a different method used to ensure age matched UK patient data?

The model allows the user to select genotypes and comparators, as well as the number of patient profiles used for each genotype-specific model run. To run the model with one patient for one genotype, the user must first select one of the four genotypes on the "Dashboard" worksheet using the check boxes. Then, in the "Patient Population" worksheet the "Number of patient profiles used in the simulation" (cell D4) should be set to 1. The model will then produce results for a single (randomly selected) patient with a single genotype run through the model one time. However, it is worth noting that the model was designed as a microsimulation; as such, running it with just one patient profile produces results that lack robustness and generalisability to the population of pwCF.

Since CFRD status was not available in all clinical trials, an alternative data source was necessary, which is why UK CF registry data was used.

B8. Please can the company elaborate on how the formula linking Annual PEx rate to ppFEV was derived from the Goss and Burns, 2007 paper?

The Goss and Burns 2007 (25) paper included two figures which plotted the mean annual rate of PEx by the mean $ppFEV_1$ in pwCF age <18 and age ≥18 years, respectively, based on data available from the 2004 US CF Registry. In 2014 the HTA

programme, part of the National Institute for Health Research (NIHR), published a cost-effectiveness analysis of ivacaftor Whiting *et al.* 2014 (26). Whiting et al. 2014 derived a mathematical relationship relating PEx to ppFEV$_1$ by fitting an exponential curve to the two figures included in the Goss and Burns 2007 publication (25). See Whiting et al. 2014 for further clarification.

Mortality

B9. **Priority: How was the Cox proportional hazard model by Liou *et al.* deemed to be the most appropriate source for estimating survival? Were any other studies specific to the UK searched for/considered? For example, did the company consider the following study using CF Registry data: Keogh, R. *et al. Dynamic Prediction of Survival in Cystic Fibrosis: A Landmarking Analysis Using UK Patient Registry Data*. Epidemiology 30(1):p 29-37, January 2019**.

The economic approach was designed to be consistent with previous appraisals of innovative treatments for people with CF and to be sufficiently flexible to capture the key clinical outcomes affecting patient survival. The CFTR modulator cost-effectiveness model framework was initially developed for IVA in 2012 and has subsequently been adapted for other CFTR modulators, including LUM/IVA and, more recently, IVA/TEZ/ELX. Notably, the CFTR modulator model framework has received favourable feedback from several HTA organizations, including NICE (TA398) and CADTH, for its design and internal validity in modelling the disease pathway. The model framework and underlying survival calculation approach, which uses the mathematical relationship between clinical characteristics in CF and mortality developed by Liou and colleagues (2001), have also been presented in multiple peer-reviewed publications. (Lopez et al., 2023 (23); Rubin et al., 2019 (24)). In addition, an exercise to validate Vertex's CFTR modulator survival model methodology and survival projections was performed by comparing 5-year model-projected mortality to observed 5-year mortality from the ivacaftor Long-term Safety Study (LTSS). The modelled 5-year survival projections tracked closely to the observed registry data from the LTSS. These findings support the validity of the CFTR modulator models based on the Liou equation in predicting long-term survival and estimating the clinical and economic outcomes of CFTR modulators. (McGarry et al., 2023) (27). Please refer to section B3.3.7.2 for more detailed information regarding the survival model chosen.

B10. **Priority: Please clarify if the data used for the underlying baseline survival curve for CF patients from the UK CF Registry was the latest data available pre-introduction of CFTR modulators?**

A) Has the company investigated the possibility that CTFR modulator treatment could influence survival separate to the factors used in the mortality model?

The underlying survival curve was derived from the 2008 UK CF Registry annual report, which reported survival for 6,082 patients grouped into five birth cohorts ranging from 1980 to 2008 (28). This was the latest available data that was publicly available from the Registry.

The model makes the assumption that all survival benefit is achieved based on the improvements in the parameters included in the model. It is possible that there are other factors which CFTRms impact that could influence survival. If so, it is probable that these would have a positive influence on survival and therefore that the current survival estimates are likely conservative.

However, the aforementioned model validation study (McGarry et al., 2023) demonstrate that the model accurately predicts CFTRm survival benefit, which implies that the clinical factors included in the model are accurate (27).

B11. **Priority: Please clarify why the model assumes that no patients in either treatment arms die between age 0-8 (Sheet “plotting”), which is lower than the general population mortality rate?**

The model does not assume that no patients in either treatment arm die between ages 0-8. The "Plotting" worksheet calculates survival using a Kaplan-Meier method observing the number of patients who are at risk and die at each age. Given the IVA/TEZ/ELX model includes only patients aged ≥ 6 years of age, there are no patients at risk (and therefore no patients who die) in the model aged <6 years of age. In the IVA/TEZ/ELX model, the youngest death occurs at age 8 years. As can be seen on the "Patient General" worksheet, patient mortality is set based on the baseline age ("Patient General" cell AH2) and is considered before age 8.

B12. **Priority: The company's model predicts that by age 100, the proportion of patients still alive with F/F and F/MF mutations treated with IVA/TEZ/ELX, 0.01184 and 0.01123 respectively, is approximately equal (or higher in F/F) to that of the general population (0.011298). Please can the company clarify if any clinical validation was undertaken for the long-term model survival predictions in order to assess if this was deemed clinically plausible?**

Mortality hazard for patients with CF estimated in the model is assumed to be no lower than that of the general population of the UK, imposed using age- and gender-specific UK life table data. Thus, it's possible that a patient may be assigned a general population mortality rate.

These projections were considered clinically plausible by Vertex's clinical and medical teams, as well as by CF physicians who were involved with model development and publication, including Ted Liou, Mike Konstan, Greg Sawicki, Gordon MacGregor, and Leonardo Pinto.

B13. The company undertook a validation exercise comparing the model predicted 5 year mortality of ivacaftor treated patients to observed 5 year mortality long term safety study (LTSS) of ivacaftor treated patients in the US CFFPR. Are there equivalent long term data now available from the UK CF Trust on ivacaftor that could instead have been used to assess if the model accurately reflects survival for UK patients?

This exercise has not been performed with data from the UK CF Registry. Outcomes from the IA2 of the UK DCA confirm that treatment effects observed in the UK CF population after initiation of IVA/TEZ/ELX, TEZ/IVA and LUM/IVA are very much in line to what has been reported in US data.

B14. The company states that the two possible groupings for the most plausible reference survival curves were 1990-2008 and 1985-2008. Please clarify why the diagnostic plots for each distribution include a separate plot for the birth year 1980-1984? In addition, please provide the overall survival distributions for both the 1985-2008 and 1990-2008 separately.

Survival distribution attached (DOF 5028).

B15. When determining the most plausible parametric distribution to fit the reference survival curve, can the company:

A. Clarify if they considered the nature of the hazard of each parametric distribution when considering the most clinically plausible fit to the data?

B. Please provide the Cox-snell residuals for each parametric distribution.

Parametric survival analysis was performed on data from the 2008 UK CF Registry to obtain a reference survival curve for the pharmacoeconomic model. All parametric curves were assessed for goodness of fit and clinical plausibility. The curve that was deemed to have the best statistical fit and clinical plausibility was the Weibull distribution fitted to the pooled 1985-2008 birth cohort data from the 2008 UK CF Registry data. The 1985-2008 cohort based on a Weibull model resulted in a plausible predicted median overall survival (40.8 years) (Table 1 on DOF5028). Although both the Gompertz and the generalized gamma distributions fitted to the pooled 1985-2008 birth cohort data also had reasonable median overall survival times, the projection declined so rapidly that no patients would be predicted to survive beyond 40 and 50 years of age, respectively (Figure 1 on DOF5028). All available residual plot functions for each distribution evaluated are provided in DOF5028.

B16. The Liou model includes the number of acute pulmonary exacerbations as a predictor of mortality. Please clarify why only pulmonary exacerbation leading to antibiotics or hospitalisations were used in the model rather than all pulmonary exacerbations, to be in line with the Liou equation.

Liou et al 2001 (29) which specified that PEx are “acute pulmonary exacerbations that require treatment” relies on data collected from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) which defines PEx as acute episodes requiring intravenous antibiotic use at home or in the hospital (30, 31).

In Vertex’s trials of CFTRms where PEx was an efficacy endpoint, PEx were defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

- Change in sputum

- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

For protocol-defined PEx, the number of PEx requiring hospitalisation and the number of PEx requiring IV antibiotic therapy were reported separately. To be consistent with the definition of PEx used in the Liou Cox Proportional Hazards model, these types of PEx were included in the survival model. This was also clarified in the publication of the Rubin 2019 publication of LUM/IVA survival projections, in which Ted Liou was a co-author ((24)).

B17. The Liou model implies that S. aureus infection leads to reduced mortality (coefficient −0.25). Please clarify why this might be the case?

The role that S. aureus plays in respiratory health in pwCF is unclear, with the main difficulty being distinguishing between true lower respiratory tract infection from colonisation. In young patients with CF, the presence of S. aureus is associated with increased inflammatory activity in the airways and a worse nutritional status (32). However, the clinical impact and the need for prophylaxis are unresolved issues and recommendations at the national level vary.

This uncertainty may be reflected in the p value associated with S. aureus infection in the multivariable model by Liou et al, 2001. Authors state that “despite high p values, S. aureus infection (OR = 0.81, 95% CI 0.64–1.02, P = 0.07) was kept in the model for two reasons:

1. It is a prominent feature of the clinical syndrome and a useful signal of health and disease as commonly assessed in isolation at the bedside
2. Together with pancreatic insufficiency, this variable substantially improved the fit of the overall model to the data".

B18. In the model patients who exceed a certain hazard threshold are modelled as experiencing an event (death/transplant). Why was the model constructed this way rather than probabilistically; i.e. if there is a 25% hazard of death at time X why not calculate cost and QoL using this probability rather than calculating as if survival is 100% until the hazard falls above 50%?

The model generates a probability of death in each cycle for an individual patient based on the mortality hazard calculated for that patient in that cycle. This allows the probability of survival to be dependent on the individual patient characteristics.

Discontinuations and subsequent treatment lines

B19. **Priority: Please clarify why discontinuation rates are not varied in the PSA? Please provide the results of the PSA with this implemented in the model**

Clinical trial discontinuation has closely matched real-world discontinuation reporting in the UK DCA. We therefore do not consider it a relevant variable for the PSA.

The UK DCA captures real-world data on discontinuations with reason for discontinuation. For IVA/TEZ/ELX the data is split by genotype, including F/RF and F/Gating. The discontinuation rate is low in the overall group [redacted] discontinued and re-initiated any CFTRm, [redacted] discontinued and did not re-initiate any CFTRm) and this is consistent across genotype. This data will be updated in the final analysis report.

B20. **Priority: Patients discontinue treatment during the long term extension studies, referred to as the post acute stage, and discontinuations are applied in the model up to the time period corresponding to the extension studies. Please clarify what evidence is available to suggest that past this time point no further discontinuations will occur for the remainder of the model duration**.

The model assumes a discontinuation rate up to the extension of the open label extension studies (e.g., 144 weeks in Study 105). No discontinuation is considered thereafter. Consulted clinicians believed this was an appropriate assumption given most discontinuations of treatment due to adverse events and tolerability occur early upon treatment initiation and if patients are still on treatment nearly 3 years after initiation, they are likely to continue treatment.

The model has ability to incorporate longer discontinuation, by changing the duration of the post-acute duration period.

B21. Please clarify why a patient who is 2-3 years old and discontinues would still receive an acute ppFEV$_1$ increment upon turning age 6?

Since ppFEV$_1$ is not explicitly tracked in the model during ages 2–5 years, for patients who initiate LUM/IVA aged 2–5, regardless of whether the treatment is discontinued, they accrue an acute increase in ppFEV$_1$ immediately upon turning age 6 (the point at which tracking of ppFEV$_1$ begins).

If a patient discontinues treatment, they retain the acute increase in ppFEV1, given that efficacy measures from the trials were determined from intent-to-treat analyses.

B22. Please clarify if the company undertook clinical validation to support the assumption that patients retain the increase in weight for age z score experienced during the trial period for the remainder of the model duration, regardless of discontinuation.

We have not conduced clinical validation on this. The UK DCA data shows weight increase across genotypes through the first year after CFTRm initiation. The final outcomes report will include additional data beyond one year.

Compliance

B23. Please clarify how patients receive prescriptions, is this done on the basis of a regular prescription provided within a set time frame or provided as and when patients request a new prescription?

Prescriptions for CFTR modulators are written by the CF clinical team either every 4, 8 or 12 weeks. For most patients in Great Britain, these prescriptions are sent to a home delivery provider via a homecare prescription form for processing and delivery to the patients' home. The home delivery provider liaises with the patient to ensure the patient needs the prescription to be dispensed and delivered. The home delivery provider contacts the patient prior to each delivery to ensure further prescriptions need dispensing to both ensure the patient has no gaps in treatment and to minimise medicine wastage. The patient can select when the delivery is made. For those patients who do not use home delivery, the prescription is managed by the hospital, and they collect their medicine at the selected frequency at the hospital pharmacy.

B24. Can the company please confirm that the model assumes no wastage of drugs and instead assumes only a reduction in treatment costs due to lower compliance?

The model assumes no drug wastage. This assumption is justified by the fact that the quantitative packaging of CFTRms reflects their posology. For example, the recommended daily dose of LUM/IVA in paediatric patients aged 2-5 years is either 100 mg LUM/125 mg IVA every 12 hours (for patients weighing less than 14 kg) or 150 mg LUM /188 mg IVA every 12 hours (for patients weighing 14 kg or more). In this population, LUM/IVA is licenced in age-adapted fixed-ratio granule formulation and packaged into sachets with two granule strengths of 100 mg LUM /125 mg IVA and 150 mg LUM /188 mg IVA which match the recommended daily dose in this population. The same relationship between packaging and dosing applies to older pwCF and other CFTR modulators, whose daily dose is an integer of fixed dose tablet formulation, precluding any drug wastage.

Pill counts in phase III trials were used to measure compliance during the acute phase of the treatment. The assumption of post-acute compliance rate of 80%, which impacts the long-term treatment cost in the model, is supported by real-world studies, as described in B3.3.10.

B25. Following the acute period, the model assumes a compliance rate of 80% for all ages based on the retrospective cohort study of a US administrative claims database by Suthoff *et al.* Please clarify if this study included patients of all ages and if so if the compliance rate was the same across different age groups.

The population of the retrospective cohort study of the Truven Health MarketScan Commercial Claims and Encounters database by Suthoff et al (31) comprised 79 patients diagnosed with CF who were at least 6 years old at the index date (date of first claim for IVA between 1 January 2012 and 31 July 2013) and had 12 months of pre-index and 12 months of post-index data. The age composition of the included subjects is shown in the table below.

Age composition of patients enrolled in the retrospective study by Suthoff et al, 2016

Number of patients, n	79
Age, mean (SD)	20.8 (11.8)
Age group, n (%)	
6-11	19 (24.1)
12-17	22 (27.8)
18-34	27 (34.2)
35-55	11 (13.9)
55+	— (0.0)

Adherence to IVA treatment was measured with the medication possession ratio (MPR; total days supplied from all IVA refills divided by 365 days of the post-index period). Unfortunately, the authors did not present the average MPR by age group. Analysis of the MPR by deciles demonstrated that 73% of patients were adherent to the therapy with MPR >0.8.

Lung transplantation

B26. The data used to inform rates of lung translation per year were based on the UK CF Registry's annual report for 2021, which indicated that 6.4% (5/78) of CF patients received a lung transplant within that year. The year prior to this there were 8.6% transplants (15/175). Did the company consider the possibility that the Covid19 pandemic impacted on the number of lung transplants able to take place in 2021?

The number of bilateral lung transplants received by pwCF annually in 2019, 2020 and 2021 is shown below (33). A marked decrease in lung transplant activity was noted between 2019, when 20.33% of evaluated patients received a bilateral lung transplant, and 2020, when only 6.86% of evaluated patients had the lung transplant procedure

(the proportion of patients receiving either lung *or* liver transplant was slightly higher, 15/175=8.6%). This decrease could have been a consequence of

- The start of the Covid19 pandemic in the UK in March 2020
- Availability of IVA/TEZ/ELX to the pwCF in England from June 2020.

When the model was run with two different probabilities of receiving a lung transplant (20.3% from 2019 and 6.4% from 2021), this parameter was found to have a minor impact on ICER: using the 2021 value reduced the ICER by less than £10,000/QALY compared to the ICER obtained with the 2019 value for the rate of lung transplant. For consistency with other model inputs, it was decided that 2021 values should be used in the base case analysis.

Data from the UK CF Registry report 2021 (33)	**2019**	**2020**	**2021**
Number evaluated, n	241	175	78
Number receiving **bilateral lung transplant** aged < 16 years, n	<5	0	0
Number receiving **liver transplant** aged < 16 years, n	<5	0	0
Number receiving **bilateral lung transplant** aged 16+, n (%)	49 (20.33)	12 (6.86)	<5 (<6.41)
Number receiving **liver transplant** aged 16+ years, n	<5	<5	0

Costs

B27. **Priority: Please can the company provide a breakdown of the specific pharmacotherapy interventions included within the non-PEx related disease management costs. Do the included interventions reflect best supportive care within the UK?**

A UK study presented at the 15th Biennial European Meeting at the Society for Medical Decision Making in 2014 (Ramagopalan et al.) (34) was used to inform both PEx- and non-PEx-related disease management costs. In this study, patients were selected from four paediatric and four adult CF centres in the UK and total annual costs were calculated through aggregated individual costs for each of the cost categories

including the pharmacotherapy costs. It was reported that: “During the study period 147 (73.5%) patients had at least one regimen of IV antibiotic. The majority of these patients initiated treatment because of a pulmonary exacerbation (n = 113, 56.5%). 87% of the patients used nebulised therapy at least once during the study period. Similarly, 90.5% of patients used oral antibiotics, 74.5% used mucolytic treatment, 96.5% used pancreatic enzyme, 74% used asthma therapy, 28% used antifungal treatment, 45.5% used PPIs, and 19% used insulin treatment at least once during the study period.”

B28. **Priority: The company applies a 70% reduction in pharmacotherapy costs and inpatient stay costs for non-PEx related disease management costs for all CFTR modulators, based on an observational study comparing healthcare resource prior to and after initiation of IVA (Simmonds *et al.* 2022):**

a) **The values used to inform the reduction in oral or inhaled antibiotic use following the initiation of IVA is based on antibiotic use due to PExs (Simmonds *et al.* Table 3). Can the company please clarify why a 70% reduction in pharmacotherapy costs is applied when differences in disease management costs due to PEx is already accounted for within the values applied for PEx-related disease management costs, per event?**

b) **The reduction applied for inpatient stays due to non-PEx related disease management costs for CFTR modulator treated patients is based on all cause hospitalisations. This reduction appears to be largely driven by hospitalizations due to PEx (Simmonds *et al.*, Table 3). Please clarify if this is double counting the reduction in costs related to PEx already accounted for in the PEx-related disease management costs?**

In the UK chart review study Ramagopalan et al. (34), because the cost of PEx were included in the estimates, the annual costs associated with hospitalization and pharmacotherapy were each adjusted to not double count the cost of care associated with PEx. The reduced hospitalization costs together with the surgery costs were captured in the economic model as annual non-PEx-related inpatient costs. Cost estimates categorized as “outpatient visits”, “pharmacotherapy” and “diagnosis” costs

in the chart review were captured in the economic model as annual non-PEx-related outpatient, pharmacotherapy, and other costs, respectively.

The Simmonds et al. was used to obtain the impact of CFTRm on disease management costs and the reduction in oral or inhaled antibiotic use was assumed to represent the reduction in pharmacotherapy costs incurred by patients treated with CFTRm.

HRQoL

B29. **Priority: Can the company please provide further details of the both the algorithm used for the utility values produced and the MMRM undertaken to infer utility benefits of treatment, including specific details of the models used and patient characteristics included?**

The development of the disease-specific preference-based utility measure in CF, the CFQ-R-8D applied methods originally developed in the estimation of a preference-based measure of health from the SF-36 (Brazier et al., 2002; Brazier et al., 1998) and subsequently used with condition specific measures in urinary incontinence (Brazier 2008), overactive bladder (Yang et al., 2009; Yang et al., 2011), cancer (Rowen et al., 2011), diabetes (Mulhern et al., 2017) and myelofibrosis (Mukuria et al., 2015). The team at Sheffield University (J. Brazier and D. Rowen) that drafted the NICE Technical Support Document Alternatives to EQ-5D for generating health state utility values (Brazier 2011) and A. Quittner, developer of the CFQ-R instrument (Quittner et al., 2005), worked with Acaster Lloyd, a research consultancy, and Vertex on development of the CFQ-R-8D (Acaster et al., 2022).

The recommended approach for development of a preference-based measure from an existing instrument such as the CFQ-R uses factor, psychometric and Rasch analysis to derive dimensions and identify suitable items for a 'health state classification system'. The classification system identifies the minimum number of health dimensions necessary to describe the primary impacts of a condition.(Brazier et al., 2002) Selected health states described by the classification system are then valued by members of the general public and these values are modeled to produce utility values for all health states defined by the classification system. The valuation

methods using time trade-off (TTO) mirror those used to value the EQ-5D and follow published guidelines (Brazier 2011).

B30. **Priority: Please clarify why PEx were not controlled for the MMRM conducted to infer utility benefits of treatment?**

In our clinical trials, CFQ-R and ppFEV1 were both evaluated at same time during regularly scheduled visits. PEx are not scheduled events, so there are no corresponding CFQ-R evaluations from which to determine the utility (or disutility) associated with these events.

B31. **Priority: A consistent measure of QoL is needed across healthcare in order to make consistent and transparent decisions in choices of healthcare funding. Given this the EAG considers the use of disease specific QoL measures inappropriate as cost and QoL cannot be fairly compared across different conditions. Given this, please can the company provide scenarios in the model using the disease specific QoL data mapped to EQ-5D and the directly reported EQ-5D data from the trial?**

EQ-5D data were not collected in the pivotal trials for IVA/TEZ/ELX and TEZ/IVA, so a scenario using EQ-5D data directly reported from the trial cannot be conducted.

Furthermore, our data collection agreement (DCA) that is in place between NICE, NHSE, The Cystic Fibrosis Trust, and Vertex, clearly outlines the collection of CFQR to address quality of life uncertainties. This data is being collected in our DCA report, and studies TRAJECTORY and MAGNIFY.

Generic preference-based measures such as the EQ-5D and SF-6D have been used in previous CFTR modulator clinical trials, but the data suggest they are insensitive to changes in HRQoL: people with CF self-report mean utility of 0.923 and 0.870 for mild and severe lung function impairment, respectively, which are higher than UK/US population norms (0.856/0.867).

The CFQ-R is a validated, reliable, and more sensitive measure of HRQoL widely used in CF. Vertex has recently developed a CF-specific, preference-based scoring algorithm (the CFQ-R-8D), according to published guidelines by the National Institute for Health and Care Excellence (NICE), which enables estimation of CF-specific health-state utilities based on the CFQ-R. At the patient level, the CFQ-R-8D is expected to capture more CF specific symptoms and provide a more sensitive measure of HRQoL and health-state utilities in CF.

Acaster et al. (2015) reported the most recent UK EQ-5D data stratified by ppFEV1. Acaster et al. conducted a cross-sectional observational study in the UK in which 401 pwCF aged over 18 years completed the CFQ-R, the EQ-5D and a demographic/clinical background form (35). The utility values from Acaster publication have been incorporated in a scenario analysis in the submission dossier (Scenario 2 results in Table 148).

An additional scenario has been conducted where Acaster utility values are applied without any other changes compared to the base case. The results are presented in the table below:

Scenario	Incr. costs (disc.)	Incr. LYG (disc.)	Incr. QALYs (disc.)*	ICER (£/QALY)*	NHB at £20,000*	NHB at £30,000*
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using Acaster utility values						

B32. The company refers to EQ 5D-5L data from TRAFFIC/TRANSPORT in figure 90 of their submission but in table 17 EQ-5D-5L is not recorded as an outcome, only EQ-5D-3L is. Please can the company clarify if TRAFFIC/TRANSPORT reported EQ-5D-5L data?

We apologise for the confusion. EQ-5D-5L data were not collected in either TRAFFIC (VX12-809-103) or TRANSPORT (VX12-809-104). The error is in the title of Figure 90, which should have been "EQ-5D-3L index scores by $ppFEV_1$ pooled across timepoints in TRAFFIC/TRANSPORT trials of LUM/IVA". The EQ-5D-3L questionnaire was administered at each study visit in both TRAFFIC and TRANSPORT, and

absolute change from baseline in EQ-5D-3L scores at Week 24 was a secondary endpoint in both studies. The single utility index score and the VAS score were analysed in both trials.

Analyses

B33. **Priority: As discussed in the model walkthrough call, please can the company provide the calibrated PEx rates with treatment discontinuation set to that of the trial and not zero?**

a. Are the company able to establish that there are no issues with calibrating the exacerbations to the trial data given the selection of patients in the model is likely to produce a "different“ cohort than was in the trials?

When re-calibrating the PEx treatment effect while including the discontinuation rates from the trial (input values used in the base-case analysis), the calibrated PEx rate ratios decrease slightly. For example, the PEx rate for F/MF changes from [redacted] to [redacted], which decreases the ICER by less than 1% (from [redacted] to [redacted]). Note that the calibrated PEx rate ratio decreases (getting closer to the trial value of 0.22) when including discontinuation in order to offset the “discontinuers” who are contributing PEx rates consistent with BSC (rate ratio of 1.0).

Per the answer to B4, the patient characteristics from the trial and that of the simulated cohort are very similar. Thus, there is no issue with calibrating using the patient profiles in the model.

Further clarification on cost-effectiveness data

B34. In line with the published validation exercise on model predicted 5-year survival for patients on Ivacaftor (McGarry et al. 2023), the company removed the application of the Liou et al. Cox proportional hazards model (based on individual patient characteristics at baseline) to the reference survival curve to generate a patients initial mortality hazard. Instead, the Cox proportional hazards model is only applied in subsequent cycles to model the impact of changes in patient characteristics on mortality. Removing this adjustment

assumes that the baseline hazard for modelled people with CF is the same as that for people with CF in the reference population of the same age, irrespective of individual patient characteristics.

a) **Please clarify if using the Liou et al. equation to only model the impact on mortality of those parameters that change overtime within the model (i.e age, ppFEV1, weight-for-age z score and pulmonary exacerbations), is failing to account for baseline impact of the remaining parameters on mortality, namely respiratory infections?**

The calibration exercise demonstrated that using the age-specific mortality of the general CF population as the estimate of baseline mortality for each simulated patient provided a better fit than the more complex approach previously employed in the model. Previously, the model adjusted the age-specific baseline mortality hazard using a hazard ratio estimated from patient-level risk factors and the Liou et al. Cox Proportional Hazard (CPH) equation. The adjustment was intended to account for differences in the individuals' characteristics at baseline versus the characteristics of the general CF population (e.g., increasing the baseline mortality hazard for a simulated patient who was "sicker" than the average CF population). However, in the absence of age-specific summary measures (e.g., mean ppFEV1 for every year of age), simulated patients' hazards were being compared to the overall average of the population (across all ages). Removing this adjustment instead assumes that the baseline mortality hazard for a simulated patient is the same as the average patient with CF of their age. This includes the impact of respiratory infections on mortality, which we believe is already captured in the estimate of baseline mortality hazard. As described in detail in the paper, removing this CPH adjustment from the baseline mortality calculation and applying it only to subsequent post-baseline model cycles improved the overall predictive nature of the model.

b) **As the coefficients of the Cox proportional hazards model are conditional on one another (i.e, if a parameter were to be removed from the model, the coefficients for other variables would change), please clarify if using the Liou et al. equation for only particular parameters is incorrectly using the coefficients of the model?**

The model does not exclude any parameters of the Liou et al. equation. The model includes all covariates from the Liou et al. equation. However, some parameters in the Liou et al. equation such as pancreatic sufficiency and respiratory infection status are assumed to remain unchanged from baseline over time. Thus, it is unnecessary to include pancreatic sufficiency and respiratory infection status to the mortality hazard calculations, as it does not contribute to the calculations (which compares patient characteristics from one cycle to the next). In addition, the findings observed in the validation study support the validity of the CFTR modulator models based on the Liou equation in predicting long-term survival and estimating the clinical and economic outcomes of CFTR modulators.

B35. The McGarry et al. validation study also undertook calibration of the survival data to ensure that median survival predicted by the model more closely matched that of current USA CF survival (pre-modulators) and give a closer match between the 5 year observed data and model predicted. As no such calibration was undertaken in the company's submitted analyses, does this mean that the company believed that model predicted median survival was an accurate representation of the UK population and that no further calibration was required?

The validation study, McGarry et al. used data collected in the ivacaftor long-term safety study (LTSS) to validate the survival projections of the CE model. The LTSS followed patients in the US and UK for a period of 5-years post-authorization, but the validation exercise was conducted in the US which had the largest sample size. The findings from McGarry et al. support the validity of the CFTR modulator models in predicting long-term survival and estimating the clinical and economic outcomes of CFTR modulators. In addition, this result suggests that models using this equation and applying similar methods can provide plausible estimates of treatment impact and outcomes and can be used with confidence to extrapolate beyond clinical trial data to provide informative predictions of long-term benefits of CF treatments.

[redacted]

[redacted] Therefore, it is assumed that the CE model is accurately capturing the mortality hazard for people with CF in the UK.

B36. The values included in the company's model for infection prevalence by age are listed below. The source for this data does not appear to be listed in the company submission, can the company clarify where this information is from?

Staphylcoccus Aureus		
Age Minimum (yrs)	Age Maximum (yrs)	Prevalence (%)
6	15	12.4%
16	31	22.5%
32	39	18.9%
40	47	17.9%
48	59	32.4%
60	100	53.3%

Burkholdia Cepacia		
Age Minimum (yrs)	Age Maximum (yrs)	Prevalence (%)
2	15	2.0%
16	31	4.9%
32	39	4.7%
40	47	7.1%
48	59	4.8%
60	100	2.8%

These input values were informed by the age-specific prevalence reported in the 2016 and 2017 UK CF Registry annual reports. The source for this data was not included in the submission, as these variables do not contribute to the model calculations. As described in the submission and responses above, baseline characteristics that do not change over time (like respiratory infection status) do not contribute to the mortality calculation.

B37. Priority: The formulation for LUM/IVA (Orkambi) for patients aged 1 to 5 years is a sachet.

a. Please confirm the details of the pack price/ pack size for the dosing regimen for patients aged 1 to 5 years (fill out the below table).

Table below completed as requested

B38. Priority: A dosing regimen for ELX/TEZ/IVA (Kaftrio) is only available for patients aged 6 years and older.

a. Please confirm the dosing/ treatment regimen for patients aged 2 to 5 years. If available, please send the draft SmPC for ELX/TEZ/IVA with details for patients aged 2 to 5 years included.

The dosing table from the draft SPC is included in the table below. The draft SPC is attached separately. Please note that the draft SPC document is confidential at this stage.

Table 1: Dosing recommendations for patients aged 2 to less than 6 years

Age	Weight	Morning dose	Evening dose
2 to less than 6 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

b. Please confirm the details of the formulation/ pack price/ pack size for the dosing regimen for patients aged 2 to 5 years (fill out the below table).

Table below completed as requested

	LUM/IVA	ELX/TEZ/IVA	
		ELX/TEZ/IVA	IVA
Age group	1 to 5 years	2 to 5 years	
Formulation	Granules in Sachet	Granules in Sachet	Granules in Sachet
Pack price (UK List Price)	£8,000.00	[redacted]	[redacted]
Pack size	**56 sachets (28 days)** a) LUM 75mg / IVA 94mg or b) LUM 100mg / IVA 125mg or c) LUM 150mg / IVA 188mg	**28 sachets (28 days)** [redacted] or [redacted]	**28 sachets (28 days)** [redacted] or [redacted]
Dose per day	2 sachets (1 sachet every 12 hours)	1 sachet (morning)	1 sachet (evening)

[redacted]

B (unnumbered 1): In respect of the response to the additional question which was submitted to NICE yesterday, the company notes that pharmacotherapy resource use consisted of: IV antibiotics, nebulized therapy, oral antibiotics, mucolytics, antifungals, pancreatic enzymes, overnight nutritional feeds, and other maintenance therapy. Can the company please provide the resource use associated with each of these therapies separately i.e. the mean proportion of patients using each treatment across the different ppFEV1 groups.

Unfortunately, we don't have the resource utilization tables from the study and therefore cannot share them.

B (unnumbered 2): In addition, the EAG has attempted to replicate the calibrated rate ratios for pulmonary exacerbations in each of the three models, using the details provided in Appendix N. However, the EAG was unable to obtain the same results as the company. Please could the company provide a copy of the three treatment models with the input parameters that are changed in the calibration exercise clearly highlighted and saved in their scenario analysis runner? This would be greatly appreciated.

The appendix N: calibration of PEx rate ratios in the economic model described the overall steps to calibrate each PEx rate ratio input in the model. [redacted].

It is also important to recognize that if any clinical inputs have changed from the submitted base case model, the PEx rate ratios should be re-calibrated following the steps of the appendix N and by selecting the appropriate population for the input.

B (unnumbered 3): Please could the company clarify the exact numbers (and the specific data table sources used for these numbers) that were used for the calculations of the [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

References

1. Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple Therapy for Cystic Fibrosis Phe508del–Gating and –Residual Function Genotypes - Supplementary Appendix. New England Journal of Medicine. 2021;385(9):815-25.
2. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. New England Journal of Medicine. 2011;365(18):1663-72.
3. Vertex. Clinical Study Report KONDUCT VX11-770-110: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have the R117H-CFTR Mutation, version 1.0. 2014.
4. Vertex. Clinical Study Report KONNECTION VX12-770-111: A Phase 3, Two-part, Randomized, Double-blind, Placebo-controlled, Crossover Study With an Open-label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D-CFTR Gating Mutation, version 2.0. 2014.
5. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. New England Journal of Medicine. 2019;381(19):1809-19.
6. Vertex. An Observational Study of Users of Kaftrio, Orkambi and Symkevi in the UK Cystic Fibrosis Registry to Satisfy Data Collection Agreement in the UK: Second Interim Analysis (IA2). 2023.
7. Southern KW, Castellani C, Lammertyn E, Smyth A, VanDevanter D, van Koningsbruggen-Rietschel S, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. Journal of Cystic Fibrosis. 2022.
8. NICE. NICE health technology evaluations: the manual [PMG36]. 2022.
9. Zorginstituut Nederland. Guideline for economic evaluations in healthcare 2016.
10. The Agency for Health Technology Assessment and Tariff System. Health Technology Assessment Guidelines Version 3.0. Warsaw; 2016.
11. Sharma D, Aggarwal AK, Downey LE, Prinja S. National Healthcare Economic Evaluation Guidelines: A Cross-Country Comparison. Pharmacoecon Open. 2021;5(3):349-64.
12. Cleemput I, Neyt M, Van De Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. Health Technology Assessment (HTA). Brussels. Belgian Health Care Knowledge Centre (KCE); 2012. Contract No.: KCE Reports 183C. DOI : 10.57598/R183C.
13. Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health Econ. 2011;20(1):2-15.
14. Gravelle H, Smith D. Discounting for health effects in cost-benefit and cost-effectiveness analysis. Health economics. 2001;10(7):587-99.
15. Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. Value in Health. 2004;7(4):397-401.
16. Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. J Cyst Fibros. 2021;20(1):68-77.

17. Vertex. Study Protocol: An Observational Study of Users of Orkambi, Symkevi and Kaftrio in the UK Cystic Fibrosis Registry to Satisfy Data Collection Agreements in the UK 2021.
18. Lee T, Sawicki GS, Altenburg J, Millar SJ, Geiger JM, Jennings MT, et al. EFFECT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS. Journal of Cystic Fibrosis.
19. Sawicki GS, Konstan MW, McKone EF, Moss RB, Lubarsky B, Suthoff E, et al. Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation. Pulm Ther. 2022;8(4):385-95.
20. Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med. 2015;3(7):524-33.
21. Foundation CF. Patient Registry: Annual Data Report. 2021.
22. Vertex. AURORA-OLE (Study 445-105): Cliniocal Study Report Week 144 Interim CSR: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation. Protocol Number: VX17-445-105. 2022.
23. Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. J Cyst Fibros. 2023.
24. Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. Ther Adv Respir Dis. 2019;13:1753466618820186.
25. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax. 2007;62(4):360-7.
26. Whiting P AM, Burgers L, Westwood M, Ryder S, Hoogendoorn M, Armstrong N, Allen A, Severens H, Kleijnen J. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technology Assessment. 2014;18(18):1-106.
27. McGarry LJ, Bhaiwala Z, Lopez A, Chandler C, Pelligra CG, Rubin JL, et al. Calibration and validation of modeled 5-year survival predictions among people with cystic fibrosis treated with the cystic fibrosis transmembrane conductance regulator modulator ivacaftor using United States registry data. PLoS One. 2023;18(4):e0283479.
28. .

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Cystic fibrosis MTA [ID3834]

Clarification questions on the Final Analysis for Kaftrio

PART 2

July 2023

File name	Version	Contains confidential information	Date
ID3834 Vertex CF Final Analysis for Kaftrio EAG Clarification Questions [AIC]	**1**	**Yes**	**05.07.2023**

Section A: Clarification on effectiveness data

Priority Questions: Due to time limitations, the EAG requests that the company address all priority questions as soon as possible, and prioritise these over the questions not marked as priority.

A1. Priority. The Company's estimate for the annual rate of change of $ppFEV_1$ for the ELX/TEZ/IVA cohort was –0.565 (95% CI: –0.755 to –0.376), compared to –1.706 (95% CI: –1.888 to –1.524) in the historical CFTRm-naive cohort. The EAG considers this estimate likely to underestimate the relative rate of decline in lung-function for patients on ELX/TEZ/IVA compared to ECM, because of:

- **The use of a historical control cohort, which typically results in an overestimation of treatment effects if the negative control effects are not accounted for;[1, 2]**
- **Factors associated with the COVID-19 pandemic preserving lung function for the ELX/TEZ/IVA cohort, such as viral shielding leading to a lower rate of pulmonary infections.[3]**

Please comment on whether the company agrees that the Final Analysis is likely to underestimate the rate of decline in lung-function for patients on ELX/TEZ/IVA. If the Company does not agree, please provide evidence that the use of a historical control cohort is unlikely to lead to an overestimation of the rate of decline for a counterfactual contemporaneous control cohort, and that COVID-19 related shielding was not associated with preserved lung function in people with CF during the data collection.

[Vertex disagrees with the conclusion that the Final Analysis underestimates the rate of decline in lung-function for patients on ELX/TEZ/IVA. In fact, sensitivity analysis testing for different types of data included in the model suggest no changes in lung function over time, in line with other studies[7].

Three phase 3 clinical study results have reported no changes over time in the lung-function of patients initiating treatment with ELX/TEZ/IVA; these studies provided data for the Lee et al. US analysis evaluating the effect of ELX/TEZ/IVA on annual rate of lung function change, which reported no changes in lung function over time (+0.39 percentage points; 95% CI, −0.06, +0.85)[7]:

- 445-102 (NTC03525444)[8],
- 445–103 (NCT03525548)[9], and
- Final Analysis (FA) of the open-label extension study 445–105 (NCT03525574)[10] – data from 2-years used in Lee et al.

With regards to the confounding factors introduced by the COVID-19 pandemic [redacted] Adjusting the analysis for the potential confounding effect of shielding/lock-down interventions during the COVID-19 pandemic needs to be further investigated when longer-term real-world data beyond 2022 on patients initiated on ELX/TEZ/IVA are available (outside of the pandemic).

Part of the Lee et al. analysis relied on clinical data collected during the time period before the start of the COVID-19 restrictions, i.e. 445-102 (completed April 2019), 445-103 (completed December 2018), and the early part of 445-105 (started October 2018). A portion of the IA3 data cut in study 445-105 was data collected from October 9, 2018 to March 25, 2021, overlapping with the COVID-19 pandemic when social distancing and mask use likely led to a decline in pulmonary exacerbations. The Final Analysis of study 445-105, which completed on January 9, 2023 and included an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, demonstrated that participants treated with ELX/TEZ/IVA continued to have on average no loss of lung function and pulmonary exacerbation rates remained low, which strongly suggests that ELX/TEZ/IVA is the primary driver behind these results and not the COVID-19 pandemic. Study 445-105 and the Lee et al. analysis show a flat rate of change regardless of the COVID-19 pandemic. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] and consistent to what has been reported in the literature. A US study found a mean annualised rate of change in ppFEV$_1$ of −1.92 (95% CI, −2.16 to −1.69) in matched controls. A UK study estimated a rate of decline in ppFEV1 of -1.52% (95% CI: -1.66 to -1.38%) in adults when accounting for age, sex and pancreatic status. The VOICE study evaluated disease progression measured by ppFEV$_1$ in a cohort of European CF patients prior to initiation of CFTRm therapy and estimated an annual rate of change of -2.17 (SE 0.30) for individuals ≥6 years. (For references see page 66 of the report).

This real-world study is a retrospective observational study based on real-world data generated in routine clinical practice and captured in the UK CF Registry without any pre-specified conditions for this specific analysis. [redacted]

[redacted]

Overall the totality of data from this study should be put into context. This large, real-world data set of people with CF who initiated ELX/TEZ/IVA in the UK showed improvements in multiple CF-related health outcomes, consistent with the literature. ELX/TEZ/IVA resulted in improvements in a broad range of clinically important outcomes in the first post-treatment year that were maintained into the second post-treatment year (these include ppFEV$_1$, PEx, nutritional outcomes, lung infections, overall survival, lung transplants). Patients were initiated during the COVID-19 pandemic, but improvements in outcomes were maintained throughout the 18-month period post easing of lock-down restrictions. This is supported by studies 445-102[8], 445-103[9], 445-105[10], which collected data before, during and after the COVID-19 pandemic. Collectively, the weight of clinical and real-world evidence available for ELX/TEZ/IVA shows that it consistently provides clinical benefits that are sustained and has the potential to modify the course of the disease.

A2. Priority. The Company's Final Analysis suggests that for patients on ELX/TEZ/IVA, ppFEV$_1$ declines in the years following initiation. The Company's base case analysis has not been updated to reflect this, and still includes a 100% reduction in the rate of ppFEV$_1$ decline relative to ECM. Please provide an updated base case including a long-term ppFEV$_1$ decline for patients on ELX/TEZ/IVA as indicated by the Company's Final Analysis.

[In responding to question A1, we have detailed the uncertainty around the analysis of rate of change in ppFEV$_1$ for ELX/TEZ/IVA in the UK registry. Given this and the weight of evidence from other studies on ppFEV$_1$ changes over time for

ELX/TEZ/IVA, Vertex believe a 100% reduction in the rate of ppFEV$_1$ decline relative to ECM in the base case is appropriate, with uncertainty in the model addressed using scenario and sensitivity analyses.

Vertex, would like to take this opportunity to request EAG to share the cost-effectiveness model and technical report of EAG's developed model used during this current appraisal.]

A3. Priority. The Company conducted matched-control analyses for ELX/TEZ/IVA, TEZ/IVA, LUM/IVA and IVA monotherapy to inform the economic models. The following point estimates in the difference in annual change of ppFEV$_1$ between CFTR modulators and established clinical management were generated: ELX/TEZ/IVA: +1.125; TEZ/IVA: +1.27;[4] LUM/IVA: +0.96;[5] IVA: +0.80.[6] In contrast, an independent analysis of IVA using both historical and contemporaneous cohorts from UK Registry data generates a point estimate of +0.49.[2] Notably, the ELX/TEZ/IVA analysis and Keogh *et al.* analysis compare UK CF registry data with UK CF registry data, whereas the TEZ/IVA, LUM/IVA and IVA analyses compare CFTR clinical trial data with registry data.

A) Given the discrepancy between the company's estimate and the independent analysis of IVA, please can the company provide a rationale to explain the difference, or acknowledge that its estimates may underestimate the rate of decline for people on CFTR modulators relative to ECM.

B) For the LUM/IVA matched control analysis,[6] the absolute difference between the slopes of LUM/IVA treated patients (point estimate: –1.33) and matched controls (point estimate: –2.29) was not reported. The EAG has therefore calculated the naïve difference in these slopes as 0.96. Please confirm if this is the same estimate as

calculated by the model, and please provide the 95% confidence intervals around this estimate.

[The difference in annual change of ppFEV$_1$ between CFTR modulators and established clinical management for ELX/TEZ/IVA of +1.125 was reported for the Sensitivity analysis: rate of change analysis excluding Managed Access Patients that initiated ELX/TEZ/IVA from 19/08/2019 to 20/08/2020. Could the EAG please provide a rational why this value was used as a reference in this question?

A very recent study, Szczesniak et al., has explored the impact of differing modelling strategies to estimating the rate of decline in lung function in individuals with CF[12]. One of the main findings of the Szczesniak et al. study was that differences in rate of decline estimates from prior studies are due not necessarily to statistical modelling strategy but rather to inherent differences in study design, inclusion criteria, or additional covariate adjustment, especially in estimating effects associated with a given exposure. Vertex believes this paper supports that we have defined an appropriate model for the rate of change analysis for ELX/TEZ/IVA in the UK DCA. Furthermore, the linear model results in the Szczesniak et al. paper aligned with previous estimates of CFTRm naïve analyses with a decline ranging from 1.3 to 1.7 in ppFEV$_1$, including the rate of decline outcome of the H-CFTRm-naïve cohort in our study.

Answer to question A3 A):

The EAG makes reference to the Keogh et al. analysis using negative control outcomes and difference-in-difference (DID) analysis to estimate treatment effects[2]. This analysis is a methods paper exploring how to apply negative control outcomes/DID approach in a new way to estimate negative-control-corrected treatment effects (NCCTEs).

Vertex believes that this methodology is not an appropriate method to be used in our study for “correcting” the treatment effect of ELX/TEZ/IVA. The “parallel trend assumption” is necessary for the DID analysis to ensure internal validity of the DID model. It requires that in the absence of treatment, the difference between the ELX/TEZ/IVA and ECM is constant over time. Vertex believes that the effect of the

COVID-19 pandemic over time cannot simply be considered as a confounding factor but violates this critical assumption for DID because of the dynamic of the pandemic over time. The answer to question A1 from the EAG already details the unexpected behaviour in the year before most patients were initiated with ELX/TEZ/IVA.

The +0.49 value as NCCTE in the Keogh et al. analysis is derived by subtracting an adjusted negative control effect (NCE) of 0.2 (Figure 3B) from an adjusted naïve treatment effect (NTE) of 0.68[2]. As a conclusion from the Szczesniak et al. paper (see above) it is not appropriate to compare different estimates of rate of change from differently designed studies that vary on data availability, data sources, follow-up time, modelling approaches, or other factors. Vertex believes that the naïve treatment effect of 0.68 is underestimating the treatment effect. Vertex has evidence on the long-term durability of IVA on reduction of change in lung function over up to 5-years in pwCF aged 6+ which was explored in a longitudinal study from the US Cystic Fibrosis Foundation Patient Registry[13]. This analysis supported the previous Sawicki et al. analysis with a difference in annual change of $ppFEV_1$ between IVA and a comparator cohort of +0.80 through 5-years of follow-up. This 0.8 is also mentioned in the Keogh et al. paper as unbiased estimate. Further, Vertex has doubts about subtracting a NCE of 0.2 given all the variability of outcomes. The lower bound of the 95% confidence interval of the NCE was 0.04 meaning potentially no bias.

In essence, Vertex believes that the methodology laid out in the Keogh et al. paper might be worth to consider. However, Vertex considers the rationale to explain the difference as valid and therefore believes the company's estimate is more reliable than the outcome of the independent analysis of IVA.

Answer to question A3 B):

Vertex confirms [redacted]

[redacted]

Further for LUM/IVA: a number of real-world analyses have been conducted for LUM/IVA that confirm the reduction in rate of lung function decline that was previously demonstrated[14-20,]. Collectively, this evidence indicates that LUM/IVA treatment results in a sizeable reduction in the rate of decline in $ppFEV_1$ over time, relative to no treatment, and confirms the estimates and methods employed in the registry-matched analysis by Konstan et al. (2017) that utilized clinical trial patients for the LUM/IVA-treated group[5].

Overall Vertex disagrees with the EAG conclusion that our estimates underestimate the rate of decline for people on CFTR modulators relative to ECM and believe the values provided in our submission are accurate.]

A4. Priority. In the Final Analysis, the company states that: "For the ELX/TEZ/IVA cohort, any $ppFEV_1$ measurements recorded within 30 days from index date were excluded, to ensure that acute improvements in lung function after ELX/TEZ/IVA initiation were removed, to avoid bias introduction. As per the pivotal clinical trials, patients gain acute improvements within the first 30 days following treatment." In contrast, for the matched-controlled estimates for TEZ/IVA, LUM/IVA and IVA, the following time-periods were excluded for the acute increase: 22 days; 21 days; 30 days, respectively. The EAG considers data from the pivotal TEZ/IVA and LUM/IVA trials, and extension studies, to show a continued increase in $ppFEV_1$ up to at least Week 4 (Day 28), or even Week 8 (Day 56). Therefore, the EAG expects the TEZ/IVA and LUM/IVA analyses of annual rate of decline to underestimate the long-term rate of

ppFEV$_1$ decline for people receiving CFTR modulators, due to not having adequately excluded the acute treatment effects.

a) Please comment on this, and provide a more detailed evidence-based justification for the use of the 30-day window in the Final Analysis.

b) Please provide an updated version of the TEZ/IVA and LUM/IVA analyses that aligns with the Final Analysis by excluding the first 30 days following CFTR modulator treatment.

[Answer to A4 a)

Vertex clinical studies for TEZ/IVA, LUM/IVA and ELX/TEZ/IVA with pre-defined visit time points i.e., at 15 days and 4 weeks after initiation. All clinical studies demonstrated the most prominent improvement in ppFEV$_1$ within the first 15 days. Vertex agrees to the EAG consideration that data from the pivotal TEZ/IVA and LUM/IVA trials, show a further increase in ppFEV$_1$ up to Week 4 (Day 28), however is much less prominent. Consequently, the acute improvements in ppFEV$_1$ reach their peak between day 15 and week 4 after initiation. Vertex cannot further specify that due to the pre-specified time points in the clinical studies.

Preclinical data and prior experience with CFTR modulators additionally support that acute improvement in ppFEV$_1$ is observed between week 2 to Day 30. The rapid change observed within the week 2 or 30-day period likely represents improvement in mucociliary clearance and removal of mucus plugs. Once the patient passes the acute phase, generally after one month, the change seems to stabilize over time. Any further improvement after the acute phase may indicate improvements in structural changes other than mucus accumulation in the airways.

Vertex is of the opinion that 4 weeks/30 days after treatment initiation the ppFEV$_1$ values largely remain flat for all three CFTR modulators throughout the follow-up period within acceptable error limits as shown with overlapping error bars[5,8,9].

For Objective 1 from the UK DCA it was decided to weigh on the conservative side by choosing 30 days to exclude the acute improvement in ppFEV$_1$. The protocol was

developed in collaboration between the UK Cystic Fibrosis Registry, UK clinical experts, NICE and Vertex, with agreement that 30 days would be sufficient.

Answer to A4 b)

Vertex does not believe that updated versions of the TEZ/IVA and LUM/IVA matched-controlled analyses are needed. The answer to A4 a) details that the 30 days were chosen for the final analysis of Objective 1 as a very conservative approach and is adapted to real-world data as data measures are captured at timepoints based on clinicians' discretion. The TEZ/IVA and LUM/IVA rate of change analysis are based on clinical trial data (with specific timings of data capture for all patients) which has shown that after 2 weeks of treatment all patients have reached the maximum improvement on $ppFEV_1$, therefore the periods of 22 days; 21 days, respectively, are appropriate.]

A5. Priority. The long-term rate of decline $ppFEV_1$ analysis in the Final Analysis is based on a mean 22.23 months (SD: 2.76) for the ELX/TEZ/IVA arm, and a similar length of follow-up is available for the long-term extension studies informing the estimates for LUM/IVA and TEZ/IVA. In the model, the company assumes the relative effects of CFTR modulators on $ppFEV_1$ decline and pulmonary exacerbations are constant for a patient's life. Please comment on the uncertainty around whether the relative long-term treatment effects of CFTR modulators compared to ECM are constant for a patient's life, especially considering that existing data have less than 5-years follow-up.

[There are a number of studies that have started to read out on the long-term impact of CFTR modulators.

In study 445-105, the 192-week open label extension study for 2 pivotal Phase 3 trials for ELX/TEZ/IVA, the improvements observed in $ppFEV_1$ were maintained across the entire 192-week follow-up period[10]. In addition, a decreased rate of pulmonary exacerbations and improvements in BMI continued throughout the follow-up period. Two Phase 3 clinical studies contributed to study 445-105: 445-102 (NTC03525444)[8] and 445–103 (NCT03525548)[9]. This clinical data was collected during the time period before the start of the COVID-19 restrictions, i.e. 445-102 (completed April 2019), 445-103 (completed December 2018), and the early part of

445-105 (started October 2018). However, portions of the IA3 data cut, which collected data from October 9, 2018, to March 25, 2021, overlapped with the COVID-19 pandemic when social distancing and mask use likely led to a decline in pulmonary exacerbations. The final analysis of study 445-105, which completed on January 9, 2023, and included an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, demonstrated that participants treated with ELX/TEZ/IVA had on average no loss of lung function which is consistent with the results seen in IA3 of 445-105. This 192-week data provides the longest follow-up of ELX/TEZ/IVA to date and demonstrates the significant and sustained benefit of ELX/TEZ/IVA.

For IVA, an analysis on the long-term impact on clinical outcomes and mortality versus pwCF not eligible for and not receiving IVA was conducted using the US Cystic Fibrosis Foundation Patient Registry[21]. The analysis used data from January 2010 to December 2019, so outside the COVID-19 pandemic. A total of 736 IVA-treated patients were matched to 2944 comparator pwCF, aged 6+, with a study follow-up duration of 7.9 years. The IVA-treated cohort had a lower adjusted hazard of overall mortality (HR 0.22; 95%CI 0.09,0.45) and lung transplant (HR 0.11; 95% CI 0.02,0.28) than the comparator cohort. In addition, IVA-treated pwCF had higher average ppFEV$_1$ (mean difference 8.46; 95% CI 7.34,9.75) and BMI scores (mean difference 1.20; 95% CI 0.92, 1.71) and lower incidence rates of PEx (51% reduction in the adjusted incidence rate) and all-cause hospitalization (50% reduction in the adjusted incidence rate) than the comparator cohort.

An analysis in the Cystic Fibrosis Registry of Ireland evaluated the long-term impact of IVA on clinical outcomes and healthcare resource utilisation among people with CF, versus a non-CFTRm-treated group[22]. The analysis used data from January 2013 to December 2019, so outside the COVID-19 pandemic. A total of 166 IVA-treated patients (mean follow-up 5.8 years) and 150 non-CFTRm treated pwCF (mean follow-up 5.6 years), aged 6+ were included in the full analysis set. At 7-years, IVA-treated patients achieved a mean absolute change from baseline in ppFEV$_1$ of 3.4 (1.6, 5.3), whilst the non-CFTRm treated cohort had a mean absolute change from baseline in ppFEV$_1$ of -7.9 (95% CI -10.1, -5.7); between group difference at 7-years of 11.3 percentage points in FEV$_1$. In addition, sustained

improvements in BMI (between group difference of 1.66), lower annualised rates of PEx (RR 0.41; 95% CI 0.33,0.52) and hospitalisation (RR 0.44; 95% CI 0.34,0.56) were observed.

The long-term durability of IVA on reduction of change in lung function over up to 5-years in pwCF aged 6+ was explored in a longitudinal study from the US Cystic Fibrosis Foundation Patient Registry[13]. The rate of change was compared between an IVA-treated cohort with ≥1 *CFTR* gating mutation, aged ≥6 years who initiated IVA on or after January 31, 2012, through December 31, 2018 and a comparator cohort with *F508del* and a minimal function mutation, aged ≥6 years not eligible for IVA treatment. The rate of change in lung function in the IVA-treated cohort was consistent over time, IVA treatment significantly reduced the annual rate of lung function decline by 33%, 36%, and 39% over 3, 4, and 5 years, respectively versus the comparator cohort. These results support IVA having a significant and sustained impact on the disease trajectory of CF

Regarding the model, and the comment from the EAG on assuming the relative effects of CFTR modulators on $ppFEV_1$ decline and pulmonary exacerbations are constant for a patient's life, the above data have the longest possible follow-up to date and demonstrate the sustained impact of CFTR modulators. In the model the uncertainty is addressed with scenario and sensitivity analyses.]

A6. Priority. For the long-term effects of CFTR modulator combinations, the EAG is aware of the absence of: long-term ECM-controlled data; data sources with follow-up times greater than 3 years and; data sources not confounded by COVID-19. If the company has any unpublished data on the long-term effects of CFTR modulators that may resolve some of these issues, from the UK or elsewhere, please provide these.

[Please see the response to question A5, that details several long-term studies that have data collected before, during and after the COVID-19 pandemic.]

A7. Priority. The EAG recognises that a descriptive analysis that does not account for the within-person correlation of pulmonary exacerbations and differing follow-up lengths, limits the ability to interpret the data presented for Object 4 (Pulmonary Exacerbations [proxied by IV antibiotic episodes]). Nevertheless, the EAG considers the two main causes of the 62% reduction in the annual rate of PEx experienced by patients on ELX/TEZ/IVA, compared to the year before treatment initiation, to be likely be: i) viral shielding and other factors associated with COVID-19; ii) a treatment effect of ELX/TEZ/IVA. The EAG notes that as follow-up for some patients is now available in the period after most social distancing guidance was lifted in the UK, that a more informative analysis of PEx following ELX/TEZ/IVA initiation may be possible. In lieu of a formal analysis similar to Objective 1, please provide the annualised PEx rate for patients on ELX/TEZ/IVA between July 2021 (the Company identified point of most COVID-19 social distance removed) and last follow-up. Please also provide these data between 1 January 2022 and last follow-up.

[The EAG is right that the descriptive analysis does not account for the within-person correlation of pulmonary exacerbations. The annualised PEx rates as defined in the protocol assume a Poisson distribution. To account for the within-person correlation would require a modelling approach which has not been planned for and agreed upon in the protocol. Accordingly, this adjustment is not possible within such kind of descriptive analysis.

Different follow-up lengths are accounted for by expressing the annualised rates as rates per patient-year follow-up.

[redacted]

[redacted]

Outside of this study, a recent real-world study in more than 16,000 patients using data from the US registry found that the annual rate of PEx decreased by 79% from pre- to post-initiation of ELZ/TEZ/IVA[23], so the findings in this study are consistent with those. Results from the final analysis of study 445-105 open label extension, which completed on January 9, 2023, and includes an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, demonstrated that participants treated with ELX/TEZ/IVA had pulmonary exacerbation rates that remained low[10].]

A8. Priority. Please clarify why the Final Report analysis for long-term change in ppFEV$_1$ was not adjusted for spirometry type or prior CFTR modulator use, and/or why justification for not adjusting for spirometry type was not included in the Final Report, following the recommendations in the previous EAG's review of the second interim analysis.

[As reported previously the spirometry type is not captured by the CF Registry, therefore it is not possible to adjust for this in long-term change in ppFEV$_1$. On prior CFTR modulator use, it has been well documented in clinical studies that there are significant improvements in ppFEV$_1$ when treated with ELX/TEZ/IVA, regardless of whether individuals were CFTR modulator naïve or previous users of Orkambi or Symkevi.

The rate of change analysis included 12+ patients with either a F/F or a F/MF genotype. Almost all 12+ F/F patients in the UK have been pre-treated before receiving ELX/TEZ/IVA while F/MF patients were all untreated. Therefore, the genotypes also represent pre-treatment/naïve. Genotype was a matching criterion. In that respect the comparison between the cohorts is adjusted for prior CFTR

modulator use. Additionally, separate models by genotype were run to ensure robustness of the overall model.]

A9. Priority. Please provide the full model output from the rate of change in ppFEV$_1$ analysis, including coefficients and 95% confidence intervals for each fixed effect parameter (treatment, time, treatment by time interaction, sex and age).

[redacted]

A10. Priority. Please clarify which analyses were considered to account for the potential confounding effects of COVID-19, and comment on whether each of the following approaches were considered:

- **Adding a dummy variable for measurements during COVID-19 lockdown restrictions/social distancing;**
- **Implementing a non-linear model, or piecewise linear or non-linear regression models to allow the slope of ppFEV$_1$ decline to change over time.**

If deemed feasible, please provide such an analysis.

[Vertex assumes that this question is referring to Objective 1 on rate of change in ppFEV$_1$ only.

Objective 1 was designed to explore the differences in the rate of change in ppFEV$_1$ in patients treated with ELX/TEZ/IVA versus an untreated cohort. Given the rapid initiation of majority of patients eligible to ELX/TEZ/IVA treatment upon regulatory approval, a study design including contemporaneous controls was not feasible; to overcome this limitation a historical cohort of untreated individuals was created to allow an analysis of differences across groups. While the current analysis was successful in avoiding the impact of shielding/lock-down interventions during the COVID-19 pandemic in the historical controls (by matching ELX/TEZ/IVA patients to untreated patients in an ascending order starting 1st January 2015), it is not feasible, to do the same for the ELX/TEZ/IVA cohort where most patients initiated treatment during the pandemic after August 2020. The shielding/lockdown effect during the COVID-19 pandemic needs to be further investigated when longer-term real-world data beyond 2022 on patients initiated on ELX/TEZ/IVA are available (outside of the pandemic).

Considerations about a “Dummy” variable added to the mixed effect model:

A potential dummy (indicator) variable might be defined as: 1 = outside of COVID-19 lockdown (either before March 2020 or after July 2021), 0 = during COVID-19

lockdown (between March 2020 and July 2021 for UK); in fact such a dummy variable indexes all measures outside of COVID-19 lockdown.

Most patients initiated ELX/TEZ/IVA in the second half of 2020 (during COVID-19 lockdown), with 92% of the baseline ppFEV$_1$ measures falling in that year. Indexing the measurements by a dummy variable as described above will split the ELX/TEZ/IVA into two distinct groups:

1. The sub-cohort of managed access patients (initiated before March 2020) with ppFEV$_1$ measures before the COVID-19 lockdowns (during their first year of treatment)

2. for the sub-cohort of patients who initiated ELX/TEZ/IVA treatment shortly after August 2020, with their ppFEV$_1$ restricted to those after COVID-19 social distancing (after July 2021) which is essentially during their second year of treatment

A linear model as currently planned will no longer be adequate taking the differences of managed access patients versus patients initiated after August 2020 into account.

Considerations about a non-linear model, or piecewise linear or non-linear regression models to allow the slope of ppFEV$_1$ decline to change over time:

The rate of change analysis includes measures up to 730 days after index date OR up to the second annual review if not included within 730 days after index date (excluding measurements within the first 30 days after treatment initiation). This time period is considered too short, and number of measures might be too small for fitting a non-linear model better than a linear one.

Vertex considers the only way to cut the 2-year follow up time into “pieces” (taking also into account the way the data are collected in the registry) would be:

- “Up to 365 days” which includes all measures after index date within a time block of 365 days OR up to first AR if not included in the block of 365 days;

- “366 to 730 days” includes all measures in the time block of 366 to 730 days after index date OR up to second AR if not included in the block 366 to 730 days

When excluding Baseline and all measures during the first initial improvement (during 30 days after treatment initiation) from the ELX/TEZ/IVA group for the rate of change analysis Vertex believes that:

- there is no hint that linearity is highly violated over the 2-year follow-up period
- with the known variability of the data a non-linear model is not assumed to be more accurate than a linear one

It is therefore not expected that a piece-wise model would result in any major difference to the specified linear model.

In summary, Vertex believes that the two proposed options proposed by the EAG to account for the potential confounding effects of COVID-19 would not result in more accurate estimates in the analyses. The proposed analysis strategy as detailed in the protocol was extensively discussed and agreed with all stakeholders (NHS England, NICE, CF Registry and Vertex) as the best/most robust approach. Any further analyses outside those in the protocol would require review and approval of a protocol amendment before implementation.

Non-Priority Questions. The EAG considers these issues to be key unresolved issues in the Company Final Analysis, but notes that the impact of these questions on the economic modelling for the MTA is lower than those identified in the priority questions. Due to the time pressure of the MTA, the EAG requests the Company focuses on answering the priority questions first.

A11. The EAG considers the eligibility criteria for the Final Analysis of the long-term rate of decline in ppFEV$_1$ to introduce selection bias into the analysis, but considers it difficult to assess the direction of any resulting bias. The EAG notes that a large number of people were excluded due to:

- Being aged <12 years (1257, 17% of total ELX/TEZ/IVA cohort with a start date after 19/08/2019);
- Not having an F/F or F/MF genotype (1447, 19% of total cohort);
- Not having ≥ 2 potential follow-up annual reviews with ppFEV$_1$ values (1295, 17% of total cohort)

The EAG acknowledges that this analysis was outlined in the protocol. Please provide any comment on the likely magnitude or direction of any bias in the long-term ELX/TEZ/IVA estimates compared to ECM, relative to ELX/TEZ/IVA as used in clinical practice, that may have been introduced by selecting this subset of patients for analysis.

[The rate of change analysis was designed to be as meaningful as possible, with clear eligibility criteria, which was agreed with NICE in the protocol, taking into account ppFEV$_1$ behaviour and ELX/TEZ/IVA approval dates.

- Younger age patients are known to have a different trajectory of lung function decline, therefore the analysis was restricted to those individuals 12+ years of age. In addition clinical studies are designed with separate age cohorts 6-11 and 12+.
- For a rate of change analysis there needs to be a minimum length of follow-up for a meaningful analysis, hence the need to have a specific number of annual

reviews during follow-up. The age cohort 6-11 could only access ELX/TEZ/IVA after approval in January 2022, and in Table 2 of the report it states that mean follow-up time was [redacted], not long enough to include in a rate of change analysis. For genotypes other than F/F and F/MF, the approval for F/Any in 12+ was August 2021, giving a mean follow-up time around [redacted], again limiting the number of patients with meaningful follow-up for a rate of change analysis.

- The amended protocol was designed after approval of ELX/TEZ/IVA in the F/F and F/MF 12+ years of age cohort.]

A12. The EAG considers the data presented in Table 18 and Table 19 of the Final Analysis report on the frequency of pulmonary exacerbations before and after the initiation of ELX/TEZ/IVA to be difficult to interpret due to the large number of 0 data points. Please provide: i) the number of patients with no days on IV antibiotics for each cell; ii) versions of these tables for the subgroup of patients who had at least one day on IV antibiotics.

[The Excel workbooks contain the number of patients with at least one IV treatment, but no further statistics are presented. The most impactful outcome for PEx and one that aligns with other studies of CFTRm, is the annualised rate. [redacted]

A13. Please provide the same analyses as requested in A12 for the number of "Days on IV antibiotics per treatment episode at home (excluding those in hospital)", currently, the data are only provided for those in hospital.

[See answer for A12.]

A14. The EAG is concerned that delayed reporting, missing data, and/or a lower number of patients at risk, could account for the reduction in pulmonary exacerbations and hospitalisations observed in Figures 13 and 14, especially in the year 2022. Please provide versions of Figure 13 and Figure 14 with the y-axis being "proportion of encounters/reviews with hospitalisation" and "proportion of encounters/reviews with pulmonary exacerbations", or another suitable method of displaying the data as proportions of the people at risk at each point, rather than the absolute number of exacerbations or hospitalisations.

[Objective 13 was an exploratory objective designed to assess the rate of PEx and hospitalisations across the entire CF population in the registry from uncleaned data, and presented as the number of events recorded each month from January 2018 to end of December 2022. The number of individuals in the UK CF registry month-on-month remains relatively stable at approx. 10,500, so figures 13 and 14 can be interpreted based on this. Interpretation of this objective should be done with caution, especially in the context of ELX/TEZ/IVA. Due to the nature of data capture for these two outcomes in the registry being from annual reviews, missing data will only impact 2022 onwards, the data will be complete to the end of 2021. As annual reviews complete through 2023, additional data will be added for 2022.]

The EAG now comments on each of the objectives reported in the Final Analysis. The EAG notes that the Final Analysis is specific to ELX/TEZ/IVA, rather than covering LUM/IVA and TEZ/IVA due to treatment switching. The EAG notes that at the time of writing, the EAG did not have access to the Workbooks that were to be provided with the Final Analysis.

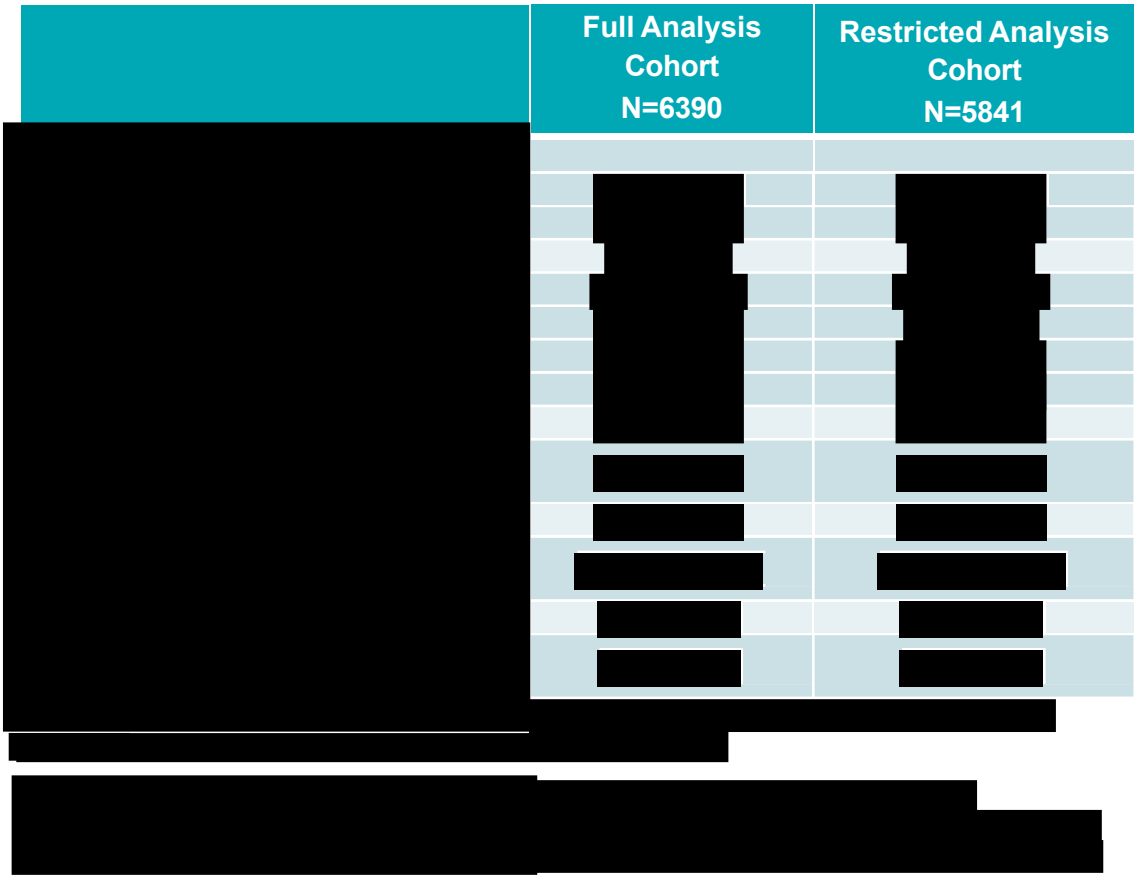
A15. Objective 3. Overall, the EAG considers the presentation of the demographic characteristics of patients at baseline to be appropriate. Nevertheless, the EAG notes the tables were not updated in-line with the recommendations of the previous EAG review of the Second Interim Analysis (to report the median time between the date of baseline ppFEV$_1$ measurement and date of initiation of CFTRm and to include comparison of patient characteristics to ensure that patients with completed

follow-up are representative of the overall study cohort). Please provide updated tables in-line with the recommendations of the previous EAG review.

[The time between baseline annual review and index date is provided in the Excel workbooks T1.1a-c and T1.2a-c. Note that the annual review will provide baseline data for most objectives, but for ppFEV$_1$ and nutritional data these will be closest measure from either annual review or encounter prior to index date.

In Table 1 below is presented the baseline demographic characteristics for the Full Analysis Cohort and Restricted Analysis Cohort (See Section 7.1.1 in the final report for definitions). Characteristics are balanced across both cohorts.]

[redacted]



A16. Objective 3. Please clarify why the mean follow-up time reported for the overall cohort in Table 2 does not equal the weighted average of the 6-11 years and 12+

years group, whereas the duration of exposure months does. Please provide either an explanation for this difference or an updated version of Table 2 with the correct data if required.

[redacted]

A17. Objective 2. Descriptive progression of $ppFEV_1$. The EAG recognises the descriptive analysis of $ppFEV_1$ progression presented in the final report, but considers the mixed-effects model of $ppFEV_1$ progression produced in Objective 1 to be more informative of the progression of $ppFEV_1$, and thus does not consider this objective further.

[Vertex disagrees with this conclusion. The study and each of the objectives were designed to answer specific research questions in collaboration with NICE and the UK Cystic Fibrosis Registry. Objective 2 is critical to understand how the overall ELX/TEZ/IVA-treated cohort behaves in progression of $ppFEV_1$, whereas Objective 1 was designed to understand the difference in rate of change in $ppFEV_1$ in a specific subgroup of patients treated with ELX/TEZ/IVA versus an untreated cohort. Objective 2 shows improvements if $ppFEV_1$ across all patient groups, including age, baseline $ppFEV_1$ levels, and genotype. It is critical to review objective 2 alongside the other improvements in multiple CF-related health outcomes, which are consistent with the literature. $ppFEV_1$ changes and other outcomes ELX/TEZ/IVA resulted in improvements in a broad range of clinically important outcomes in the first post-treatment year that were maintained into the second post-treatment year. Collectively, available evidence for ELX/TEZ/IVA shows that it consistently provides clinical benefits that are sustained and has the potential to modify the course of the disease. Therefore, Vertex feel it is inappropriate to disregard Objective 2.]

A18. Objective 4. Pulmonary exacerbations. The EAG has requested further analyses and clarification in questions A7, A12, A13 and A14.

[Noted.]

A19. Objective 5. CFTR Modulator Discontinuation. Please could the company provide the exact time frame used for the analysis of discontinuation?

[Discontinuation of ELX/TEZ/IVA was measured as the number and proportion of treated patients who discontinued ELX/TEZ/IVA treatment documented at each annual review after index date. Therefore data on all 6,390 patients from index date through all annual reviews was considered for the analysis up to study end date of December 31st, 2022.]

A20. Objective 5. CFTR Modulator Discontinuation. Please could the company clarify if any of the patients included in the reported discontinuations data had also participated in the OLE studies? If so, would patients who discontinued treatment in the OLE also be classed as a discontinuation in the Registry data or does the time frame of data collection not overlap?

[It is not possible to determine from the UK CF Registry if an individual participated in the OLE studies. The UK CF Registry has complete ascertainment of treatment initiation and also whether a patient observes a stop date, with or without a new start date for a CFTRm. Therefore, all treatment initiation and stop dates will be captured in the registry regardless whether an individual is in a clinical study or not.]

A21. Objective 5. Priority. CFTR Modulator Discontinuation. Please provide a plot of discontinuations over time for: i) all patients; ii) patients who switched therapies; iii) those patients who did not switch or restart a CFTR modulator?

The EAG notes this was highlighted in the previous EAG review of the second interim analysis.

[redacted]

A22. Objective 6. Nutritional Outcomes. Similar to the previous EAG critique, please clarify if the reported absolute changes in BMI in Table 22 are paired change from baseline statistics or the difference in the average of the full cohort at baseline and the restricted cohorts at year 2 and year 3. If they are not the paired differences, please provide these as paired differences.

[The absolute change in Body Mass Index from baseline until the closest measure up to 1-, 2-, and 3-years during follow-up was calculated. The absolute changes in BMI were paired change from baseline statistics.]

A23. Objective 7. Use of inhaled therapies. If not contained within the workbooks, please provide details on the use of the separate individual nebulised therapies (Tobramycin, Colistimethate, Aztreonam, Levofloxacin, Hypertonic saline, Dornase Alfa and Mannitol) at baseline compared to post ELX/TEZ/IVA initiation?

[The design of this objective was to look at the burden of inhaled and nebulised therapies as the total number rather than splitting by individual therapies. [redacted]

A24. Objective 8. Hospitalisation for non-IV antibiotic treatment. The EAG notes that interpreting these statistics is very difficult due to there being no statistical analyses accounting for within-person correlation, differing lengths of follow-up and the confounding impact of the COVID-19 pandemic. Please either provide an appropriate statistical analysis or an interpretation of these data that discusses the likely limitations of the descriptive analysis not accounting for within-person correlation, differing lengths of follow-up and the confounding impact of the COVID-19 pandemic.

[The EAG is right that the descriptive analysis does not account for the within-person correlation of hospitalisations. The annualised hospitalisation rates as defined in the protocol assume a Poisson distribution. To account for the within-person correlation would require a modelling approach which has not been planned for and agreed upon in the protocol. Accordingly, this adjustment is not possible within such kind of descriptive analysis.

Different follow-up lengths are accounted for by expressing the annualised rates as rates per patient-year follow-up.]

A25. Objective 9. Overall Survival. Please comment on the likely impact of delayed reporting of mortality statistics to the decrease in the number of deaths reported in the UKCFR from 2020 to 2022.

[redacted]

A26. Objective 10. CF-Related Complications. Following the previous EAG critique of the Second Interim Analysis, it is unclear why only the incidence of CF-related complications are reported and not the overall prevalence, accounting for the number of patients available at each time point. Please provide data on the prevalence as well as incidence of CF-related complications over time.

[The prevalence of CF-related complications is presented in Table 27 of the report.]

A27. Objective 11. Lung infections. The EAG notes that interpreting these statistics is very difficult due to there being no statistical analyses accounting for within-person correlation, differing lengths of follow-up and the confounding impact of the COVID-19 pandemic. Please either provide an appropriate statistical analysis or an interpretation of these data that discusses the likely limitations of the descriptive analysis not accounting for within-person correlation, differing lengths of follow-up and the confounding impact of the COVID-19 pandemic.

[Lung infections are captured at each annual review and the data recorded is whether an individual had a particular lung infection since last annual review. No dates are

captured, so adjustment for follow-up can't be done. The most meaningful analysis that allows for within person correlation is the incidence of lung infections, which is presented in the report. The incidence of lung infections at baseline and annual reviews 1, 2 and 3 post-initiation of ELX/TEZ/IVA are shown. [redacted]

A28. Objective 12. Organ transplant. Please comment on the likely impact of delayed reporting of transplant statistics to the decrease in the number of transplants reported in the 1-2 years after ELX/TEZ/IVA initiation. Please also comment on whether COVID-19 related factors likely reduced the number of transplants performed in this window.

[Organ transplantation is captured at the annual review so, data could be incomplete for 2022, and will be captured at 2023 annual reviews. COVID-19 would have had an impact on the number of surgeries that were performed. That being said, the overall the number of lung transplants is very low from this large ELX/TEZ/IVA-treated patient cohort.

Further, data from the NHS Blood and Transplant report for 22/23 shows a decrease in transplants during 2020, with the overall numbers increasing in 21/22 and 22/23, see table below[25]. In the UK CF Registry the number of bilateral lung transplants in all individuals in the registry decreased in 2020, which then continues to decline in 2021 and 2022 (numbers not final yet in 2022).]

Total Bilateral Lung Transplants

Year	17/18	18/19	19/20	20/21	21/22	22/23
NHS BT Data	178	146	141	81	91	92
Year	2017	2018	2019	2020	2021	2022
UKCFR Data Age 16+	51	58	49	12	<5	<5

A29. Objective 13. The impact of COVID-19. Please see A14.

[Noted.]

Section B: Miscellaneous

B1. Priority. In response to Clarification Question A26 of the original submission, the Company stated that Vertex is exploring a *post-hoc* analysis of the relationship between baseline lung function and clinical effectiveness, "and will share with NICE once this is available". Please confirm when the outcome of this analysis will be available, and provide any materials that are currently available related to this analysis?

[Within the Final Report and Excel Workbooks, progression of ppFEV$_1$ from objective 2 is presented for patients initiating ELX/TEZ/IVA by baseline ppFEV$_1$ <40 and ≥40 (Table 4 in the report and Workbook T2.1b-c). Improvements in ppFEV$_1$ were achieved regardless of disease severity, with both groups with baseline ppFEV$_1$ <40 and ≥40 both showing sustained improvement in ppFEV$_1$. In addition the Excel Workbooks also contain data by genotype for baseline ppFEV$_1$ <40 and ≥40 (Workbook T2.2b-c). Linking back into question A17, this is one reason why it is inappropriate to disregard Objective 2.

In addition, we have uploaded analysis for absolute change from baseline on FEV$_1$ from studies: 445-102: 24 weeks for F/MF 12+ population, 445-109: 24 weeks for F/F 12+ population, 445-106 Part B: 24 weeks for F/F and F/MF 6-11 population. We would advise caution when reviewing the analysis from study 445-106 Part B, given the low patients numbers in the age group of the study. These analyses are showing only the acute improvements in FEV$_1$ recorded at week 24 by FEV$_1$ at baseline across the age groups.]

B2. Priority. The company's economic models assume that upon discontinuation of CFTR modulators, patients retain the acute increase in

ppFEV$_1$ obtained upon treatment initiation. The company states that this is due to the efficacy data being determined from intention-to-treat analysis in clinical trials and therefore accounts for patients discontinuing during the trial period; however, the EAG does not consider this a valid reason to not implement any loss of treatment effect upon discontinuation in an individual patient simulation. Please can the company provide evidence from the data collected for the Final Analysis, or from crossover trials that include a washout period, such as Rowe 2017, to show that the acute increase would be maintained once patients stop taking CFTR modulator treatments?

[The model does assume loss of treatment effect after discontinuation. The model assumes that patients who discontinue treatment have no further treatment benefit - their ppFEV$_1$ decline is at the same rate as a patient receiving standard of care alone. To remove the acute ppFEV$_1$ benefit from those who discontinue during the trial, the acute benefit would need to be re-estimated to be amongst only those who stay on treatment for the entire trial (which would lead to a greater treatment benefit for those remaining on therapy than in the intent-to-treat analysis but would not change the average treatment benefit across all patients). Unfortunately, we don't have data on ppFEV$_1$ after discontinuing CFTRm.]

References

1. Hoo ZH, Lai LY, Sandler RD, Daniels TE, Dawson S, Hutchings M, et al. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis". J Cyst Fibros 2023; **22**: 587.
2. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Using Negative Control Outcomes and Difference-in-Differences Analysis to Estimate Treatment Effects in an Entirely Treated Cohort: The Effect of Ivacaftor in Cystic Fibrosis. Am J Epidemiol 2022; **191**: 505-15.
3. Doumit M, Chuang S, Middleton P, Selvadurai H, Sivam S, Ruseckaite R, et al. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic. J Cyst Fibros 2023; **22**: 581-6.
4. Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. The Lancet Respiratory medicine 2021.

5. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. The Lancet Respiratory Medicine 2017; **5**: 107-18.
6. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med 2015; **192**: 836-42.
7. T. Lee, G. S. Sawicki, J. Altenburg et al. Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis. Journal of Cystic Fibrosis, 2023;22(3):P402-406.
8. P. G. Middleton PG, M. A. Mall, P. Dřevínek et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med, 2019;381:1809-19.
9. H. G. M. Heijerman, E. F. McKone, D. G. Downey et al. Efficacy and Safety of the Elexacaftor Plus Tezacaftor Plus Ivacaftor Combination Regimen in People with Cystic Fibrosis Homozygous for the F508del Mutation: a Double-Blind, Randomised, Phase 3 Trial. Lancet, 2019;394:1940-48.
10. D. Polineni, C. L. Daines, E. Tullis et al. Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People With Cystic Fibrosis (CF) and At Least One F508delAllele: An Open-Label, 192-Week Extension Study, 2023: 2023 ECFS presentation.
11. E. McKone, C. Castellani, H. Heijerman et al. Disease Progression and Burden in Patients With Cystic Fibrosis Homozygous for F508del Across Europe in an Observational Registry (VOICE study), 2019; S57-S190 (P066).
12. R. Szczesniak, E-R. Andrinopoulou, W. Su et al., Lung Function Decline in Cystic Fibrosis: Impact of Data Availability and Modeling Strategies on Clinical Interpretations. Ann Am Thorac Soc, 2023;20:958–68.
13. C. Merlo, C. Scirica, T. Thorat et al., Long-term Durability of Ivacaftor (IVA) Treatment Benefit in People with Cystic Fibrosis (PwCF). European Respiratory Journal, 2022;60:4652; DOI: 10.1183/13993003.
14. E. Bourgani, E. Stagaki, M. Gioka et al. Two years' experience of lumacaftor/ivacaftor treatment at an adult cystic fibrosis centre in Athens, Greece; Proceedings of the 42nd European Cystic Fibrosis Conference; Liverpool, UK. 5–8 June 2019; p. 267.
15. L. C. K. Ejiofor, I. H. M. Mathiesen, S. Jensen-Fangal et al. Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment. Pediatric Pulmonology, 2020;55:3364-70.
16. I. Loukou, M. Moustaki, M. Plyta et al. Longitudinal changes in lung function following initiation of lumacaftor/ivacaftor combination. J. Cyst. Fibros, 2020;19:534–539. doi: 10.1016/j.jcf.2019.09.009.

17. S. J. King, D. Keating, E. Williams et al. Lumacaftor/ivacaftor-associated health stabilisation in adults with severe cystic fibrosis. ERJ Open Research, 2021;7:00203-2020; **DOI:** 10.1183/23120541.00203-2020.

18. D. Muilwijk, D.D. Zomer, V.A.M. Gulmans et al. Real-world Trends in Long-term Clinical Outcomes of Lumacaftor/Ivacaftor. J. Cyst. Fibros, 2020;S70-S71.

19. K. Tong, D. Barker, M. France et al. Lumacaftor/ivacaftor reduces exacerbations in adults homozygous for Phe508del mutation with severe lung disease. J. Cyst. Fibros, 2020;19:415–420 doi: 10.1016/j.jcf.2019.12.006.

20. J. Bower, T. R. Zahigian, A. Sewall et al. Disease Progression in F508del Homozygous (F?F) persons with Cystic Fibrosis Traeted with Lumacaftor/Ivacaftor (LUM/IVA): Interim Results of a Long-term Safety Study Using Data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). J. Cyst. Fibros, 2020;19: DOI: 10.1016/s1569-1993%2820%2930233-2.

21. C. Merlo, M. DerSarkissian, C. Nguyen et al. Long-term impact of ivacaftor on health outcomes and mortality in people with cystic fibrosis in the U.S. CF Foundation Patient Registry (CFFPR). J. Cyst. Fibros, 2021;S88.

22. B. Plant, L. Kirwan, Y. Lou et al. Long-term impact of ivacaftor (IVA) in people with cystic fibrosis in Ireland. J. Cyst. Fibros, 2023;S31.

23. J. K. Bower, N. Volkova, N. Ahluwalia et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study. Journal of Cystic Fibrosis, 2023; doi: 10.1016/j.jcf.2023.03.002.

24. UK Cystic Fibrosis Registry 2021 Annual Data Report: https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Trust%20Annual%20Data%20Report%202021%20-%20WEB.pdf

25. NHS Blood and Transplant report for 22/23: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/30157/section-2-overview-of-organ-donation-and-transplantation.pdf

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology(ies) 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 10,900 people in the UK. The Trust fund vital and impactful research that accelerates breakthrough science and therapeutics, improve care and the way its delivered and provide 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(ies) bringing the treatment(s) 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 a total of £72,245.13 from Vertex Pharmaceuticals in the last 12 months to support key charitable activity to improve the lives of people with CF: • £15,845.13 to support the UK Clinical Trials Conference on 4th March 2022 • £36,000.00 for sponsorship of the UK CF Research Conference on 11th May 2022 • £6,000.00 for Clinical Trials Accelerator Programme (CTAP) Feasibility Services for VX21-522-001: A Phase 3 study evaluating for the pharmacokinetics, safety, and tolerability of VX121 / Tezacaftor / Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 years of age. • £6,000.00 for sponsorship of the UK CF Registry Annual Meeting 2022 and conference in November 2022 • £8,400.00 for a UK CF Registry epidemiology data request from 2021 cohort Cystic Fibrosis Services Limited, a subsidiary of the Cystic Fibrosis Trust, hosts the UK CF Registry and has received funding for ongoing pharmacovigilance studies and the HTA study agreement. The Trust have received no funding from any of the comparator treatment companies in the last 12 months.
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	Our submission has been informed by a wide range of experiences of Orkambi, Symkevi and Kaftrio, through the support we have provided the CF community since these medicines become available. In addition, Cystic

experiences of patients and carers to include in your submission?	Fibrosis Trust ran an online survey between February 2023 and March 2023, receiving 1,179 unique responses. • 39% of respondents were people with CF, 33% were parents of children with CF, 15% were parents of adults with CF and 13% were carers/spouses/other family members of people with CF. • 93% of respondents had experience of Orkambi/Symkevi/Kaftrio, with 4% not taking either of the three and 3% had previously taken a modulator but were not currently. • 89% of respondents were taking, or had previously taken Kaftrio, with 9% taking or previously taken Orkambi, and 2% taking or had previously taken Symkevi. We received 985 individual responses to the question 'How would you describe the impact of Orkambi, Symkevi and/or Kaftrio on you, or others?'. We received 686 individual responses to the question 'Is there anything else you would like NICE or Cystic Fibrosis Trust to know about your experience of Orkambi, Symkevi and/or Kaftrio?'. The results of the survey alongside focus groups made up of people with CF and parents/carers have informed our submission. Our submission also includes evidence from a survey conducted by the Trust's Youth Advisory Group in Winter 2020 about the feelings related to the access to Kaftrio and the results of the Trust's 2017 and 2018 Insight Survey[1].

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 38 in 2021[2]. 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

[1] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/CF%20Insight%20Survey%20full%20report%202018.pdf
[2] https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Trust%20Annual%20Data%20Report%202021%20-%20WEB.pdf

	priority refresh[3]. 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. The 2017/2018 Insight Survey found that on average, the time spent on daily CF care was 2.5 hours. 25% of parents of children with CF spent more than 3 hours per day on treatment[4]. 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. People with CF and 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 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

[3] https://www.cysticfibrosis.org.uk/news/refreshed-top-10-research-priorities-for-cf-revealed
[4] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/CF%20Insight%20Survey%20full%20report%202018.pdf

	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[5]. The condition is associated with increased morbidity, mortality, and a faster decline in lung function[6]. 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. 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. The results of the 2017/2018 Insight Survey show that 45% of respondents visited their CF centre

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

	between five and nine times per year, with 23% visiting between 10 and 14 times. An outpatient appointment for people with CF takes 4 hours and 50 minutes, including the mean travel time[7]. 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[8]. 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)[9]. 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.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	After advisement from NICE, Cystic Fibrosis Trust are highlighting how the experience and treatment of CF has changed with access to these treatments as they are the current standard of care.

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

	People with CF and their families highlighted increased health stability, reduced hospital admissions, and reduced use of antibiotics as a major change to CF care since they have had access to these medicines: *"Since I've been on Kaftrio, I've been in for other hospital admissions, but I haven't been in for a chest exacerbation or chest infection. So that's a big difference in that because I would tend to go in probably two to three times a year depending on, you know how things were."* *"I went from having IVs sort of every 10 to 12 weeks…It was three years before I needed to have another set of IVs".* *"I now tend to respond to two or three weeks of oral antibiotics rather than four weeks or five weeks of antibiotics and then maybe ending up on IVs."* Increased health stability has the potential to reduce the high treatment burden for CF. People with CF reported that their medicine *"use dropped drastically"* and they *"didn't feel the need to do…"* some treatments anymore as well as reduced airway clearance activities because they are less productive: *"I used to do an hour of airway clearance a day plus exercise…I'm not as productive so now I do 3 40 minutes a week of airway clearance. And I probably don't even need that. But I'm, you know, after 40 odd years, it's hard to get out of the habit."*
8. Is there an unmet need for patients with this condition?	The interim access agreement enables every person with CF who is eligible to access these modulator therapies. As the agreement also included access for any future licence extensions, children aged two and older can access Orkambi and children aged six and older can access Kaftrio. As future licence extensions are granted, the unmet need for people with CF who are eligible for these treatments will reduce. These medicines were the first disease-modifying treatments for the vast majority of people with CF and the agreement satisfied a huge unmet need.

Advantages of the technology(ies)

9. What do patients or carers think are the advantages of the technology(ies)?	Access to these medicines for many of the CF population under the interim access agreement has transformed outcomes for CF in the UK, including several populations who can access these treatments off-label via the commissioning policy[10]. There are a huge range of advantages to these medicines, from improved lung function, increased opportunities for education and employment, and a newfound ability to plan for the future. 82% of respondents felt that access to Orkambi/Symkevi/Kaftrio had significantly improved their health/health of their family member with CF and 14% reported slightly improved health. People with CF and their families identified a wide range of benefits to these medicines including, improved physical health and wellbeing, improved lung function and reduced coughing, fewer medical interventions, and less time in hospital as well as the potential for a reduced treatment burden because of increased health stability. For some people with CF, these medicines became available when they were running out of options as their health declined, for others they have transformed their current health status and potential life expectancy. Some have seen dramatic improvements in their lung function, as well as reduced coughing and more energy. *"Lung function has increased about 62% in one year."* *"I was at end stage lung disease and ineligible for transplant due to drug allergies. I was desperately counting down every day of the approval process. I've gone from a rapidly declining lung function of 26% to a stabile 35%. It's hard to state how huge this is!"* *"My 10-year-old daughter's lung function went down to 44% last year and thanks to Kaftrio it is back up to 90%. I don't think this would have been possible without modulators."* *"My lung function has improved to 62% so has my quality of life. For the first time after 20 years, I started running again and in 2021 I climbed my first mountain!"* Constant coughing was described as *"exhausting and an overwhelming experience"* and *"embarrassing."* Parents described lying awake at night listening to coughing and children wetting themselves because of continued coughing, as well as difficulty breathing, *"broken ribs and ruptured blood vessels."* As a result of these treatments,

[10] https://www.england.nhs.uk/wp-content/uploads/2021/03/Commissioning-Statement-CF-modulator-therapies-for-Cystic-Fibrosis-UPDATED-2022.pdf

	people with CF say they can now *"perform daily tasks without coughing,"* can *"go out more freely and not be embarrassed"*: *"I can now have a proper belly laugh or a yawn without breaking into a coughing fit. Until that stopped happening, you realize, oh yeah actually that was really annoying."* People with CF require more energy to fight lung infections and compensate for poor digestion, and therefore they need more calories. Periods of exacerbations and poor health can also lead to weight loss. Since starting modulator treatments, many people with CF have reported experiencing a positive weight gain. Parents have described seeing their children become "chubby for the first time in her life" and the enormous cultural shift: *"We are used to just chucking the food down our children's throats, shovelling it in like a runaway train, and then suddenly it's like oh, that's working. Ah, OK, let's add butter, you know, not the whole cake this time."* The previous pressure on parents to maintain children's' weight can also be overwhelming, particularly for those with younger children. The increased health stability has a significant impact: *"My son struggled to gain weight from very early on and takes quite a lot of Creon. And now that he gains weight more easily and it's just that, you know, not like mounding the cheese on him, like heaping on the butter until it's like so gross that you wouldn't want to eat it yourself. And it's just that ability to say, OK, well, you're not hungry. That's fine. You don't have to finish your plate. Like that's a joy. I love that."* For adults living with CF, the weight gain and increased stability has been remarkable: "*I think I've put on out 10 kilos in a matter of like months…something that I've never had before, whereas I was always struggling to put on weight, and I was told to eat more, eat more and then suddenly it was like actually you need to stop eating, you know, you eat too much."* *"I've put on a couple of kilos, which isn't a huge amount in the grand scheme of things. But when you were only 50 kilos to start with, then going up to 53 kilos is proportionally, it's quite a big thing."* Such remarkable improvements in weight can also bring challenges. An adult with CF told us: *"Particularly for those of us adults, I had 35 years to learn how to eat, you know, eat everything and so to suddenly have that big change psychologically of actually having to watch what I'm doing…it's a lot".*

Improved lung function, reduced coughs and weight gain have led to increased energy levels. People with CF have described that they *"finally have energy"* and *"can live a normal life."* The increased energy levels have been heralded as the *"most life-changing thing"* and people did not realise pre-modulator treatment that they *"never realised it was possible to feel this good day after day"* and parents described their children as *"rebooted."* Increased energy levels mean that exercise is easier, physiotherapy can last longer as people are not as breathless and sleep is improved:

"I have far more energy than I've ever had, improving motivation to get active and work out, not feel the dread of the day aftereffects from a day out and just being able to be present in the moment. Not worrying about if you're going to be coughing your lungs up because you walked briskly for half an hour."

Parents of people with CF have also described the impact of increased energy levels:

"He has much more time and energy and he's much more optimistic about the future. He's able to put much more energy into his career, relationships and personal goals and he is noticeably much happier."

Improved quality of life is a significant outcome for people living with CF and their families:

- 66% 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 Orkambi/Symkevi/Kaftrio, with 15% reporting feeling slightly more positive.

A key benefit of these treatments has been the options it gives to people living with CF. The 2017/2018 Insight Survey found that 77% of those with CF who participated in the survey felt CF had impacted on their career or education and 88% of respondents had their leisure activities impacted by CF[11].

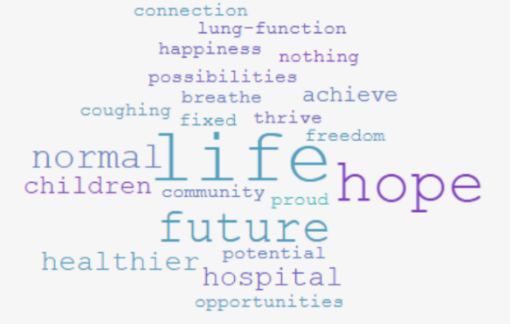
Since starting Kaftrio, an adult with CF told us: *"It gives options which were never necessarily there before..."* and others told us *"We're all talking about a future"* and *"I feel positive about my future for the first time ever…which is a wonderful thing."* These options include increased opportunities for education, employment, starting a family and homeownership as well as a feeling of being able to contribute to society. There has been a remarkable increase

[11] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/CF%20Insight%20Survey%20full%20report%202018.pdf

in the number of women with CF becoming mothers over the past few years[12] and a common theme in our research has been stories from people with CF who never thought they could start a family. Whilst people with CF recognise they still have the condition, they say *"…this version of CF is nothing*" and that they *"didn't realise how much CF impacted my life until Kaftrio took it away".*

Parents have described when thinking about their child with CF, they *"no longer think in terms of how long they will be able to work or even live. We can see a future for them"* and they are no longer planning funerals for their children. Parents told us how they have *"dreamt of a future"* for their child with CF for years, and that for the first time *"CF was not the first thing we all thought about."* Parents have wished they could *"go back to diagnosis day and tell those two very scared and devastated parents how CF will be significantly different one day and the future will be bright."* We have heard countless examples of parents and carers being able to return to work, children missing far less school and plan holidays without bringing huge amounts of medical equipment with them.

The overwhelming emotion felt by young people living with CF in Cystic Fibrosis Trust's Youth Advisory Group after Kaftrio was made available was hope. When asked about the best thing about Kaftrio being available to some people, the primary response was that of a normal life and a future. The wordcloud demonstrates responses, which appear larger depending on the frequency they were mentioned.



An adult with CF told us how their quality of life has significantly improved:

"At the age of 50 I was facing declining lung function, a punishing regime of treatments, and an uncertain future. Within weeks of starting, my health improved. I am fitter and healthier than I have been in decades. I have reclaimed hours a day by not needing time consuming physiotherapy or nebulisers. I have been able to increase my work hours, go for a promotion, and provide security for my family. I have also had more time and energy to pursue hobbies, and interests. I can't imagine life without Kaftrio."

[12] https://www.cysticfibrosis.org.uk/news/new-research-into-pregnancy-rates-in-women-with-cf

Disadvantages of the technology(ies)

10. What do patients or carers think are the disadvantages of the technology(ies)?	Approximately 10% of people of CF are unable to benefit from these lifesaving treatments. Some parents have described the difficulty of their child coming to terms with a different identity since starting modulator treatment: *"She doesn't know who she is without CF. She missed so much school and qualifications. What kind of job can she do now?."* This was also echoed by members of Cystic Fibrosis Trust's Youth Advisory Group: "*I've gotten so used to being sick during my childhood that the prospect of being so well feels slightly unknown and scary to me. I'm fully versed on how to be sick, not so much on how to be healthy."* People with CF described how the prospect of a new future can cause significant anxiety and worry for some: *"I kind of looked reflected back on life… oh God, if I'd have known that I had this future, then I would have probably chosen to do things a lot differently"* and coping with these feelings has been challenging: *"I didn't know how to cope with the fact that I had got such a life changing drug...I've got such an opportunity"*. Some of the CF community are apprehensive about the long-term use of such transformative medicines, particularly the mental health side-effects of modulators: *"Although my physical health has greatly improved, my mental health deterioration has made me question whether I wanted to stay on the drug as it can be overwhelming to live with at times. No one seems to be able to explain why this is happening."* People with CF and their families have also cautioned that despite access to these medicines, they still have CF and co-morbidities: *"It isn't a panacea… we still have got CF. We've still got illness, but it has improved things for most."* People with CF have expressed their concern that CF services will need to adapt to provide support for the new needs of some people living with CF: *"I believe the mental effects of having these new tablets can be very overwhelming and having lived your whole life with the idea that you'll die younger that everyone around you potentially to now having to retrain your mind to the fact that you will live longer than ever expected and I feel that possibly there should be more help regarding that."*.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology(ies) than others? If so, please describe them and explain why.	Over many years, CF lungs become increasingly damaged, and the ultimate goal of CF treatment has been to prevent as much decline as possible. Access to these treatments has resulted in a generation of children and young people with CF growing up healthier than ever before and with a different disease profile to those who have started modulator treatment in later life. As research into these treatments continues, it is important that access is expanded to include those people with CF with mutations that may be responsive but aren't currently included in the access arrangements.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology(ies)?	

Other issues

13. Are there any other issues that you would like the committee to consider?	As NICE has recognised, this is a unique appraisal, with thousands of people with CF already taking these treatments. It is vital that all flexibilities are utilised.

Key messages

14. 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 entire 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 relentless CF. • Access to these treatments has profoundly changed the experience and care of living with CF, 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. • The overwhelming response to these medicines has been the hope it brings people with CF and their options for the future – including starting a family, increased opportunities for education and employment. • Advances in CF care and treatment have resulted in the median age at death increasing, from 31 in 2019[13] to 38[14] in 2021. The predicted median survival age of people with CF born today has increased to 53 years[15], from 49 years in 2019[16] and we anticipate further improvements. This is hugely significant for people with CF and their families and represents generations of people with CF who can lead more fulfilled, healthier lives.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

[13] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/2019%20Registry%20Annual%20Data%20report_Sep%202020.pdf
[14] https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Trust%20Annual%20Data%20Report%202021%20-%20WEB.pdf
[15] https://www.cysticfibrosis.org.uk/sites/default/files/2022-12/CF%20Trust%20Annual%20Data%20Report%202021%20-%20WEB.pdf
[16] https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/2019%20Registry%20Annual%20Data%20report%20%20at%20a%20glance.pdf

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology(ies) 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	CF Voices
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	CF Voices is a voluntary group formed of parents of children with CF. The group set up with the specific aim of gathering information to fully understand the impact of treatment with CF modulators on patient families and carers, and to give them a voice within the healthcare system in the UK. CF Voices has a core organising group of 3 parents and over 300 members from across the UK, registered via website &/or as part of Facebook group. The group is self-funded.
4b. Has the organisation received any funding from the company(ies) bringing the treatment(s) 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.**	No
4c. Do you have any direct or indirect links	None

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	CF Voices carried out research in the Spring of 2020 to inform the single TA originally planned for Elexacaftor, tezacaftor and ivacaftor (that was subsequently cancelled). The report is attached as an Appendix with 11 illustrative case studies at the back (respondents willing to be published). The study aimed to investigate the caring and life experiences of CF carers, providing insight into how CF-specific care routines, and CF-specific emotional experiences, impact the carer in terms of their mental and physical health, relationships, productivity, lifestyle and overall wellbeing. The methods used – including a comprehensive survey (151 respondents) and 50 in-depth interviews – produce a range of data and outputs including the use of existing quantitative measures for assessment of subjective carer burden and carer wellbeing as well as established measures for aspects of mental health. Qualitative data from the interviews provides rich insight into the lived experiences of carers' relationships with the disease. The research design for both the survey and interview included reflective answers to generate insight into impacts of CF care over a period of time, to complement the snapshot of current feeling provided by the validated questionnaires. The diverse outputs are attempts to make carer-centric data available that represents carer experiences over a long period of time, and in a form that can be included in the complex health economics processes of NICE and other bodies; an attempt to help to meet the need for greater presence of the impact on carers in health policy decision making that has been identified (van Exel et al., 2008), by informing calculations of the lifetime accumulated burden associated with CF care. Resources do not allow for a follow-up study of the same scale and complexity to compare the results since the full-scale roll out of the three drugs being assessed. However, CF Voices will perform limited follow-up with the carers included and we will be nominating a patient expert who managed the research and has lived experience to share (Christina Walker).

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?	Caring responsibilities are diverse in CF cases, reflecting the diversity of patient condition and disease severity, but caring invariably involves the sacrifice of time and energy to help the patient manage their illness, as well as the emotional impact of being part of patients' relationship with the disease (Sawicki et al., 2009). The chronic and severe nature of CF can make caring for sufferers demanding, involving daily activities such as manual physiotherapy, administration of medicines and supplements, sterilising medical equipment, facilitating hospital visits, to name just a few. Lifestyles and daily routines are affected as CF care takes precedence over other activities – even affecting the work-life of the carer. Caring comes at an opportunity cost, as time, energy and other resources are spent looking after the sufferer, rather than on other activities (Sawicki et al., 2009). On top of these practical tasks, emotional pressures manifest through the testing relationship of carer and patient and the experience of witnessing a loved one suffer through a disease (Fitzgerald et al., 2018). Studies have investigated the impact of caring activities on carers in relation to a range of other illnesses and common among most of them are increased prevalence of complaints such as stress, anxiety and depression, physical health complaints and various other health-related impacts, and higher mortality rates have even been attributed to the burden placed on carers by their responsibilities (Kanters et al., 2013; Martín et al., 2013; Mowforth et al., 2019; Post et al., 2005; Schulz & Beach, 1999; van Vliet et al., 2010; Wilson et al., 2007). As a genetic condition, CF brings these kinds of impacts to carers for the whole life of the patient, so carers can be subject to these impacts for decades. Thus, the lifetime accumulated burden of CF care is expected to be high. The findings detail a relatively high subjective burden of care reported by CF carers as measured by CarerQol-7D and this is illustrated comprehensively in the qualitative interview data. The burden of care is often linked to specific acute incidents in lives when discussed in the interviews, but the context throughout makes it clear that these experiences always come on top of the regular, day-to-day care burden that most carers accept as part of their lives. The experience of care detailed by CF carers is one that is constant and inescapable, present for many years and decades. It is clear from the data that associated impacts, such as those on mental health, are present. The self-reported measures of depression and anxiety in the survey generated scores for GAD-7 and PHQ-8 measures. These depression and anxiety scores were extreme (around half of respondents reported scores indicating moderate anxiety and depression, and around a quarter recorded scores indicating severe levels) and, while the sample cannot be shown to be entirely representative of the general CF carer population in normal times, the sheer quantity of people reporting these symptoms during this snapshot is striking. The qualitative data provides context, with participants recalling accounts of anxiety and other mental health issues - not a single interview was concluded without mention of at least one mental health topic - strengthening claims of significant mental health impact. It is unsurprising therefore that self-reported levels of happiness measured by CarerQol-VAS is lower than in other carers and the general UK population. 73% surveyed reported at least some mental health problems, 73% at least some physical health problems. Some interviewees had accessed NHS treatment for direct health impacts, mostly relating to mental health, others had

	not - often citing time constraints. Additional and consequential effects on the physical health of CF carers were documented throughout the analysis of qualitative data, alongside decreases in general productivity, ability to work, career satisfaction and financial wellbeing. “my wife lost her good job because she didn't want anyone else to look after our [child].. that was a big burden for her and I went self-employed part-time which was virtually not working. Both of us became fulltime carers and dedicated our life to our [child]. The rest of our life just disappeared.” 56.3% in the survey and 84% interviewed were in households with 2+ carers. Accounts of parents and couples experiencing relationship difficulties due to the pressure of a care, or because of disagreements over how to manage care, were commonplace in the interviews. Importantly, the range of impacts were felt beyond these primary carers – affecting extended families and social networks, with significant impact on siblings of CF children being described. Evidence of siblings experiencing anxiety, disrupted schedules, and emotional impacts such as feelings of neglect were presented and examples of extended families, particularly grandparents, sharing the emotional burden were also present. Extended families were sometimes described as taking an active role in the care, though these accounts were rare with reasons given including the skills required in specific care routines for CF. This dynamic itself had impacts, including a common feeling of isolation in carers and feelings of guilt in all family members. The study took place during the time that the UK was affected by the covid-19 pandemic, and there was a clear influence of covid-19 detectable within the results. This is probably reflected in the elevated scores for anxiety and depression generated from the quantitative measures in the survey. Qualitative data contained explicit mention of covid-19 and the effects of the increased risk and conditions of lockdown. However, as presented above there was also clear evidence that anxiety and depression existed in these carers long before the pandemic started. The data shows clearly that the CF specific care burden brings with it elevated levels of anxiety and other mental health symptoms, due to characteristics of the disease such as its life-long, incurable and progressive nature and the constant nature of the care duties and risks to the patient associated with everyday practices and experiences. From the reflective question in the survey asking about experiences over the last six months, it is clear that the impacts seen here are not just brought about by the pandemic. There are examples of impacts related to diagnosis at birth or from heel prick test, experiences of school by CF patients, experiences of moving out to University and examples detailing experiences that took place over a number of years. In the data are examples of adult care and life-long responsibility. What is clear from the data collected is that, not only does the CF carer burden negatively impact the mental and physical health of the carer, their productivity and their financial wellbeing, it also affects their families and wider networks of contacts and – crucially – it does so from the start of their child’s life and over a period that can be decades-long. From health problems at birth through childhood, to ‘backup’ care in adulthood and then primary care as condition of the patient decreases in later life, the burden of care is ever-present. “at the beginning my health declined massively both physically and mentally... extra exhaustion through sorting out timings for medicines and physio. Mentally I really struggled it was very different. We spent 5 months in and out

	of hospital. I struggled a lot with post traumatic stress of this experience in hospital and then once we got home it was very lonely and isolating. .. Mentally it affects you massively and physically with the tiredness. Your sole purpose is to look after your child so you're not eating right, you're not exercising right because you're so stressed out and concerned about this new baby." The bleak assessment of life caring for CF patients without the new modulator drugs provided in this quote illustrates: "In January he started it {Orkambi} and we are full of hope. Whereas before CF felt like you're on a treadmill and you know where the path is leading in the end and its not good … There's suddenly hope and the thought that we might not just be on a treadmill until he's dying; that his condition can be managed." Clinical evidence provided elsewhere has shown that new modulator drugs can have enormously positive impacts on patient condition and quality of life, and the data presented in this study suggests that, in these early stages of UK-wide rollout of Orkambi and Symkevi at least, modulators have hugely positive effects on carers directly as well. Immediate psychological boosts of positivity and optimism have lifted the spirits of carers across the country, possibly translating into genuine improvements in mental health. In time, carers expect that the burden of care, in terms of time and energy, will also be reduced through modulator therapy, with further improvement in their wellbeing and quality of life. Overall, there are positives to care as expressed in the data, with accounts of pride, love, and celebration of achievements, but these seemed clearly to be islands of positivity and optimism present within an ocean of grief, fear and burden. There is clear evidence of constant negative impact on CF carers from a high subjective care burden, which manifests through multiple dimensions from detrimental mental and physical health effects to negative social and financial implications. The EQ-5D aspects are either irrelevant or do not cover the breadth of impacts in CF care. These very real impacts on every part of carers lives over long periods is evidenced in the research using other measures that can be quantified and utilised to influence calculations of the lifetime accumulated burden. The future now appears vastly different and the improvement in lives of the families and easing of the effects noted above, after years/decades, has been significant for CF families. Of course, experiences have varied, with those receiving treatment before major damage has been caused and those who don't experience any side effects having a particularly life changing experience. Among the families caring for a patient who had extensive existing and irreversible damage and those who've experienced concerning side effects, potentially having to change dose or even come off the medicine, there is understandably a different viewpoint and much ambivalence. Carers of very young eligible patients, receiving a diagnosis since the availability of modulators, will never experience the same as carers have previously detailed in the research, because the condition has been changed so dramatically forever.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Opinions from participants in the 2020 research about their experiences of care were mixed – many still had no access to modulators at that time. There was a strong theme present which praised NHS clinical teams and staff, often describing the personal service provided as wonderful and appreciating the long term relationships. At the same time, though, there was a theme outlining disenchantment with NHS services for CF in general. Lack of funding, lack of priority for CF services in comparison to services for other illnesses, delays to the start of modulator therapies Orkambi and Symkevi and other complaints were described. Carers of patients with access to the modulator therapies were almost all incredibly happy with access to these new drugs. Stories of improvement in patient condition, and also family life and subjective carer burden were common. “My [child] started [modulator] medicines..and it has revolutionised our lives. Before we were always cancelling meet ups, holidays, activities, birthdays and cancelling work. It affected everything really.”
8. Is there an unmet need for patients with this condition?	The research project uncovered a number of perceived unmet needs in CF care, including equipment for home care, support with and relief from day-to-day care burden, psychological support for patients and carers and improved access to NHS facilities and services. However, these tended to be present in small numbers in the data and were dwarfed by the responses which expressed a perceived need for modulator medicines. The previous standard of care that could only treat symptoms, was improved with the first generation of modulators that delayed disease progression for some patients, but at the time of the research most were waiting for access to Orkambi/Symkevi and most were waiting for the highly effective treatment to tackle the root cause of CF in the way that Elexacaftor, tezacaftor and ivacaftor has.

Advantages of the technology(ies)

9. What do patients or carers think are the advantages of the technology(ies)?	The 2020 data shows that when patient condition improves, mental health problems – and also a lot of the other problematic dynamics caused by CF within families – can be reduced, as illustrated: “Amazing. [patient] is on it [Trikafta], his lung function, physically, mentally, socially. It's had a massive impact on our life, massive change, last couple of years, brilliant. Everything about our family life has really been more positive. He's up for going out. He's very artistic and has been in the workshop a lot more. It's a better household to be in. The impact on us as a family has been amazing” There are expected direct effects on carers documented in the interview data – reductions in care burden, improvements in mental health, optimism and positivity, as illustrated by these quotes from interviews: “some people have been able to stop some medications, stop physio and stop taking nebulisers so it [Trikafta] reduces the amount of meds and treatments and so reduces the worry and the amount of time taken to every day to check all the right meds are taken at the right times and in the best of all worlds that takes at least an hour and doesn't include physio or ordering the drugs and chasing for the drugs and where its stuck in the system which happens every month” “I think it can change everything it could mean the difference of between night and day as to our approach to life, it would mean we don't have to worry so much about him catching coughs and colds and we could start planning for the longer term future and our links with other people would be much more relaxed and not have this tension that we have at the moment because of CF.” The CF Voices Patient Expert will be able to update the committee with life-changing personal experience and updated feedback from the group at the Appraisal stage in October.

Disadvantages of the technology(ies)

10. What do patients or carers think are the disadvantages of the technology(ies)?	When asked about the disadvantages of Trikafta in the 2020 research project, carers named the cost to NHS of purchasing the drug and the inability of this therapy to treat all mutation categories as disadvantages. Some respondents cited potential side effects including insomnia, anxiety, depression and liver disease.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology(ies) than others? If so, please describe them and explain why.	The carers of patients receiving treatment before damage has occurred and perhaps when it can be prevented entirely, will benefit the most by experiencing reduced care burden and markedly reduced negative mental health impacts. The lives of their loved ones and the whole family will be significantly different to those with substantial existing illness, for whom treatment burden remains heavy, even though their future pathway is improved.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology(ies)?	

Other issues

13. Are there any other issues that you would like the committee to consider?	CF Voices did not address the devastating impact on families of bereavement of a CF patient within its research, but we request that the committee considers the significant and lasting effect that premature death has. Intervention with this technology could significantly extend life expectancy and change the future where many CF parents bury their children, to one where they instead watch them thrive and where patients could routinely outlive their parents. No utility data on bereaved family members are available for patients with CF, but an approach to handling this effect was identified in an economic evaluation of meningitis vaccination in England. Following Christensen et al (2014), the additional quality of life-related QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss. (Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. BMJ. 2014; 349:g5725.) Prior to modulator therapies, CF was a singular disease, with treatment focused on slowing the decline in health by treating symptoms. With the emergence of breakthrough innovative modulator therapies, CF has split the disease community by genotype into those that can access therapies to tackle the root cause of their disease, and those that cannot. Current patient access for Kalydeco, Orkambi and Symkevi has a ripple effect on to carers and whole families, while those of patients untreated continue to have a bleaker outlook. The prognosis for each sub-group is very different now, with quality of life and care burden potentially substantially differing over time. Trikafta has the potential to provide an equality of life chances to 90% of CF patients. Tragically, not to all.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The life-long nature of CF as an incurable genetic condition, if unaddressed through effective modulator therapy, can potentially mean carers are substantially affected over a period of decades, leading to a high lifetime accumulated burden of care. • Utilising quantitative metrics (including CarerQol, GAD-7, PHQ-8) within a survey plus qualitative interviews, the data gives a strong basis to suggest that subjective carer burden in untreated CF is multi-dimensional and is equal to or higher than for other carers. • The impacts of the carer burden extend beyond the primary carers, with extended families, including grandparents, being impacted, with significant impact on siblings of CF-children being described. • Modulator therapy has brought huge improvements in the quality of life of carers and families, as well as patients, through positive mental health impacts as well as through the reductions in care burden brought about by poor patient condition. • Elexacaftor, tezacaftor and ivacaftor in particular, has changed CF from life-limiting, and for many untreated, to a manageable chronic condition. By creating such a revolution for patients, the same effect is extended to the lives of those who care for them. Futures that were previously impossible have opened up to 90% of the CF community and should prevent many families from burying their loved one prematurely.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) 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.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted] [redacted]
2. Name of organisation	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 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 manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	£6,000 from Vertex Pharmaceuticals sponsorship to support ACPCF Virtual study days in 2022. Transferred in June 2022 Outstanding invoices from Vertex and Mylan. Both owing £1,800 as sponsorship for stand at ACPCF study days in 2023.
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 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. We have been cautious about including a reduction in IV/ bed days here, as while this has been observed as a clinically significant treatment response, we have concerns that the changes (reduction) in symptoms for many on Kaftrio are potentially leading to respiratory under-treatment. This is, as yet, unstudied but may lead to less optimised long-term outcomes.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Prior to interim access to Kaftrio there was inequity in the ability for people with CF to access highly effective precision medicines. There had been access to Ivacaftor for the 5% of people with a gating mutation but the majority of people only had access to standard therapies. Standard therapies are designed to manage symptoms and progression rather than the cause of the disease. Orkambi and Symkevi became available in 2019, however the efficacy of these technologies was significantly less than Ivacaftor. **Change in outcomes following interim access to Kaftrio** Prior to access to Kaftrio average age of death was 31 (2019), the most recent registry data shows that since interim access to Kaftio this has increased to 38 (2021).[1] Prior to access to Kaftrio, median days on IV antibiotics was 26 (14-43)[2], the most recent registry data shows that since interim access to Kaftio this has decreased to 15 (14-31)[3]. These statistics include those ineligible for 'technologies' and would likely demonstrate further improvement if they included only those eligible for 'technologies'. IV antibiotics are prescribed when a person with CF has an exacerbation, when they will often feel unwell, need to take time off work or education, suffer a reduction in FEV1- this reduction of time spent on IVs (2019 vs 2021 data) represents a significant improvement in overall health and wellbeing.

1. The cost of cystic fibrosis - June 2022 p12
2. 2019 Registry Annual Data report Sep 2020.pdf (cysticfibrosis.org.uk) p17
3. The cost of cystic fibrosis - June 2022 p35

Paediatrics

Even with current access to Kaftrio, there remains an unmet need for those <6 years of age. There is access in other countries from the age of 2 while, in the UK, this remains age 6 and over.

The 10% ineligible

Approximately ~10% of people with CF are ineligible for 'technologies'. Since the interim access to Kaftrio we have seen a significant gap in health and health care demand between people who are and who are not eligible. Those without access continue to experience a deterioration in their health annually and rates of lung transplant referral and death remain ISQ.

Patients from black, Asian and minority ethnic backgrounds are significantly less likely to be eligible for Kaftrio based on the current prescribing policy in the UK. The CF community need to urgently address the unmet need for effective targeted therapies for patients without F508del [1].

1. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies - ScienceDirect

Optimising outcomes with modulator therapies

Real-world outcomes with Ivacaftor demonstrated an efficacy-effectiveness gap between clinical studies and real-world outcomes. There was a decline in lung-function back to baseline by year five post initiation of Ivacaftor[1]. Studies have highlighted the decline in use of preventative treatments such as inhaled antibiotics and mucolytics and in intravenous antibiotics post initiation of Ivacaftor[2]**.** We expect that the use of other standard therapies used in the clinical trials, such as airway clearance, will also have declined, though there isn't yet data to support this. This is in contrast to the clinical studies where CFTR modulators were an add-on therapy to standard treatment. Studies demonstrate that people engaged in clinical trials are more likely to be highly adherent to prescribed treatments[3]. There is an opportunity to better understand co-adherence to treatments in order to optimise outcomes with Kaftrio, aiming to minimise the efficacy-effectiveness gap which should be

	minimal with a precision medicine. This has been found to be key for other transformational treatments in other conditions such as biologics in asthma management. 1. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review - PMC (nih.gov) Figure 3 2. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? - PMC (nih.gov) Figure 1 3. Adherence pattern to study drugs in clinical trials by patients with cystic fibrosis. - Abstract - Europe PMC

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	**Multi-Disciplinary care** Treatments for cystic fibrosis (prior to the 'technologies') manage the symptoms and complications rather than the cause of the disease. **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 medications[1]. Part of physiotherapy treatment will be to support the patient

	with their routine and habit formation. 1. The cost of cystic fibrosis - June 2022 p41 **Other 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 support
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 of care interim 2022.pdf (cysticfibrosis.org.uk) • Cystic fibrosis (nice.org.uk) 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.)	There was a well-defined pathway of care prior to interim access of Kaftrio and the global pandemic, with some regional or centre variance to suit patient profile, transport, geography of patient location. Since 2020 CF care in the UK has had to adapt to a rapid change; • post global pandemic, we saw all people with CF advised to shield at home and the advent of virtual clinics and home monitoring, • interim access to Kaftrio, where we saw a huge clinical change in the health status and therefore health care needs of the majority of our patients. This has meant that CF specialist centres have had to rapidly evolve, in relative isolation, with limited long-term

	real-world data and a difficult task to detangle the effects of lock-down and shielding vs the effects of Kaftrio[1,2,3]. Data is beginning to help to detangle these effects however there are challenges as the initial data has been obtained during the global pandemic, with shielding as part of this response. While open label data shows a halt in lung function decline with Kaftrio[1], part of this dataset was collected during the global pandemic[2]. Australian registry data demonstrates lung function improvements in a largely 'technology' naive population[3]. Further real-world, data outside of shielding and the global pandemic, may be more helpful to understand real-world outcomes and any efficacy-effectiveness gap. While uncertainties remain and while the real-world outcomes of the 'technologies' outside of the global pandemic are being assessed, there are and will be differences in the views of different clinicians, different professional groups and different CF centres. A review of the CF trusts consensus standards of care and a NHSE cystic fibrosis review are both currently underway but not yet ready to report. 1. EFFECT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS - PubMed (nih.gov) 2. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis" - PubMed (nih.gov) 3. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic - PubMed (nih.gov)
9c. What impact would the technology(ies) have on the current pathway of care?	There has been access to these 'technologies' since 2019, with access to Kaftrio since 2021. Impacts have included; • Improved BMI and FEV1 • Reduced referrals and need for lung transplant • Reduced deaths • Reduced requirement for IV antibiotics and inpatient care • Increased uptake in exercise • Improved female fertility resulting in increased pregnancies and live births • Increased focus on preventative and planned care rather than responsive and unplanned care

	Since interim access, 'technologies' have had a huge positive impact on our patient population. These changes, along with changes driven by the global pandemic, have affected the pathway of care. The pathway of care has moved to more planned, preventative and complex complication management which remain resource intensive. Data from open label studies on Kaftrio suggests positive effects are maintained beyond >18 months when used alongside standard care. However, we are seeing in clinics that patients are reducing their uptake of 'standard care', despite advice to continue, due to the beneficial impact of Kaftrio on their health. This is a similar effect to that seen and documented with Ivacaftor[1]. There is a lack of data on the impact of co-adherence to 'standard care' alongside Kaftrio. Further investment and data collection is needed to analyse the impact of this. 1. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? - PMC (nih.gov) Figure 1
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	'Technologies' are currently prescribed and provided to patients via 'home care' via private companies. Throughout the UK, centres have reported issues with homecare leading to periods without 'technologies'. With this model of provision, when a patient with CF is admitted to hospital, they need to bring in their home supply of the 'technology'. If they forget this can mean that they miss doses when at their most unwell, when they arguably need it the most. Consistency of provision is vital and currently not guaranteed. Real-world outcomes with Ivacaftor demonstrated an efficacy-effectiveness gap between clinical studies and real-world outcomes. There was a decline in lung-function back to baseline by year five post initiation of Ivacaftor[1]. Studies have highlighted the decline in use of preventative treatments such as inhaled antibiotics and mucolytics and in intravenous antibiotics post initiation of Ivacaftor[2]. This contrasts with the clinical studies where CFTR modulators were an add on therapy to standard treatment. There is an opportunity to better understand co-adherence to standard treatments in order to optimise outcomes with Kaftrio aiming to minimise the efficacy-effectiveness gap, which should be minimal with a precision medicine. Currently the evidence suggests that the 'technologies' should be used in the same way and alongside standard care.

	1. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review - PMC (nih.gov) Figure 3 2. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? - PMC (nih.gov) Figure 1
10a. How does healthcare resource use differ between the technology(ies) and current care?	• Population size in paediatric CF centres is not likely to increase. If 'technologies' become available to younger age groups, health is likely to improve and there will be a move from acute care to preventative care. • Due to the positive impact on health and life expectancy adult CF centres will need to plan for growth in-line with increased numbers of people with CF, with regards to both capacity and resources, e.g., specialist MDT to provide recommended level of care, including preventative approaches. • Both adult and paediatric CF centres have had to maintain adequate provision/ facilities for non-emergency and emergency and acute care and provision for those pwCF not eligible or intolerant of 'technologies' who remain on standard care only. • The plan for growth in numbers in adult CF centres will need to take into account the likely increased prevalence of age dependent CF and non-CF complications within the population. • The addition of 'technologies', and particularly Kaftrio, changes the healthcare needs of a person with CF. CF MDTs have needed to adapt to this, providing care for, as an example, increased pregnancies and age-related non-CF and CF related complications. As highlighted in sections 9 and 10, a focus on preventative care and careful monitoring in order to optimise outcomes is also needed. The resourcing for care in the post modulator era remains important and an area for investigation. • There will need to be thought as to how to retain sufficient skills, knowledge and expertise to treat severe complications of CF which are likely to occur less frequently so potentially leading to deskilling of clinicians. This could potentially lead to particular inequities for those not eligible for or unable to take these 'technologies'.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist	Specialist CF centres.

clinics.)	
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	Interim access to Kaftrio has had a huge positive impact on our patient population who are eligible. Data from open label studies suggests positive effects are maintained beyond >18 months when used alongside standard care. However, we are seeing in clinics that patients are reducing their uptake of standard care, despite advice to continue, due to the beneficial impact of Kaftrio on their health. There is a lack of data on the impact of co-adherence to 'standard care' alongside Kaftrio. The clinical trials utilised these technologies as add on therapy and open label studies continue to demonstrate outcomes in people who are engaged with continuing standard therapy. Further investment and data collection are needed to analyse the real-world outcomes for people who access these 'technologies' and continue standard therapies or discontinue standard therapies . Projects such as project Fizzyo (Project Fizzyo) and CFHealthHub (Home - CFHealthHub.com) have the technologies to do this but are not clearly commissioned and resourced to do so. As detailed in section 9b, the interim access to Kaftrio arrived during the global pandemic and so the first two years of real-world data is likely to be impacted by the unique conditions created by shielding. Investment is needed for longer term evaluation of Kaftrio outside of the impacts of shielding. Investment continues to be needed to adequately resource CF centres and teams to provide care both to those eligible and able to take the 'technologies' and those who are unable and have different clinical needs. The care pathway needs to continue to be responsive to changes and new evidence as these 'technologies' continue to be embedded in care.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes, this has been demonstrated since interim access, with improved lung function, quality of life and with meaningful changes to the ability to achieve life events, for example pregnancies. Sustaining these benefits will need careful assessment of the longer term and real-world outcomes with Ivacaftor and why the lung function benefits were sustained in the clinical trials[1] and not in the real-world studies[2]. The need for standard therapies should be carefully assessed in these first years of access to the 'technologies' in order to obtain optimum benefit for people with CF. With a halted rate of lung function decline there is an opportunity for a normal life expectancy for people with CF able to access Kaftrio. If the pattern seen with Ivacaftor is repeated, where clinical trials demonstrated sustained improvements whereas real-word

	data demonstrated decline to baseline, then this opportunity will be missed. 1. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST) - PubMed (nih.gov) 2. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review - PubMed (nih.gov)
11a. Do you expect the technology(ies) to increase length of life more than current care?	Prior to access to Kaftrio average age of death was 31 (2019), the most recent registry data shows that since interim access to Kaftio this has increased to 38 (2021)[1]. 1. The cost of cystic fibrosis - June 2022 p12 As detailed in other sections, further thought and research is needed in order to realise the potential for a normal life expectancy with these 'technologies'.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes. this has been demonstrated since interim access, with improved lung function, quality of life and with meaningful changes to the ability to achieve life events, for example pregnancies.
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	Technologies are specific to CF genotype. **The 10% ineligible** Approximately ~10% of people with CF are ineligible for precision medicines. Since the interim access to Kaftrio we have seen a significant gap in health and health care demand between people who are and who are not eligible. Those without access continue to experience a deterioration in their health annually and rates of lung transplant referral and death remain ISQ. Patients from black, Asian and minority ethnic backgrounds are significantly less likely to be eligible for Kaftrio based on the current prescribing policy in the UK. The CF community need to urgently address the unmet need for effective targeted therapies for patients without F508del[1]. 1. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator

	therapies - ScienceDirect There are also a small number of people with CF who are unable to tolerate the 'technologies'. These people will also experience disease progression in the same way as those ineligible. Further research is needed into how adverse effects can be managed for these people.

The use of the technology(ies)

13. Will the technology(ies) 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.)	Additional monitoring includes blood tests to assess liver function quarterly in first year and annually thereafter. These 'technologies' alter people's perceptions of their health and, at times, their ability to detect changes such as exacerbations. There has always been an emphasis on the ability to measure lung function, weight and adherence as part of the clinical assessment. With a change in the ability of people to detect changes in their health, regular objective measurement is even more important. The frequency of various monitoring needs to be defined in the care pathway following the interim access to the 'technologies'. Adequate support and resourcing is needed to provide patient centred ways of accessing the long-term monitoring needed. This may include remote monitoring. Resourcing this needs investment in both the equipment and technology needed and in appropriately skilled and resourced CF multidisciplinary teams.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	These 'technologies' alter people's perceptions of their health and, at times, their ability to detect changes such as exacerbations. The improvements in health, coupled with a period of less face-to-face attendances at clinics, due to the global pandemic, may have impacted on the attendance for routine monitoring. There needs to be thought and consideration about how to balance the benefit and risk of stopping or continuing transformational and other

	treatments where monitoring such as liver and lung function isn't obtained at the frequency needed. For those who are unable to tolerate the 'technologies' due to adverse effects, there is emerging data that being able to monitor levels, or at least surrogate markers such as repeated sweat tests, may be helpful in dose titrating. Further research and resource is needed in order to ensure access for as many people as possible to the technologies.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not that we are aware of.
16. Do you consider the technology(ies) 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?	These technologies are transformational treatments which, as detailed in other sections, confer huge benefits in terms of disease progression, quality of life and the potential to live a normal life expectancy while being able to experience more important life events such as raising a family. As detailed in other sections there are unknowns about how to ensure that the potential benefits are realised. Longer-term real-world research and assessment is needed in order to increase the possibility of realising the full potential of these technologies.
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Yes. As per section 11 the 'technologies' offer an opportunity for normal life expectancy and for life opportunities which may have previously been more limited, such as having a family and enjoying lifestyle choices such as travel, a career, etc. This opportunity though needs careful assessment and management in order to realise the

	potential benefits.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	As detailed in other sections prior to these 'technologies' there was an unmet need.
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Some people have experienced predictable side effects such as elevated liver markers, etc. and some people have experienced less predictable and understood effects such as mental health issues. This can induce anxiety for people with CF with additional monitoring needed and a worry for them that they may not be able to continue the 'technologies'. Some people have had to discontinue the 'technologies' and this needs careful and often intensive support. Clinical psychologists and pharmacists are vital members of the CF MDT in order to support these situations. For those who are unable to tolerate the 'technologies' due to adverse effects, there is emerging data that being able to monitor levels, or at least surrogate markers such as repeated sweat tests, may be helpful in dose titrating. Further research and resource is needed in order to ensure access for as many people as possible to the technologies.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	The clinical trials of these 'technologies' largely reflect current UK clinical practice. However, the clinical trials of CFTR modulators were using these treatments as add on therapy in addition to standard care. As detailed in other sections, our experience is that many people with CF are decreasing or discontinuing standard therapies such as airway clearance and inhaled therapies. This was seen with Ivacaftor[1] and, while weight continued to increase over five years of Ivacaftor use, lung function dropped back to baseline over the five years following

	initiation of Ivacaftor. The open-label studies of Kaftrio included data over the global pandemic while people with CF were shielding and so will not reflect viral exposure and potential for exacerbations as we move out of the pandemic[2,3,4]. 1. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? - PubMed (nih.gov) 2. EFFECT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS - PubMed (nih.gov) 3. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis" - PubMed (nih.gov) 4. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic - PubMed (nih.gov)
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?	A reduction in the annual rate of FEV1 decline. Improvement in BMI and/ or body composition. We have been cautious about including a reduction in IV/ bed days here, as while this has been observed as a clinically significant treatment response, we have concerns that the changes (reduction) in symptoms for many on Kaftrio are potentially leading to respiratory under-treatment. This is, as yet, unstudied but may lead to less optimised long-term outcomes.

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?	Mental health issues and abdominal issues have been reported in a way not seen in trial data but it is difficult to currently know whether these reports are related to physical effects of the medication or to the effects of starting a transformational treatment or to the timing of starting these treatments during a global pandemic while shielding.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We are concerned that airway clearance and inhaled antibiotics were not included within the scope or protocol of this review as a comparator or as part of best supportive care. Both of these important aspects of care are clearly established and, particularly for inhaled antibiotics, evidence based clinical practice. This may mean that some evidence is either not found or is excluded based on the protocol. We have highlighted this issue to the NICE team.
20. How do data on real-world experience compare with the trial data?	Real-world data interpretation to date has been problematic as the introduction of interim access to Kaftrio was during the global pandemic and during shielding for those with CF. As detailed in other sections, while open label data shows a halt in lung function decline with Kaftrio[1], lung function decline was also halted for those not able to access modulators[2]. This is likely due to decreased viral challenge and exacerbations[3]. Longer term follow-up outside of the shielding period is important in order to understand real-world outcomes[3]. A series of examples we were able to access from clinicians who are interested in understanding co-adherence to standard therapies while also taking these 'technologies' demonstrated that the improvements in lung function seen following initiation of Kaftrio were sustained in those who continued to have optimised adherence to inhaled therapies while lung function dropped back down from the peak in those whose adherence to standard inhaled therapies dropped. Further work is ongoing to assess this within a five-year cohort, observational study[4].

	1. EFFECT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS - PubMed (nih.gov) 2. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic - PubMed (nih.gov) 3. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis" - PubMed (nih.gov) 4. Inhaled Therapy Adherence and Outcomes to Kaftrio in Cystic Fibrosis - Full Text View - ClinicalTrials.gov

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	**The 10% ineligible** Approximately ~10% of people with CF are ineligible for precision medicines. Since the interim access to Kaftrio we have seen a significant gap in health and health care demand between people who are and who are not eligible. Those without access continue to experience a deterioration in their health annually and rates of lung transplant referral and death remain ISQ. Patients from black, Asian and minority ethnic backgrounds are significantly less likely to be eligible for ivacaftor/tezacaftor/elexacaftor 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 Access to appropriate care for those ineligible or unable to tolerate the technologies needs to be considered. If care pathways and resourcing are changed with a focus on those who can access and take the technologies, then there will be inequitable and suboptimal care for those with other needs.
21b. Consider whether these issues are different from issues with current care and why.	This inequality is different from any issues with standard care as all other aspects of standard CF care are not dependent on genotype.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• CFTR modulators (or 'technologies') are highly effective treatments, with the potential, demonstrated in clinical trials, to halt lung function decline and normalise life expectancy. • Interim access to Kaftrio was granted during the global pandemic and during shielding for people with CF. This makes the real-world data currently available difficult to interpret due to lack of viral challenge and exacerbations. Longer term follow up is needed. • CFTR modulators (or 'technologies') offer an opportunity to optimise health, longevity, and wellbeing for people with CF. This needs careful real-world follow up outside of confounders such as the pandemic response and with consideration of co-adherence to standard therapies or other changes in use from the clinical trials. • The Ivacaftor data suggests that real-world outcomes for modulators may be different to the clinical trials. Data show decreased use of standard preventative treatments such as inhaled antibiotics and mucolytics following initiation of Ivacaftor, as opposed to the clinical trials where these continued. Understanding the outcomes of people who continue and who stop standard therapies will be important to optimise outcomes with CFTR modulators. • The addition of CFTR modulators (or 'technologies'), and particularly Kaftrio, changes the healthcare needs of a person with CF. CF MDTs have needed to adapt to this, providing care for, as an example, increased pregnancies and age-related non-CF and CF related complications. As highlighted in sections 9 and 10, a focus on preventative care and careful monitoring in order to optimise outcomes is also needed. The resourcing for care in the post modulator era remains important and an area for investigation.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) 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.

About you

1. Your name	[redacted]
2. Name of organisation	British Dietetic Association Cystic Fibrosis Specialist 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).	The British Dietetic Association (BDA) is the only body in the UK representing the whole of the dietetic workforce. It is also a trade union and professional body representing the professional, educational, public and workplace interests of its members. It is a member funded association.
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **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 study of CFTR modifier medications is a major revolution in CF treatment because these agents target the basic defect as opposed to targeting the effects of the disease. Previous medical therapies were unable to target the underlying genetic cause of CF and could only address symptoms. These new drugs can now affect CF at the genetic level. The sweat chloride test measures the chloride content of the patient's sweat as an indicator of CFTR function. The main aim of the treatment is to decrease the sweat chloride to non-CF values, which then correlate with improved clinical outcomes, such as improved lung function, improved nutritional status /growth, reduction in chest infections, reduced hospital admissions, increased life expectancy and an improved quality of life.
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.)	The sweat chloride test measures the chloride content of the patient's sweat as an indicator of CFTR function. A sweat chloride value of more than 60 mmol/L is diagnostic for CF. A decrease in sweat chloride to non-CF values would be a clinically significant response. Significant outcome would be an improvement in lung function and respiratory symptoms. Poor outcomes in CF include - malnutrition, poor growth, frequent respiratory infections, breathing difficulties, and eventually permanent lung damage. Lung disease is the usual cause of death in most patients. A significant response to treatment with these new drugs would be improved growth and optimal nutritional status on an individual basis, reduction in respiratory infections, antibiotics and hospital admissions and increased survival. CFQ-R is a measurement tool used to determine changes in health-related quality of life for CF patients. A clinically significant change in the CFQ-R score is defined as a change of 4 points.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a lack of evidence on long term outcomes for patients with CF (pwcf) on these new treatments. For example, absorption, vitamin levels and bone densitometry. We also need more information on body composition in our patients, fat mass as opposed to lean body mass. Varying gastro-intestinal symptoms have been reported in several patient groups on these new drugs and so more research and data is required.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Patients are mostly managed in their own home and reviewed regularly in clinic, face to face and virtually, home visits and occasionally require hospital admission.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are numerous clinical guidelines used in the treatment of this condition. Relevant to our specialist area are: - **CF Trust guidelines include**: Standards for the Clinical Care of Children and Adults with cystic fibrosis in the U K. Second edition. Dec 2011. Consensus document on nutritional management of cystic fibrosis. Published: September 2016 Consensus document on managing CF Diabetes. Published: November 2022 **European guidelines** ECFS Standards of Care: Standards of Care for Cystic Fibrosis ten years later European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre European Cystic Fibrosis Society Standards of Care: Best Practice guidelines European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis European cystic fibrosis bone mineralisation guidelines (2011) ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis (2016) NICE: - Cystic Fibrosis: Diagnosis and management NICE Guideline 2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand (2017)
9b. Is the pathway of care well defined? Does it vary or are there differences of	The pathway of care is well defined within the care of CF. All patients with CF have access to a specialist MDT team, who are experienced in the care of patients with CF.

opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Access is sometimes varied depending on availability and staffing and location. Paediatric care is managed slightly differently to adult care with the addition of network clinics.
9c. What impact would the technology(ies) have on the current pathway of care?	Presently, the current pathway of care has not been impacted on as we are still in the early stages of the new treatments. Also, for some patients, they have experienced changes that have required an increase in intervention, such as excess weight gain, and GI symptoms. There is limited evidence to show what the long term impact of these therapies will have on patient care. We are aware of the current needs evolving with a large proportion of the CF Cohort and their care. Yet, in some cases, the care has resorted back to “previous” CF care. There is an ongoing need for the CF specialist MDT potentially in varying proportions dependant on the individual needs.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	At present, the new drug treatment is being used in the same way as current care. The treatment has been provided in NHS care to the CF patients since 2019.
10a. How does healthcare resource use differ between the technology(ies) and current care?	At present, there is no difference between the two.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	They need to be used within specialist CF clinics/centres, where patients can be monitored and supported closely by MDT specialising in CF care. The MDT comprising of: CF Consultant, Specialist Nurse, CF Physiotherapist, CF Dietitian, CF Pharmacist, CF Psychologist, CF Social Worker, CF Practitioner if appropriate and available.
10c. What investment is needed to introduce the technology(ies)? (For	Extra pharmacist time is required within the hospitals. Patients may require 3 monthly blood levels for the first year of the treatment. Extra blood test maybe required if any abnormalities seen e.g. increase in liver enzymes or vitamin levels.

example, for facilities, equipment, or training.)	MDT support and education
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes, this has been shown over the past few years and would hope to see the trend sustained.
11a. Do you expect the technology(ies) to increase length of life more than current care?	Yes more than care prior to introduction of modulator therapies.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes more than care prior to introduction of modulator therapies. However there may be an impact on QOL that needs to be supported and managed appropriately by the MDT in relation to mental health or adjustment to "new" patient role (i.e. not the sick role)
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	Only patients with CF with certain genetic mutations are eligible for the new treatment. There is a small percentage of the CF population who not able to access or receive the treatment based on the genetic mutation.

The use of the technology(ies)

13. Will the technology(ies) 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,	They should not be more difficult to use than current care. However, at present, it is not known as to whether patients can stop any of the other treatments, until more research has been carried out. Therefore, patients are being advised that this is additional treatment, on top of their present treatment load.

any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Extra clinical requirements for the first year include 3 monthly blood tests. Patients will have to be monitored more closely for any adverse reactions. Patients not responding as expected will need to be re-assessed and dosing reviewed.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Patients will be taken off the drugs if any adverse reactions or side effects are noted. Alternatives to be considered if a patient unable to tolerate a specific modulator.
15. Do you consider that the use of the technology(ies) 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(ies) 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, the technology(ies) are innovative in its potential to make a significant and substantial impact on health-related benefits. It might improve the way that current need is met by reducing in- patient admissions. CF care may therefore be met primarily as an out-patient service and via “virtual wards”.

	There may likely be a reduction in the current clinical care needs, in the future and yet increase in other aspects of general medical care i.e. antenatal care etc.
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Yes.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes. It is the first drug treatment to target the basic defect of CF, as opposed to targeting the effects of the disease. Previous medical therapies were unable to target the underlying genetic cause of CF and could only address symptoms. These new drugs can now affect CF at the genetic level and provide a very effective treatment, potentially giving patients with CF the chance of a good quality of life with a normal life expectancy in line with the general public.
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Patients will require blood tests every 3 months for the first year of the new treatment. If side effects or adverse effects occur the patient likely to be unable to sustain on the medication and will be managed as per current CF Care, thereby not being able to incur the benefits of the therapy. Thus impacting on their clinical and quality of life.

Sources of evidence

18. Do the clinical trials on the technology(ies) 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?	As dietitians, we are primarily concerned with nutritional status. For this reason, we have highlighted these key outcomes. **Nutritional status and monitoring** Improvements in weight, height and BMI were reported as secondary or exploratory outcomes in the randomized controlled trials (RCTs) underpinning approval of CFTR modulators. Data on linear growth and body composition is limited for elexacaftor-tezacaftor-ivacaftor. Longitudinal data is needed to establish whether the effects of elexacaftor-tezacaftor-ivacaftor on anthropometric status are sustained beyond 48 weeks, and to assess the effects on body composition. It is important to establish that the correct weight is being increased rather than increasing fat mass and leading to a higher normal weight obesity issue. **Dietary and nutritional issues** In pwCF with G551D taking ivacaftor, there have been reports of decreased energy expenditure, increased small intestine pH and decreased gut inflammation. Data from clinical trials and real-world studies of pwCF are needed to determine the long-term effects and the physiological mechanisms with different modulators. As evidence is lacking regarding macronutrient requirements, it is recommended

	that current practice continues to assess energy requirements individually, depending on age and clinical status until further evidenced. Emerging data suggest vitamin levels can be affected by CFTR modulator therapy and longer-term data are required to quantify the impact on need for vitamin supplementation. Similarly the need for salt supplementation on VST has not been assessed and should be monitored closely, as per the usual practice of the CF service. Early initiation of ivacaftor may mitigate existing pancreatic damage and prevent or delay further damage in young children with CF. Further research characterizing the impact of VST on children is paramount, especially the role of faecal elastase measurement for monitoring pancreatic function. At present, there is no evidence to warrant reducing or stopping pancreatic enzyme replacement therapy (PERT) upon commencement of VST although this is an important question for pwCF. It is important to understand the underlying mechanisms of the VST on the gut and GI side effects? **Effect of CFTR modulators on CF Diabetes** CFTR modulator therapy has been shown to impact glucose handling. Ivacaftor has a significant beneficial effect on glycaemia and the combinations of ivacaftor and Lumacaftor or tezacaftor have also shown a small benefit in glucose handling. Elexacaftor-tezacaftor-ivacaftor has in some cases been shown to improve continuous glucose monitoring (CGM) markers of glycaemia in pwCF with and without known CFRD. Hence, it is important to monitor glucose handling in pwCF established on VST.

	Management of CF Diabetes While changes in glucose handling have been observed with CFTR modulator therapy, the impact upon CFRD management is not fully established. Glucose levels should be closely monitored, and treatment modified, as required. Similarly, nutritional status should be closely monitored, with appropriate dietary modifications recommended where applicable. Improvements in survival will result in people living with CFRD for longer. Therefore, close on-going monitoring of diabetes-related complications is important, especially for microvascular and macro vascular disease.
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?	Gastro-intestinal disturbances (variations – diarrhoea, constipation and increased wind) Variations in glycaemic control. Impact on the role of faecal elastase measurement for monitoring pancreatic function. Skin – acne issues for a few patients. Behaviour changes Some mood changes have been considered

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes, patient experiences. *"The nutritional and gastrointestinal experiences of people with CF taking CFTR modulator therapy".* *UK CF Dieitians group of the BDA*
20. How do data on real-world experience compare with the trial data?	Studies reporting within-group change for pwCF treated with ivacaftor consistently showed improvements in lung function, nutritional parameters, and patient-reported respiratory and sino-nasal symptoms. Benefits were evident as early as 1 month following ivacaftor initiation and were sustained over long-term follow-up. Decreases in pulmonary exacerbations, Pseudomonas aeruginosa prevalence, and healthcare resource utilization also were reported for up to 66 months following ivacaftor initiation. In studies comparing ivacaftor treatment to modulator untreated comparator groups, clinical benefits similarly were reported as were decreases in mortality, organ-transplantation, and CF-related complications. The safety profile of ivacaftor observed in these real-world studies was consistent with the well-established safety profile based on clinical trial data. This systematic review of real-world studies shows ivacaftor treatment in pwCF results in highly consistent and sustained clinical benefit in both pulmonary and non-pulmonary outcomes across various geographies, study designs, patient characteristics, and follow-up durations, confirming and expanding upon evidence from clinical trials. *J Clin Med. 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527.Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review.*

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	All eligible patients have access to the treatment yet it is a concern for the small proportion of the CF population that are not currently eligible for the modulator therapies.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• More long term data is required on nutritional status, dietary intake, CF diabetes and glucose handling, bone mineral density, pancreatic absorption and gastro-intestinal issues. • Reviewing nutritional status outcomes – BMI and Body composition and impact on QOL • We may have a healthier population of people with CF but the CFTRm will not reverse disease progression it will merely slow it down. • Follow up is still required due to consequences of an increased life expectancy and as yet the unnown effects of long term CFTRm use. • Monitoring may become more challengig with responses to CFTRm treatments eing variable. Side effects or tolerability issues and adherence to CFTRm (and other treatments) is challenging. • There is a need to adapt and respond to the needs of the people with CF in this changing landscape and focus on the individual and treat appropriately.

Thank you for your time.

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Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) 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.

About you

1. Your name	[redacted]
2. Name of organisation	British Paediatric Respiratory Society (BPRS)
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? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BPRS is a multidisciplinary organisation which exists to promote the respiratory health of all children and to improve the health of children with respiratory disease. Membership of the Society is open to health care professionals who are active in the field of paediatric respiratory medicine. It is funded by membership fees paid by the members
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No funding from manufacturers. (comparator products – not applicable)

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 the above therapies in the context of a patient with cystic fibrosis (CF) is to curtail progression of the disease, improve respiratory function, reduce exacerbations, and potentially prevent future complications.
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.)	1. Improvement in lung functions as measured by spirometry (>/= 5%, mean) 2. Improvement in other parameters (e.g., Decrease in number of exacerbations, improvement in well-being measured by QOL questionnaires, improvement in other measures of lung function e.g. LCI)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	CF is a multiorgan disease, but dominated by respiratory manifestations, which can eventually lead to bronchiectasis, respiratory failure and need for lung transplant. Management (prior to the modulator therapies) consisted of symptomatic management including airway clearance, antibiotics, and nutritional support (conventional therapy). Despite conventional therapy, patients still had shorter life expectancy and decrease in quality of life. Therefore, these were unmet needs prior to these therapies. There is still a proportion of patients with cystic fibrosis, whose mutations are not amenable to these treatments. This represents the current unmet need.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Prior to 2016, conventional therapy was the main mode of management. Modulator therapies have been approved stepwise, starting with Ivacaftor for gating mutations, followed by combination therapies (lumacaftor-ivacaftor, tezacaftor-ivacaftor (2019) and Elexacaftor-tezacaftor-ivacaftor(2020))
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are many guidelines, including NICE guidelines on management of cystic fibrosis (Cystic fibrosis: diagnosis and management. NICE guideline [NG78] Published: 25 October 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 broadly similar across the UK. The standards of care are defined by the CF trust document : 'Standards for the clinical care of children and adults with cystic fibrosis in the UK'. NHS clinical care is based on service specifications for cystic fibrosis (children and adult). Many of these documents have not been updated following the approval of the newer modulator therapies.
9c. What impact would the technology(ies) have on the current pathway of care?	As the modulator therapies are quite new, the clinical effects are only just becoming apparent (in the real world). How this translates into changes in pathway of care is to be determined. It is likely that the following will eventually change- frequency of admissions, the frequency of clinical reviews, the medication and therapy burden on the patient (list not exhaustive) – due to the benefit of modulator therapy.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	The modulators are currently used as additional to existing medical therapy in the patients. It is our observation that it is possible to reduce medication and therapy burden on the patient with the modulator therapies.
10a. How does healthcare resource use differ between the technology(ies) and current care?	The technology (modulator therapy) comes at a cost to the NHS. The current arrangement between NHS providers and manufacturer is privileged information, so it is not possible to quantify the difference between the technology and conventional therapy. (Please note that we have not used the term 'current care' as the technology being appraised is currently already in use)

10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	It is initiated in secondary and/or tertiary care clinics, but the modulators are used at home (usually a twice daily oral medication)
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	The technology has already been introduced, and the necessary training has been provided. Therefore, this question is not applicable.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes, as discussed above.
11a. Do you expect the technology(ies) to increase length of life more than current care?	Yes, as discussed above.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes, as discussed above
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	This therapy/ technology is for patients with cystic fibrosis. There are specific mutations within cystic fibrosis where the technology does not work (approx. 10% of CF population)

The use of the technology(ies)

13. Will the technology(ies) 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 therapy does not completely replace current care, but generally additional to it. It is simple to use (oral medication). As discussed above, in many cases, it reduces burden of treatment, therefore there is a potential that it makes day to day management easier for patients (and healthcare professionals). They are generally well tolerated. There is additional monitoring of side effects (e.g. liver function tests regularly)
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Yes, commencement of therapy is based on age criteria and specific mutation of the patient. Mutation is already known in most cases due to newborn screening for cystic fibrosis.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The technologies are expected to result in improvement in QALYs. There may be additional benefits, e.g. delay in onset of complications and a general sense of well being that may not be easy to measure with QALYs.

16. Do you consider the technology(ies) 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. As discussed above, it might: 1. Improve life expectancy 2. Improve Quality of life 3. Decrease exacerbations 4. Decrease CF related complications 5. Improve sense of well-being 6. Reduce medication/ treatment burden and decrease need for healthcare contacts.
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes, refer to question 8 and 16.
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Adverse effects are generally mild and self-limiting. Some may need temporary halt in medication.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	Yes, in general.

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?	Improvement in lung function, improvement in quality of life, improvement in nutritional status and decrease in number of exacerbations. They have been measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Lung function measures are ultimately a surrogate marker of duration of life. However, it is known that in adults with lung disease, decreasing the rate of lung function decline increases life expectancy. Indices for quality of life have also been measured in the studies of modulators. Taking these two together, we can be assured that they predict improvement in QALYs. However, this is less clear in studies done in children between 2-5 year old (which have just recently been published). It mainly includes surrogate markers (mainly because of difficulty in measuring lung functions in children), although lung clearance index, which is a newer way of measuring lung disease has been measured.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unaware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Unaware of any.

20. How do data on real-world experience compare with the trial data?	We feel that it compares well with trial data.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are some mutations where the currently available modulators do not work. Research is being done for the population with these mutations.
21b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology is already in use in patients with cystic fibrosis in the UK • There are benefits, including improvement in lung function and quality of life measures which should improve QALYs • The technology is generally safe and well tolerated • There are few burdens on healthcare providers following initiation of therapy (limited to monitoring of side-effects) • It is currently a costly therapy

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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).	British Thoracic Society BTS is registered charity and a company limited by guarantee. BTS activities cover all of the UK and seek to work collaboratively with others and maintain a global outlook focussed on improving respiratory care and removing inequalities in access to care and respiratory health outcomes.
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **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 improve quality of life and reduce development of complications and ultimately improve survival in those living with Cystic Fibrosis.
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 of CFQR resp domain >4, reduction in infective exacerbations and improvement of FEV1% predicted and body mass index.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there remains significant reduction in life expectancy and impaired quality of life and disease burden even for those eligible for CFTR modulators as well as those not eligible.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	CF trust standards of care—currently being updated, NICE guidelines, European CF guidelines
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	CF trust standards of care—currently being updated, NICE guidelines, European CF guidelines

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.)	Yes generally well defined as regard to CFTR modulators
9c. What impact would the technology(ies) have on the current pathway of care?	These modulators are as an addition to standard care in those who are eligible to receive them
10. Will the technology(ies) 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(ies) and current care?	These modulators are as an addition to standard care in those who are eligible to receive them
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Initiated and monitored from a specialist CF centre only
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	Staff training, patient information, initiated and monitored at specialist centre and needs regular safety monitoring of liver tests

11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes- see trial data and emerging real world evidence
11a. Do you expect the technology(ies) to increase length of life more than current care?	yes
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	See current licensing for list of genotypes eligible

The use of the technology(ies)

13. Will the technology(ies) 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	These are in addition to current therapies regarded as standard care. Of note there are now several trials looking at people with CF stopping other medications now they receive these modulator therapies—e.g CF Storm/ SIMPLIFY

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(ies)? Do these include any additional testing?	Not currently used
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Clinical experience shows that patients are more stable and may re enter education/ careers/ job and may be reduced carer burden. Also a number of patients have been removed from lung transplant lists as no longer currently require lung transplant
16. Do you consider the technology(ies) 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
16a. Is the technology(ies) a 'step-change' in the management of the condition?	yes

16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Not a cure but a significant advance for those living with CF who are eligible
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Regular monitoring of Liver tests, some people cannot tolerate and stop or adjust dose, currently not routinely measuring drug levels

Sources of evidence

18. Do the clinical trials on the technology(ies) 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?	Change in FEV1% predicted, Body mass index, number of exacerbations and Quality of life..yes measured
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?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Our data-unpublished- from a large centre of real world use looks reflective of trial data

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes—often ethnic minorities with Cystic Fibrosis may not be eligible for these therapies as their gene alterations are rarer and may not have been tested
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Access may be slightly different in England to devolved nations due to slight variation in commissioning • These modulators are a step change in therapy but do not cover all people living with CF • Important to capture data on those removed from transplant lists as no longer required and to ensure capturing data on quality of life and productivity • Many people with CF may be stopping other historic therapies that were standard of care now they have been on modulator therapy. This may be as part of a trial in conjunction with their clinical team or from the patients' own choice • There is currently no long term data on ETI therapy as to length of effects and whether gains in real world are maintained. Some real world data may be difficult to interpret as ETI therapy rolled out during COVID

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About you

1. Your name	[redacted]
2. Name of organisation	CFDigicare CFDigiCare - CFHealthHub.com
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).	CFDigicare was established as a Learning Health System to optimise self-care in Cystic Fibrosis. The programme was initiated when it was identified that adherence to preventative self-care in all long term conditions was low and this impacted CF outcomes. The Programme team (5 Universities and CF clinicians) secured a 5 year £2 million programme grant from NIHR (An intervention to support adherence to inhaled medication in adults with cystic fibrosis: the ACtiF research programme including RCT (nihr.ac.uk)) to co-produce an intervention to empower people with CF to form habits of self-care. NHS England commissioned 2 CQUINs supporting CFHealthHub over 4 years (2016 NHS England » Prescribed Services CQUIN Scheme: IM2 Cystic Fibrosis Patient Adherence and 2019 NHS England » PSS3 Cystic Fibrosis Supporting Self-care PSS CQUIN Indicator) with the CQUINS providing an additional ~£6 million. The learning health system is now funded by the ~50% of adult centres in England who use the programme alongside various research grants including the North American CF Foundation which is supporting the real time health technology assessment of Kaftrio National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) programme: a prospective observational study - CFHealthHub.com .

5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No. However [redacted] received funding from Vertex to give a talk and the CFHealthHub platform team has received funding from Pari to support a Physiotherapist/programme manager. CFHealthHub also received funding from Gilead to support evaluation of adherence to inhaled therapy in the post-Kaftrio era
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.)	CF treatment aims to enable people with CF to have as long and as normal a life as possible. The 2 year open label extension data from the 2014 Ivacaftor HTA was an evaluation that helps us to understand how the effectiveness of CFTR modulators can be evaluated (Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov)). This 2014 HTA can now be considered in the context of a further 9 years of real world data allowing us to understand how conclusions arrived out in the 2014 HTA mapped to the cost effectiveness of Ivacaftor over the next 8 years. The Ivacaftor 2-year open label extension data suggested that when Ivacaftor was provided to patients with G551D mutation a normal life expectancy was possible annual on the basis of achieving an FEV1 decline of <= 1% per annum. (see Lancet Resp Med Dec 2016 http://dx.doi.org/10.1016/ S2213-2600 (16) 30465-9). This Ivacaftor 2-year open label extension data was influential in shaping the conclusions of the 2014 HTA. However real world data that has become available over the past decade showed that Ivacaftor did not deliver the attenuated FEV1 decline promised in the 2-year open label extension data and this was almost certainly because CF clinical teams have not paid sufficient attention to the importance of co-adherence to inhaled therapies in adult patients taking CFTR modulators. Thus the aims of "treatment" as a whole in CF should also consider interventions that allow high cost drugs to deliver the potential seen in open label extension data. Thus the main aim of treatment includes a broader view of treatment that includes interventions used alongside the CFTR modulators that create habits of self-care that includes treatment that is necessary for high cost treatments to reach their potential. (This is similar to the recognised importance of co-adherence to preventative inhaled therapy alongside high cost biologics in asthma)
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 clinically significant response will reduce exacerbations, increase weight and reduce FEV1 decline. If the target FEV1 decline is 1% or less this should allow many patients to achieve a normal life expectancy (see . It is crucial to assess the Kaftrio data in the context of the Ivacaftor HTA data (Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov)) where FEV1 decline was less than 1% in the open label extension presented in the HTA and contrast this with the real world data that demonstrated real world data decline equated to the HTA pessimistic scenario Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, De Iorio F. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review. J Clin Med. 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527. PMID: 33917386; PMCID: PMC8038673

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The 2014 Ivacaftor HTA (Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov)) demonstrated that in the highly engaged population in the 2 year open label extension that FEV1 decline could be reduced to ~ <1% per annum that for many patients could restore a normal life expectancy. However the real world data J Clin Med 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527 showed that in the real world FEV1 decline was greater with other data suggesting that a lack of co-adherence to inhaled therapy accounted for the difference between open label data and the real world. **There is thus an unmet need for co-adherence to inhaled therapies in adults using CFTR modulators to allow the full potential of CFTR modulators to be realised .**

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Regular review in clinics to measure the key metrics of lung function and weight. Interventions are then added when lung function and weight is suboptimal. In common with other long term conditions this requires the clinical teams to support patient activation in self-care ie supporting patients with the knowledge skills and self-efficacy in preventative self-care Supporting people to manage their health: An introduction to patient activation (kingsfund.org.uk)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CF Guidelines
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 recent Digital review in CF emphasises the importance of the measurement and support of adherence in CF and this has also been emphasised in the 2016 NHS England CQUIN NHS England » Prescribed Services CQUIN Scheme: IM2 Cystic Fibrosis Patient Adherence which invested in building a model of care that supported adherence and this was followed by the 2019 CQUIN that consolidated the CQUIN from the previous 3 years NHS England » PSS3 Cystic Fibrosis Supporting Self-care PSS CQUIN Indicator which emphasised the importance of objective adherence measurement and support in CF. Though more than 50% of Adult centres in England now use objective adherence measurement this is not universal. CQUIN programme has created the infrastructure that has allowed real time health technology assessment of Kaftrio via the NEEMO programme that takes into account the impact of co-adherence to preventative inhaled therapies in adults taking Kaftrio on the cost

	effectives of Kaftrio in those in whom co-adherence is achieved compared to patients where co-adherence is unsuccessful and Kaftrio is used without inhaled therapies National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) programme: a prospective observational study - CFHealthHub.com . This issue will be discussed below but mirrors the effectiveness challenges that have been seen in the use of biologics in Asthma and the important role of co-adherence to inhaled steroids.
9c. What impact would the technology(ies) have on the current pathway of care?	It is important to recognise that we have already seen the impact of CFTR modulators on the care pathway when we look at the case of Ivacaftor. There is no reason to expect that Kaftrio would create an impact that differs much from the impact seen in Ivacaftor. It is important to recognise that adults with pre-existing lung damage when they start Kaftrio will behave differently to children with relatively health lungs and the suggestions in this response from CFDigicare account is relevant to the adult population since CFDigicare is a collaborative that works with adults with CF. The Ivacaftor HTA Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov) suggested an ICER of £335, 000 if FEV1 remained stable (optimistic scenario) and £1,274, 000 if FEV1 continued to decline (pessimistic scenario) and the real world data demonstrated that the pessimistic scenario was in fact what was observed in the real world. Thus there is a compelling argument that the impact of Kaftrio on the care pathway can be observed by looking at the impact Ivacaftor had on the care pathway. The impact of Ivacaftor was that patients experienced an immediate life changing improvement in lung function and weight. The marked increase in lung function with CFTR modulators means that many patients may have reduced perception for exacerbations which go unreported and untreated. In Ivacaftor we saw that as patients started Ivacaftor and experienced a rise in lung function preventative inhaled therapy reduced. In the case of Ivacaftor over 5 years the patients' lung function returned to the pre-Ivacaftor baseline. A similar picture can be expected in Kaftrio except that the COVID shielding period which has made a major difference to viral infections will delay the return to baseline when Kaftrio is compared to Ivacaftor. *Granger E, Davies G, Keogh RH. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? J Cyst Fibros. 2022 Mar;21(2):316-322. doi: 10.1016/j.jcf.2021.08.014. Epub 2021 Sep 6. PMID: 34497037; PMCID: PMC9097695 and Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, De Iorio F. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review. J Clin Med. 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527. PMID: 33917386; PMCID: PMC8038673.*
10. Will the technology(ies) be used (or is it already used) in the same way as	The technology will likely be used in a similar way to Ivacaftor. The key issue around the way that Ivacaftor was used was that in many centres where Ivacaftor was started there was no objective electronic data capture that measured co-adherence to inhaled therapies. As a consequence of not measuring and supporting co-adherence to inhaled therapy the evidence suggests that co-adherence to inhaled therapy fell and this is likely to be an

current care in NHS clinical practice?	important reason that the ICERs for Ivacaftor in the real world mapped most closely to the pessimistic rather than the optimistic scenario. However sections of the clinical community (including CFDigicare CFDigiCare - CFHealthHub.com) recognise that whilst Kaftrio is a powerful treatment its physiological impact is essentially the same as Ivacaftor and consequently the open label Kaftrio data is likely to show preserved lung function (especially since the 2 year Kaftrio data is impacted by viral shielding) but the real world data is likely to show FEV1 decline in a similar way to Ivacaftor. Given the lessons learned from Ivacaftor sections of the clinical community are using Kaftrio within the CFDigiCare - CFHealthHub.com Learning health system and whilst carrying out real time health technology assessment National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) programme: a prospective observational study - CFHealthHub.com to enable deterioration in the efficacy of Kaftrio to be detected in real time and the CFHealthHub community of practice supports complex interventions to support Kaftrio users to maintain preventative inhaled therapy use.
10a. How does healthcare resource use differ between the technology(ies) and current care?	Considering adults. If the experience of Ivacaftor is repeated with Kaftrio we will see an immediate fall in the detection of respiratory exacerbations, an immediate fall in hospital admissions and intravenous antibiotic use and a fall in the use of preventative inhaled therapies. Over around 5 to 7years (unless co-adherence to inhaled therapy is supported) FEV1 will decline, exacerbations will be reported and hospital admissions will climb again. This pattern is seen in the real world Ivacaftor data. BMI will increase from soon after starting Kaftrio and the Ivacaftor real world data suggest that BMI will be maintained. This will markedly reduce the need for Percutaneous gastrostomy tubes and overnight feeding. It is important to note that the differential impact on lung health and weight/gut health is because in adults lung health is influenced by pre-existing damage which needs to be managed by preventative inhaled therapy which is much reduced by patient choice. In the case of the gut co-adherence to pancreatic enzymes is important but patients continue to take enzymes since they get major symptoms otherwise. In addition the increased weight is accompanied by a sense of wellbeing. The continued weight gain emphasises that the falling impact on lung function is not primarily due to Kaftrio non-adherence (since gut impacts continue) but is due to non-adherence to inhaled therapies.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Kaftrio will be prescribed and monitored in tertiary care specialist clinics

10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	As outlined above, if the effects of Kaftrio are to be maintained beyond the open label extension period ie FEV1 stable to 2 years there must be investment in routine adherence monitoring to inhaled therapy (as recommended by NHS England Digital review) and habit formation to sustain that adherence. The adherence intervention was demonstrated in a 600 participant, 19 centre RCT funded by NIHR and requires training for staff within the MDT to support co-adherence. Across CFDigicare centres this training I already in place.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes. The caveat is that in adults this benefit to the lungs is likely to be lost in 5 to 7 years without investment in measuring and supporting co-adherence to inhaled therapy. (Providing this adherence monitoring and habit formation is a trivial cost when compared to the current ball park cost of Kaftrio at £95K per patient per year). It is important to recognise that Kaftrio improves CFTR function and impacts lung health and patient health by the mechanism of improved CFTR function which is the same mechanism by which Ivacaftor impacted patients with G551D and there is no reason to suspect that Kaftrio would therefore impact long term lung health differently than Ivacaftor in the G551D population. The 2 year data for Kaftrio is impacted by Viral shielding during lockdown (see Hoo ZH, Lai LY, Sandler RD, Daniels TE, Dawson S, Hutchings M, Wildman MJ. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis". J Cyst Fibros 2023 Mar 20 [Epub ahead of print])
11a. Do you expect the technology(ies) to increase length of life more than current care?	Yes. And it is crucial in carrying out this Kaftrio Health Technology appraisal to learn from the Ivacaftor HTA (informed by Ivacaftor 2 year open label extension data (see ref in 9c above) taken alongside the real world data for Ivacaftor that accumulated over 5 to 7 years (see Duckers ref in 9c above). The 2 year open label extension data for Ivacaftor suggests that a normal life expectancy can be achieved for the majority of adults (on basis of FEV1 annual decline<= 1%) using Ivacaftor if patients adhere to preventative inhaled therapy alongside Ivacaftor (with maintained weight in all the real world data suggesting that adherence to Ivacaftor is good) . The open label extension patients contributing data in the Ivacaftor HTA were closely monitored and adherent to inhaled therapy. Thus Kaftrio will also offer the possibility of a normal life expectancy and this is illustrated by the 2 year Kaftrio data. However, all patients in the 2 year Kaftrio data set had at least some viral shielding for part of the open label extension and it was seen in a large Australian registry study that patients not on Kaftrio increased lung function during the viral shielding created by lock-down (Hoo ZH, Lai LY, Sandler RD, Daniels TE, Dawson S, Hutchings M, Wildman MJ. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis". J Cyst Fibros 2023 Mar 20 [Epub ahead of print]). Thus an important task of the Kaftrio HTA is to recognise that the data submitted to Kaftrio the appraisal might not be representative of what happens over time just as the Ivacaftor 2 year open label extension

	data misled the NHS in setting prices for Ivacaftor ie the Ivacaftor 2 year open label extension data supported the optimistic scenario whereas the 5 year real world data suggested that the pessimistic scenario was observed.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes and this was confirmed by CFQR in the Kaftrio Randomised controlled trials, however the caveat exists of attenuation over time as observed in Ivacaftor.
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	Roughly 10% of adults have stable established habits that support the maintenance of preventative inhaled self-care and we would expect these adults to show stable lung health over many years. As such this subset of patients who received Ivacaftor would demonstrate the stable FEV1 seen in the optimistic scenario described in the Ivacaftor HTA, Individuals who find sustained use of preventative inhaled therapies burdensome and difficult because they have not been supported to create habits of preventative inhaled self-care might be expected to experience the pessimistic scenario described in the Ivacaftor HTA (box 9c above). The Difference in ICER between the optimistic scenario £335K and the pessimistic scenario >£1 million is a major issue for pricing.

The use of the technology(ies)

13. Will the technology(ies) 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	The technology is a twice daily tablet and will be easier to use than treatments that are required if Kaftrio is not taken such as twice daily physiotherapy, overnight feeding and calorie supplements and home and hospital intravenous antibiotics and intense inhaled therapy regimens. Kaftrio is a powerful and impactful medication. In the first 2 years of Kaftrio the need for liver function monitoring adds complexity. The main issue is that in adults with some pre-existing lung damage prior to starting Kaftrio there is a need to measure and support habit formation to preventative inhaled therapy if Kaftrio is to realise its potential of delivering a normal life expectancy. This cost should be considered in the Kaftrio Health technology assessment since had this strategy been applied to Ivacaftor it is possible that the HTA optimistic

use or additional tests or monitoring needed.)	scenario might have been observed instead of the pessimistic scenario with a major impact on cost effectiveness and NHS waste.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	The main reason to stop treatment will be side effects and the main side effect leading to stopping will be hepatotoxicity . Detecting the liver toxicity has involved regular blood tests to 2 years.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The EuroQol will not capture benefits such as “feeling the best I have ever felt”, and other changes in disease specific symptoms which will be apparent on the disease specific CFQR.
16. Do you consider the technology(ies) 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?	Kaftrio is innovative (in the same way that Ivacaftor was innovative for people with the G551D genotype).
16a. Is the technology(ies) a ‘step-change’ in the management of the condition?	Kaftrio is a step change in management for those with Delta508 in the same way that Ivacaftor was a step change in the treatment of patients with Ivacaftor. We now have ~ 8 years experience of that that step change means in the short term (in the 2 year open label data for Ivacaftor use in patients with

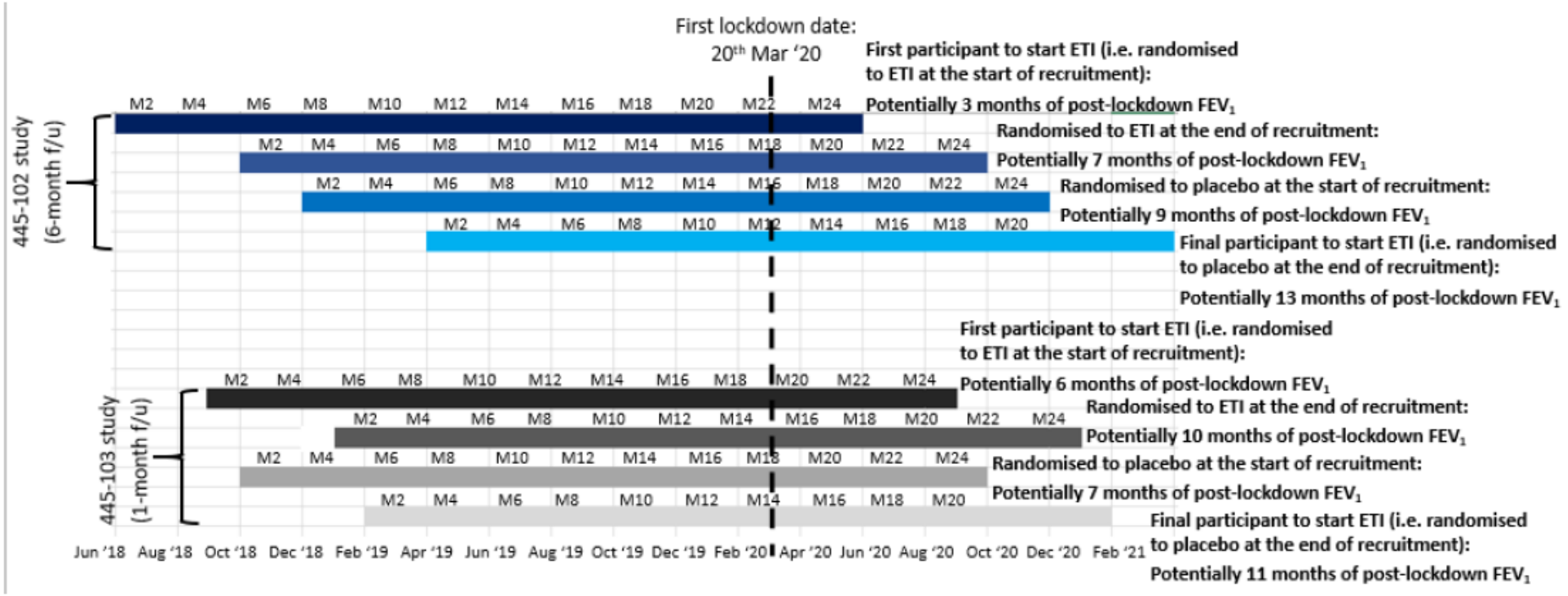
	G551D and the HTA carried out at 2 years see Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov)) and in the longer term real world data by looking at the impact of Ivacaftor in the 2.5-5% of the CF population with G551D (see Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, De Iorio F. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review. J Clin Med. 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527. PMID: 33917386; PMCID: PMC8038673). The real world data for Ivacaftor suggests that though there is the potential for a sustained step change that was NOT what we saw with Ivacaftor and understanding the loss of the "step-change" in adults on Ivacaftor is critical to making a measured Health Technology Assessment of Kaftrio. This is particularly important since the 2 year Ivacaftor data was highly favourable despite that data being collected in a period that was not impacted by viral lockdown which will impact the 2 year Kaftrio data see Hoo et al JCF (Hoo ZH, Lai LY, Sandler RD, Daniels TE, Dawson S, Hutchings M, Wildman MJ. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis". J Cyst Fibros 2023 Mar 20 [Epub ahead of print]).
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes , it is transformative in specifically correcting the impact of the gene on chloride channels for patients with delta508 and as such is a gene specific targeted therapy that corrects the pathological abnormality that drives CF
17. How do any side effects or adverse effects of the technology(ies) affect the management of	The main issue in a subset of patients is liver damage that may require the therapy to be stopped.

the condition and the patient's quality of life?	Most patients gain weight on Kaftrio and in most cases this is beneficial. In a subset of patients the weight gain can lead to obesity which can impact quality of life. It may be that the weight gain that leads to obesity is related to eating a high calorie diet that was appropriate before Kaftrio; that is to say that weight gain leading to obesity may reflect a mismatch between a "pre-kaftrio diet" and the diet that would be appropriate after Kaftrio.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	The internal validity of the trials is good and the trials were global. The issue for the Health technology assessment is the external validity of the trial and the 2-year open label extension data and how those data can be used to inform benefits in the real world.
18a. If not, how could the results be extrapolated to the UK setting?	There are two major issues for external validity (1) High adherence to kaftrio and inhaled therapies in the RCT. Hih co-adherence to inhaled therapies is likely since a small number of patients were recruited from a large number of centres distributed globally with recruitment targeting highly engaged participants able to continue other therapies (most importantly co-adherence to inhaled therapy) . This means that recruited patients were highly likely to continue inhaled therapies. Hence the global Kaftrio trial and open label extension has the same vulnerabilities as the Ivacaftor RCT and OLE in predicting system cost effectiveness in the real world data (2) However the Kaftrio open label extension data has another critical issue that impacts the usefulness of the Kaftrio open label extension data in informing cost-effectiveness in the real world. The two figures below show how the 2 year open label extension overlaps with the COVID pandemic which is important to understand the impact of viral shielding during lockdown on FEV1 trajectory which is a key metric in the Kaftrio HTA. Data from an Australian registry study (Journal of CF

	https://doi.org/10.1016/j.jcf.2022.09.006) with a sample size of 3662 that looked at FEV1 decline in people with CF during lockdown (with the resultant lock down behaviour change leading to viral shielding) showed a mean improvement in FEV1 during lockdown of 1.76% (95%CI 1.46-2.05 compared to an FEV1 decline of -0.13% (95%CI -0.36 to 0.11 prior to lock-down) in a population where most patients were not taking Kaftrio. This unprecedented improvement in FEV1 during lockdown in this Australian sample makes it clear that the extrapolation of the 2 year Kaftrio open label extension data to the post viral shielding real world in the UK is difficult. This is important because the optimistic scenario that was informed by the 2 year Ivacaftor open label extension Health technology assessment suggested an FEV1 decline of ~1% per annum with the highly adherent open label extension population but in fact the real world data showed that the pessimistic scenario pertained. This was likely due to high levels of co-adherence to inhaled therapy in the open label extension population. (The optimistic cost per QALY was ~£335K but the pessimistic scenario was > £1 million). The 2-year data for Kaftrio has both the issue of a highly adherent trial population and the impact of viral shielding so that the 2 year Kaftrio open label extension data has the potential to exhibit a major problem if used to predict cost effectiveness in real world data post covid lockdown. The importance of this issue for health economic evaluation is illustrated by the mismatch between the Ivacaftor real world data and the Ivacaftor open label extension and with the impact of COVID on the Kaftrio open label extension it is feasible that the mismatch between the 2-year open label extension data for Kaftrio might be of at least as great a magnitude as seen with Ivacaftor. This issue suggests that a further year of data will be required for this health technology assessment to provide sufficient data for decision making. The Diagram below explores how viral shielding maps to the 2 year Kaftrio open label extension study.



18b. What, in your view, are the most important outcomes, and were they measured in the trials?	FEV1 and FEV1 decline, exacerbations and BMI and these were all measured. In addition the CFQR disease specific HRQOL , with FEV1 decline an important metric that was evaluated in the 2 year open label extension study
18c. If surrogate outcome	FEV1 decline is likely a good surrogate for life expectancy and function in the long term. As explained in box 18a above , in adults the impact of co-adherence in an atypically engaged trial population and the impact of viral shielding during COVID lockdown will make the FEV1 decline observed in the Kaftrio open label extension data unlikely to provide a good estimate of long term outcomes. This is clearly a somewhat

measures were used, do they adequately predict long-term clinical outcomes?	controversial assertion and it is important to remember (1) Kaftrio is essentially impacting pathophysiology in the same way that Ivacaftor impacted pathophysiology. (2) The Ivacaftor Health Technology assessment based on 2 year open label extension data was strongly suggestive that Ivacaftor would reduce FEV1 decline to ~1% per annum (HTA optimistic scenario) but real world data showed that FEV1 decline was unchanged compared to pre-Ivacaftor period (pessimistic scenario). It is very important to consider the risk of this health technology assessment generating an incorrect estimate of real world cost effectiveness if the Ivacaftor data is dismissed as irrelevant to the Kaftrio analysis (see Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis - NCBI Bookshelf (nih.gov) and real world data Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, De Iorio F. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review. J Clin Med. 2021 Apr 6;10(7):1527. doi: 10.3390/jcm10071527. PMID: 33917386; PMCID: PMC8038673 and impact in single centre Longitudinal effects of ivacaftor and medicine possession ratio in people with the *Gly551Asp* mutation: a 5-year study Thorax. 2021 Sep;76(9):874-879.doi: 10.1136/thoraxjnl-2020-215556. Epub 2021 Feb 12
18d. Are there any adverse effects that were not apparent in clinical 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?	We have already learned a great deal about the health economics of CFTR modulators thru the Ivacaftor HTA and real world data that powerfully sign posts the vulnerability of the traditional HTA process in the evaluation of a drug where pre-existent pathology and co-adherence to inhaled therapies mediate the usefulness of RCT and open label extension data in predicting subsequent real world effectiveness. If these lessons are not made the benefits of CFTR modulators to patients and the health service will be markedly reduced in a similar way to what was observed with Ivacfator. The concept of co-adherence has already come to the attention of NHSE with the biologics in asthma. The Ivacaftor HTA and subsequent real world evidence is highly relevant to interpreting the Kaftrio open label extension data, (see section 18a and 18.c). CFTR modulators are high cost drugs where the drug's efficacy is likely modulated by 2 crucial issues which were demonstrated in the Ivacaftor

	HTA and real world data (1) Co-adherence to a drug (inhaled therapies critical to lung health) that modulates the high cost drug's benefits and (2) An interaction with the pre-existent organ damage that exists when the CFTR modulator is started and a 3rd issue which is unique to the evaluation of Kaftrio during the COVID epoch: the impact of an absence of viral challenge to FEV1 decline . The Ivacaftor HTA and real world Ivacaftor data is relevant evidence since it signposts the vulnerability of a HTA based on a global randomised controlled trial with the selection of the most engaged/ adherent patients creating an RCT with high internal validity but low external validity with the consequence of accepting the Ivacaftor HTA optimistic scenario for drug pricing and then observing the pessimistic scenario in the real world. By understanding the implications of the Ivacaftor HTA the following lessons are likely important (1) For patients who have relatively undamaged lungs when the CFTR modulator is started the CFTR modulator alone is likely to create benefit that is not much impacted by co-adherence to inhaled therapy or viral challenge. (2) For older patients with extensive lung damage when CFTR modulators are started Co-adherence to inhaled therapy is likely to be much more important and viral shielding will modulate this impact. The Ivacaftor HTA and real world data sign post what we will see with Kaftrio and that unless the lessons of Ivacaftor are learned the Kaftrio HTA will repeat the errors seen with Ivacaftor. In the case of Kaftrio the risk of the open label extension being misleading is even greater because of the impact of viral shielding which means that impact co-adherence to inhaled therapy and pre-existent lung damage will be invisible in the absence of viral challenge as evidenced by the absence of FEV1 decline in the Australian registry study that looked at FEV1 decline in ~3000 CF patients during viral shielding see Hoo ZH, Lai LY, Sandler RD, Daniels TE, Dawson S, Hutchings M, Wildman MJ. Regarding the article entitled "Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis". J Cyst Fibros 2023 Mar 20 [Epub ahead of print]).
20. How do data on real-world experience compare with the trial data?	The 2-year real world data and the Kaftrio RCT data are powerful in suggesting that Kaftrio will create a marked improvement in FEV1 and then prevent long term FEV1 decline in people with CF. However as illustrated in section 18a above the open label extension data and early real world data is influenced by the impact of viral shielding which makes the 2 year data unreliable for the decision making of this HTA. In addition, it is critical to remember that in a global RCT recruiting modest numbers of participants the

	patients recruited are typically the most engaged with all treatment and since the RCT protocols required continuation of co-adherence to inhaled therapy it is likely this will occur and this will have the consequence of creating high internal validity for the RCT and open label extension data. However, if co-adherence to inhaled therapy is important in older patients with pre-existing lung damage we might expect real world data to show the signals seen in Ivacaftor where FEV1 decline was unchanged over 5 years. The Kaftrio data that was impacted by viral shielding is even more likely to mislead in this regard. In the case of Ivacaftor it is understandably difficult to extrapolate beyond the data available at the time of the HTA but in the case of Kaftrio the Ivacaftor data provides a Rosetta stone to impute appropriate caution and when this is taken alongside the impact of viral shielding it becomes clear that the data set available to this HTA is of insufficient duration to predict future real world effectiveness in adults with pre-existing lung damage.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	It has long been realised that patients who are under served by existing care models have worse outcomes. The likely interaction between co-adherence to inhaled therapy and Kaftrio means that there will be a major lack of equity in outcomes unless the CF community adopts systematic support for co-adherence to inhaled therapy alongside the provision of Kaftrio. When a drug such as Kaftrio is so expensive the relatively cheap interventions that will protect the cost effectiveness of Kaftrio could be considered as part of the HTA. See Int J Technol Assess Health Care. 2023 Jan 17;39(1):e6.doi: 10.1017/S0266462322003373 A model-based economic analysis of the CFHealthHub intervention to support adherence to inhaled medications for people with cystic fibrosis in the UK Tappenden et al
21b. Consider whether these issues are different from issues with current care and why.	The cost of Kaftrio, the claims for its immediate and long term effectiveness and the potential impact of co-adherence on that effectiveness creates a unique scenario that is different to other treatments within CF care. The potential of CFTR modulators to achieve a normal life expectancy as outlined by Rowe in a Lancet Respiratory Medicine piece "A little CFTR can change a lot" Lancet Resp Med Dec 2016 http://dx.doi.org/10.1016/ S2213-2600 (16) 30465-9 suggests that an FEV1 decline of ~1% per annum potentially equates to providing a normal life expectancy. The Kaftrio 2 year open label extension data suggests that Kaftrio can deliver an FEV1 decline of < 1% per annum and the Ivacaftor 2 year open label extension data also suggested that Ivacaftor could deliver an FEV1 decline of ~1% per annum. However the real world data for Ivacaftor saw that the promise of the 2 year open label extension was not realised in the real world with poor co-adherence to inhaled therapy a likely contributor to the poor real world outcomes. The support for co-adherence of adjunctive inhaled therapies alongside CFTR modulators is different to the situation we see with treatments such as inhaled therapy alone because of the high cost of CFTR modulators compared to the costs of inhaled therapy. For example if the published cost for Kaftrio at around 95K per annum per patient is top sliced by ~1% that would allow a CF centre to create the funds to allocate one band 6 physio to support co-adherence for every 50 patients that might allow the "optimistic scenario" seen with the Ivacaftor HTA to be delivered in real life by supporting inhaled therapy co-adherence. However, the cost of inhaled therapies is much less so top slicing the cost of inhaled therapies budget to increase effectiveness by supporting habit formation would be more difficult from a financial perspective.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The Ivacaftor Health Technology assessment based on 2 years' open label extension data generated an optimistic scenario (~335K per QALY) but the 5-year real world data suggested the pessimistic scenario was observed (~£1 million per QALY) • It is likely that a difference in co-adherence to inhaled therapy between the highly engaged trial/open label extension participants and patients in the real world played an important role in the observed FEV1 decline seen when Ivacaftor was used in the real world • Both Kaftrio and Ivacaftor act to optimise CFTR function and as such the Ivacaftor HTA is invaluable in understanding how early 2-year Kaftrio open label extension data is likely to translate into the real world with the Ivacaftor HTA & subsequent real world Ivacaftor data providing a Rosetta stone to predict the real world cost effectiveness of Kaftrio • In addition, the Viral shielding created by lock down will have attenuated FEV1 decline in the Kaftrio CF population with the consequence that the 2-year epoch of the Kaftrio evaluation is much less informative than the 2-year epoch when Ivacaftor was evaluated. If the 2-year data currently available to understand the real world effectiveness of Kaftrio is assumed to be representative, it is highly likely that the HTA process will accept an optimistic scenario of minimal FEV1 decline repeating the misleading interpretation of the Ivacaftor evaluation. • We recommend that the data collection to evaluate Kaftrio continues for a further year (allowing more data to be accumulated that is not impacted by viral shielding) with the adoption of methodologies advocated by the NICE Learning Health systems approach where real world data is collected on Kaftrio outcomes alongside objective data collection to understand the impact of co-adherence to inhaled therapy. National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) programme: a prospective observational study - CFHealthHub.com

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Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) 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.

About you

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? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes (I have published a number of Cochrane systematic reviews on this topic) Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK CFMA has around 250 members, all doctors in the UK with a special interest in the care of people with CF. The organisation receives administrative support from the UK CF Trust but runs independently. The UK CFMA receives no funding or sponsorship (including for educational purposes) from pharma. Professor Southern is also Director of the ECFS Standards of Care Committee and has no conflicts of interest
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **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 improve quality of life and survival
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.)	An improvement in quality of life that enables people with CF to have increased engagement with school/employment and other fun activities that are compromised by their condition (metrics would be increased QoL measures, improved respiratory function and reduced need for treatment (PEx). In addition, the new therapy should lay the framework for improved survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Whilst the outlook for people with CF has improved with standard therapies has improved steadily, pwCF still experience considerable morbidity despite a substantial therapeutic burden. In parallel, the improvements in survival have been steady but the outlook is still poor with median survival in the mid 40's and many still dying in childhood or young adult life. There is a urgent need for therapies that correct the underlying genetic and molecular defect, rather than addressing the sequelae.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Standard therapies address three key areas, 1) maintaining excellent nutrition (using PERT, supplemental feeding, diabetes treatment if required), 2) maintaining a rigorous exercise programme (supported by the CF team) and 3) keeping the airways clear of infection and inflammation (using a regimen of airway clearance techniques, muco-active therapies and close surveillance for airway infection with pro-active antibiotic therapies, sometimes chronic. For more advanced disease, support with breathing may be required and transplant assessment and completion is an option. In addition, people with CF experience a myriad of complications, including subfertility, which require attention.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines and ECFS best practice guidleines
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 are clear care pathways from diagnosis. There is good consistency across the UK with respect to treatment approaches. The fundamental principles are followed in all centres.
9c. What impact would the technology(ies) have on the current pathway of care?	Correcting the underlying defect will have a profound impact on the well being and QoL of pwCF, as well as survival.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	It will supplement current standard care
10a. How does healthcare resource use differ between the technology(ies) and current care?	A therapy that corrects the underlying defect may enable pwCF to reduce their treatment burden, which is a key priority identified by the James Lind Alliance research priority setting exercise.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Should be available for all eligible patients in secondary care

10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	Increased input from CF Pharmacists is essential to ensure the optimal implementation of these new therapies, to help monitor for adverse reactions and check for drug-drug interactions.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes, but important not to conflate the impact of dual therapies (LUM-IVA and TEZ-IVA), which are minimal with the impact of triple therapy (ELX-TEZ-IVA), which is substantial.
11a. Do you expect the technology(ies) to increase length of life more than current care?	Yes, difficult to define precise improvement in survival, but likely to be considerable
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes, substantially as demonstrated
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	These therapies are variant specific, there are people with CF who have variants of the their CFTR gene that are not eligible for CFTR modulator therapy.

The use of the technology(ies)

13. Will the technology(ies) be easier or more difficult to use for patients or healthcare professionals than	Tablets (or micro-granules) taken twice daily. This is extremely convenient and has had a particularly profound impact on our patient population from less well-resourced backgrounds. Health inequalities are significant in CF, amounting to around 5% FEV1 respiratory function measure, and access to CFTR

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.)	modulators has had a significant impact on patients, both adults and children, who are less well supported financially and socially.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	With the clinical trial and systematic review data, starting and stopping rules are not appropriate for ELX-TEZ-IVA. Dual therapies are reviewed on an individual patient basis
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	For ELX-TEZ-IVA - Better school and college attendance - Better work attendance and employment opportunities - Increased pregnancies (tripled) and more men with CF undergoing IVF - Reduced inpatient episodes and frequency of outpatient appointments - Reduced need for additional therapies such as antibiotics

	- Reduced need for transplant In addition, patients established on ELX-TEZ-IVA may be able to redcuce their treatment burden, but this needs to evaluated in robust clinical trials to ensure that stopping or reducing standard therapy is safe.
16. Do you consider the technology(ies) 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?	This is an innovative approach to CF care
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Yes, absolutely
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes, it is a much needed addition to the CF armentarium
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Overall the safety profile is good. There are some transient side effects that likely relate to the mechanism of action. These include increased airway secretions, sinus pain, testes pain, abdo pain and behavioural issues. Other side effects are idiosyncratic, but also tend to be transient. These include increased BP, rashes, transaminitis and depression. The raised liver enzymes (transaminitis) resulted in a NPSA notification

	and request for careful monitoring. The EMA recently suggested a possible causal link between ELX-TEZ-IVA and depression, and urged careful monitoring. Most women choose to continue ELX-TEZ-IVA during pregnancy and the teratogenic effects are not yet clear. Recently there have been six case reports of children (6-12) experiencing raised intracranial pressure whilst on ELX-TEZ-IVA, which resolved with treatment or interruption of dosage.

Sources of evidence

18. Do the clinical trials on the technology(ies) 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?	- FEV1 - QoL - Need for additional treatment/hospitalisation

	- PEx - Nutrition All were measured, although QoL was only measured with a disease specific tool (CFQR)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Sweat chloride measurement is an excellent surrogate outcome, but the correlation with longterm survival is not clear.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Possible associations include - Adverse mental health issues (depression and anxiety) - Raised intracranial pressure (rare)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We now have considerable real life experience in this population and registry data are valuable in monitoring longer term progress. We also have “yellow card” adverse event monitoring data for the UK
20. How do data on real-world experience compare with the trial data?	For ELX-TEZ-IVA the real world data confirm the efficacy outlined in the RCTs

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Absolutely, the impact on health inequalities is described above. In addition, the outlook for women with CF has always been significantly poorer than the outlook for men and this intervention may help to redress that inbalance.
21b. Consider whether these issues are different from issues with current care and why.	Current care has not been able to reduce the HI issues above, even following the introduction of newborn screening for CF. This likely reflects the considerable treatment burden our patient population faces on a day-2-day basis.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• It is important to assess these technologies independently and not conflate results • Triple modulator therapy has improved the lung function and quality of life of eligible patients • Although modulator therapies have a good safety profile, there have been significant AEs reported • This therapy has a profound impact on the lives of our patients, impacting social and life experiences • This therapy has the potential to reduce health inequalities in our community

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) 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.

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).	The UKPPCF is a consortium of clinical psychologists and social workers working into Cystic Fibrosis across the UK. We share learning from our practices, and consult with CF affiliated bodies such as the CF Trust to provide a psychosocial perspective of any projects being pursued. The UKPPCF is not funded and is ran by a committee of clinicians who have substantial experience working into CF centres.
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **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.)	Prevent progression and improve quality of life
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 or stabilisation of lung function and wider CF related health indicators, long term decrease in treatment burden footprint in patients' life, and an improvement in ability to engage with daily living activities. With the improvement in prognosis long term, I also anticipate this treatment having a significant impact on patients' ability and willingness to consider a fulfilling future which will have considerable positive implications for their mental health.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is some emerging evidence of potential mental health implications for this medication. With CF centres psychological resources being as limited as they are, it may not be viable to increase monitoring of patients' psychological health when using modulator treatments in some centres. However, there are potential risks of acute low mood and suicidal ideation beginning to emerge, which if not accounted for in terms of psychology provision and monitoring of risk possess notable concern for patients' potential safety using this new medication. At present it is anticipated that increases in low mood or suicidal ideation as a result of this medication will be marginal. As new research evidence becomes available a clearer clinical picture will emerge as to the level of unmet need. The medication and potential for improvements in overall well-being and functioning also possesses unique psychological implications for a cohort of people with a known limited life expectancy, which could now be longer than expected. The specific psychological sequalae of this is still emerging and will need appropriate CF specialist psychological resources to respond to it.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Through a full MDT approach; physiotherapy, diet, exercise, antibiotics, diabetic treatments (e.g. insulin).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are guidelines around the provision of psychological care within CF centres, there are some tentative guidance published following the dissemination of modular therapies concerning the psychological complexities associated with the modulator therapies. There is however recognition that the successful use of these treatments will likely result in unique adjustment difficulties specific to the effectiveness of this treatment.
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 an established care pathway for psychological provision contained within the CF standards of care and consensus documents. It is recognised that this pathway needs to be adapted to meet local population needs and within available resources. At present there is no consensus documents or CF standards of care regarding modulator therapies; however, a review of the clinical psychology CF guidelines is underway and I am aware that the impact of modulator therapies is acknowledged within this. Anecdotally it has been noted throughout the UKPPCF that the modulator therapies have often coincided with development or increase in severity of mental health difficulties. However, at time of writing there has been no agreed set pathway as to how this should be best monitored or managed. Some centres being able to increase monitoring, and/or be more vigilant to changes in mental health statues, however due to historically limited psychological provision within CF care, many centres may struggle to respond to such need as effectively due to limited psychological provisions.
9c. What impact would the technology(ies) have on the current pathway of care?	It is unclear whether the reduction in symptoms will result in reduced psychological need long term, however it anticipated that the long-term trajectory of care will need to be reduced as patients are able to remain consistently well, for longer. It has been observed clinically across the UKPPCF that there has been increased need for psychological support due to the complex psychosocial impact of the treatment. In additional to the complex psychological motives for none adherence to treatment plans when this treatment is viable. If this need remains present; additional structured, regular monitoring of patients' mental health may be required, beyond what is currently provided.

10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology(ies) and current care?	Not able to offer comment due to remit of professional competencies.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	It is my opinion that this treatment should be offered within tertiary specialist services offering full MDT care, including psychosocial resources, due to the unique health and psychological profiles of the condition, and the potential complications from treatment.
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	If there is an increase in psychological need found to be associated with the treatment, either due to side effects or the existential significance of the improvements because of the treatment; additional funding for CF specialist psychological support would be required.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	It is hoped that people using this treatment will experience an improved quality of life due to increased health outcomes; including a decrease in treatment burden, with fewer inpatient admissions and outpatient clinic appointments required. Improved mental health outcomes are expected as many of the psychosocial stressors associated with a living a life with CF will be reduced significantly. As a result of these improvements it could also result in people feeling able to pursue educational and employment aspirations they may have not otherwise been able to pursue as a result of the obstacles their CF previously posed.
11a. Do you expect the technology(ies) to increase	It is my understanding that this treatment has the potential to increase length of life.

length of life more than current care?	
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes, due to the potential for the significant reduction in the symptoms of this condition, and the consequent reduction in the associated psychosocial stressors.
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	In terms of psychological appropriateness a person's mental health would need to be considered, and if there are any clinically significant concerns prior to commencing treatment, a care plan should be developed and agreed as to how their emotional well being will be monitored and support provided should any detrimental changes occur. This could range from changes in their medical management through psychologically informed care, and/or directly accessing CF specialist psychological support.

The use of the technology(ies)

13. Will the technology(ies) 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 treatments are tableted, so should generally be easier for patients to use, particularly in comparison to other treatments such as nebulisers/insulin monitoring and treatment. Due to the improvement in overall health and functioning I understand this may also impact the need for other tableted medication. I understand the regular monitoring will be required to ensure there are no detrimental side effects from the modulators. It is unclear as to the length of the monitoring required; this will needed to be discussed with patients to ensure they understand engagement with the CF centre is still required to enable safe monitoring of their

14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Given emerging observations of the potential impact of modulator therapies regular mental health screening should take place, and if detrimental changes in mood are observed; the use of the therapy should be reviewed within the MDT. This screening should be done under the supervision of the service's clinical psychology provision.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients have reported feeling more able to plan for the future; career, relationships etc. Resulting in some feeling more hopeful, others it bringing a number of existential questions about what they would like their future to look like that they had not previously felt was relevant given their state of health and life expectancy. In addition to changes in role, identity and having to navigate aspects of adult life they may have not anticipated, e.g. employment, financial independent etc. This is important to capture as it has notable implications for psychological well-being but would not be accounted for in a quality-of-life measure/calculation.
16. Do you consider the technology(ies) 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?	There is the potential for a notable and previously unencountered positive impact on patients' overall well-being including their mental health. However, this may not necessarily be immediate as they will need to adjust to these changes (improvements) in their health and what this means for how they understand themselves (changes in; identity, illness roles, family dynamics, family and societal expectations etc).
16a. Is the technology(ies) a 'step-change' in the management of the condition?	With patients' health being improved, stable and over a longer period of time, services will need to consider how they support patients in managing and reviewing their health, balancing their improved

	wellbeing with need for review and management (e.g. treatment burden), likely through a paradigm shift in inpatient and outpatient clinics and admissions.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	For those that are eligible, and it is effective, it poses notable existential questions around the individual's expectations of their health and what they previously expected their lives to look like. Whilst this may initially be understood as positive, it could have notable psychological repercussions as they will be faced with new possibilities and opportunities that they may not be psychologically prepared for; having not developed the suitable psychological strategies in place to navigate these new opportunities and the challenges inherent in pursing them. In contrast there will also be psychological repercussions for those that start this treatment, aware of the life changing potential it holds for them; however then are unable to continue with the treatment due to any adverse side effects.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	Research evidence is still emerging to enable clarity on the psychological and/or pharmaceutical mechanism through which changes in mood following commencing these treatments may occur, with studies being on relatively small cohorts. Furthermore, to the writer's knowledge, there has not been a

	treatment used in medicine before that could cause such a notable shift in well-being for a life limiting condition. As such this is new territory for clinical health psychology. UK based guidelines exist (Southern,. et al 2023) to shape practice; recognising the psychological implications of such a shift and the adjustments needed by patients and their families. However, given how new these treatments are, the intricacies of these adjustments are still being understood and how best to work with them from a psychological perspective are still an unknown. Reference: Southern, Kevin W. et al (2023), Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis .Journal of Cystic Fibrosis, Volume 22, Issue 1, 17 - 30
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?	I'm unaware as to whether the impact on mental health was initially monitored at trial stage, however as noted there is anecdotal and some published evidence emerging suggesting this is an issue being encountered and should be explored on a larger scale.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. How do data on real-world experience compare with the trial data?	I am unaware as to whether trial data monitored any potential mental health status/psychological well-being, as such I am unable to comment on how they compare. I feel it is important to recognise that the potential psychological impact that can and has been reported to occur as a result of the intended outcome of this treatment is inherently complex and still being investigated. Previous psychometrics of psychological distress using paradigms of anxiety or low mood/depression typically used in CF care may not adequately capture the psychological repercussions of the existential shift that patients are reporting.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients socio-economic profile may play a role in terms of how they approach this treatment, e.g. patients reliant on various benefits may be concerned as to how this will effect what they are able to access; mindful that this is a new treatment and will not know how it will impact functioning long term and as a result what housing, financial etc support they can access. Furthermore, patients with more robust social economic status/support will likely find it easier to navigate the new challenges improved well-being brings; e.g. entering employment, education etc. Whilst a person's social economic profile should not be a barrier to accessing treatment it should inform care planning.
21b. Consider whether these issues are different from issues with current care and why.	Please see above.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• This treatment holds the potential for life-changing change for a large proportion of the CF population, and could fundamentally shift what CF looks like in the future. • Whilst the evidence is still emerging there is an indication that this treatment/s can increase incidents of detrimental changes to psychological well-being. We do not fully understand why these effects occur; however it is reasonable to suggest that the existential adjustment needed by patients and their families is a considerable contributing factor. • Given the newness of this treatment and potential consequent psychosocial complexities there should be an increase in MDT vigilance to identify such issues as early as possible, and appropriate specialist CF psychology services available to respond. • Consideration should also be given to patients who are not eligible for this group of treatments (due to gene type or severe side effects), mindful of the psychological ramifications of comparison to peers who have access to effective treatment not available to them.

Thank you for your time.

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Multiple Technology Appraisal

Guidance review following a period of interim access

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Committee Meeting – 12 October 2023

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with cystic fibrosis or caring for a patient with cystic fibrosis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the MAA Revaluation Organisation Submission Guide (attached). **Please note that you do not have to answer every question** – they are prompts to guide you.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **14 June 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with cystic fibrosis

Table 1 About you, cystic fibrosis, current treatments and equality

1. Your name	Christina Walker
2. Are you (please tick all that apply)	☐ A patient with cystic fibrosis? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with cystic fibrosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Fellow members of CF Voices group – other CF carers ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

Patient expert statement

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with cystic fibrosis? **If you are a carer (for someone with cystic fibrosis) please share your experience of caring for them** Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	My son was diagnosed with CF from the heel prick test and I was informed when he was 3 weeks old. I was nursing my son at the time and the telephone call and subsequent confirmation of diagnosis devastated me and consumed my life almost totally until recently. At that time I was 38 years old, the median life expectancy for someone with CF at that time. We were given a hopeless outlook, being told the condition was incurable and treatments only existed to deal with symptoms. [redacted] was immediately affected in that he couldn't get sufficient nutrition from my breast milk so he woke screaming every 2-3 hours for feeding and had to be winded throughout his feeds. This made nursing him very stressful and led to me developing infected mastitis and eventually needing a surgical removal of a large, infected abscess. This set the tone for what caring for a child poorly with CF would be like. Within a month I was having to perform percussion physiotherapy on my tiny baby, and administer several medicines by syringe and through nebuliser with a face mask causing him huge distress, after he was found to have Pseudomonas in his lungs. [redacted]'s elderly grandmother (my mother) couldn't bear to witness this and became depressed around this time, which was very difficult to handle on top of everything else. As a family we were all constantly worried and unable to carry out usual activities. Daily life was all about keeping my son alive. I was never able to get treatment for the damage caused to my body during the birth and have struggled with self-care for chronic back problems and the depression I suffered periodically ever since. Until recently I could only work part time from home and together with all the extra expenses of having a child with CF, this has had a major financial impact. Sending [redacted] to pre-school and then school was extremely challenging, due to the nature of groups of children of that age being in close quarters and the bacterial and viral exchanges between them. Until he started on Orkambi, just getting a cold would inevitably lead to a chest and sinus infection, requiring [redacted] to have significant physio, a course of antibiotics, disruption to sleep, time off school and

	sometimes time spent in hospital for IV antibiotics. All of these caused a great deal of upset and distress to [redacted] and all who love him. His first half term at primary school was spent in [redacted] Hospital having IVs and this really impacted the fledging friendships he'd made – as the Head Teacher told me when he struggled upon his return 'young children close the gap when someone is absent'. Being different from his peers, like having to go to the office to take pancreatic enzymes before food, characterised [redacted]'s earlier life and increasingly upset him. The fear of infection also meant that many significant events with friends and family were missed, especially during the autumn and winter which were periods of great dread until recently. The unpredictability of CF meant that life, physical and mental health could be massively interrupted at any time, hence anxiety was constant. For example, on [redacted]'s 7th birthday he ran around a local zoo keeping up with his friends seemingly well and happy. One week later he was coughing up blood in the clinic appointment and another week later was having a bronchoscopy in [redacted] which found his lungs full of highly antibiotic resistant NTM. His team were not confident that his body could cope with the toxicity of treatment required to eradicate, or if that indeed was even a possibility, and I was counselled to expect the worst. Thankfully a month of multiple drug IV's and 3 years of extensive home treatment have thus far appeared to deal with the infection – although I find myself still too scared to say more than that and [redacted] continue to monitor all his sputum for recurrence. The home treatment involved daily clearing of large amounts of sputum, particularly for the first two years with hypertonic saline, extensive airway clearance physiotherapy, adult dose Ciprofloxacillin and Azithromycin, nebulised Amikacin, regular hearing, chest and sputum tests. I never missed a day of this care and added food supplements to improve nitric oxide levels in the body to [redacted] 's regime. His care was all-pervasive during this period and it was only due to long service that I managed to retain my part-time employment, especially difficult during the month in [redacted] when I was taking phone calls in my son's hospital bathroom and working next to his bed as he slept. Before modulators, [redacted] could never enjoy eating; mealtimes were very long and full of conflict and upset. We were aware that he needed 50% more calories than a child without CF just to maintain weight, but he clearly found eating unpleasant and

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	needed to drink milk with every mouthful of solids, right up to day 5 on Orkambi when this all changed forever. Mentally, seeing your loved one suffer in this way and the sacrifices of your own life required in the care are hard enough – but the worst element by far was that you knew despite all your best efforts, they were never going to be enough, merely postponing the inevitable. Your child would still get progressively more unwell, progressively more different and increasingly separated from his friends, declining towards an early death. While trying not to linger on that reality every day, at times of health decline, it was impossible not to think about it which triggered periods of depression on top of the constant state of anxiety. In the research CF Voices carried out, the impact of the 'constant and inescapable' stress and anxiety was found to lead to long term pessimism, and I can now look back on the first 11.5 years of [redacted]'s life and state that this was by far the worst factor for me and his other family – the lack of hope. Lack of hope for my son to have a future. Lack of hope that he could be happy, healthy, ever have adult relationships, children of his own, travels, a career, outlive us. All of that seemed impossible.
7a. What do you think of the current treatments and care available for cystic fibrosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	It's no understatement to say that our lives have been transformed by CFTR modulators being made available to [redacted] on the NHS and that I think their provision for all eligible patients is essential. Previously CF was untreated – therapies were only able to address symptoms and there was nothing to tackle the root fault that caused disease. There are no comparators. While still not a cure, CFTR modulators have changed the whole nature of the condition to one that can be managed over the long term and particularly for patients treated before damage occurs, should provide decades of high-quality life. Writing this statement actually feels like talking about someone else – because we now have hope and our lives feel relatively normal at last. The long-term pessimism has subsided. CF no longer rules our existence. [redacted] is a healthy, happy, thriving [redacted]-year-old who has not missed any school time in 2 years due to CF (aside from for clinic appointments). His lung function is consistently over 100%, he shrugs off a cold (and did so with Covid) so my constant anxiety has finally ebbed away and we

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	can plan more confidently. [redacted] no longer has sinus problems, he needs fewer pancreatic enzymes, and has had no time in hospital for nearly 2 years. [redacted] doesn't need to do any airway clearance physiotherapy anymore and his sweat test is well within healthy range. Wider family and friends no longer worry regularly about us. Unfortunately, [redacted] developed Type 1 diabetes in August 2021 which has been the main focus for his care since then. But I'm not sure how either of us would have coped with that diagnosis and the subsequent efforts involved in bringing blood sugars to the managed state they are now, had CF not effectively gone into the background in our lives. Lung infections and inflammation have a major effect on blood sugars, so his stable health state has been enormously helpful with diabetes management. As [redacted] says 'CF is fine' – it's the Type 1 that challenges us nowadays. I know that our situation is widely mirrored across the community, which has been changed forever by access to these drugs, of course with sad exceptions. To quote another CF parent: 'CFTR modulators have transformed my son's health and given us so much hope for the future. The burden of care has been lifted and we feel like we have a normal life.' The whole nature of caring for someone with CF has become that of caring for someone with a manageable condition, rather than caring for someone through a painful and progressive decline to early mortality. Families have been able to get on with normal life and think more about the everyday challenges and issues, released from the constant all-pervading presence that untreated CF was. A clinician said to me some months ago that 'no one wants to come to clinic anymore as they're so well!'. Of course, the experience does vary and for those, particularly adults, who had significant and irreversible damage already, care needs are still likely to be high and for those who suffered intolerable side effects that could not be satisfactorily dealt with, the disappointment of not sharing in life changing gains felt by the wider community, can be devastating.
8. If there are disadvantages for patients of current NHS treatments for cystic fibrosis (for example, how	Compliance with any daily medicine can be a challenge, particularly for those with additional conditions such as autism spectrum/ADHD, however given that taking

they are given or taken, side effects of treatment, and any others) please describe these	daily CFTR modulators usually leads to reduction in other more burdensome treatments, this should not be a consideration. Side effects have been experienced by some patients – a number of which have been effectively dealt with by taking a reduced dose (mental health impacts seem to respond particularly well for many in this instance). Sadly, for a minority this has not been the case and they've had to stop treatment, triggering a return to the inevitable decline of untreated CF.
9a. If there are advantages of ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	The advantages for me as a CF carer can be summarised: • Improved mental health via reduced depression caused by the long-term outcome associated with untreated CF (long term pessimism has given way to hope for the future) and reduction of daily anxiety associated with infection risk • Improved mental health by seeing my son happier, healthier and having to spend less time caring for him during periods of illness • Improved quality of life via stability in my son's health, meaning I can plan as confidently as anyone can, am able to carry out usual activities, predictability in life has become as much of a reality as it can be for anyone • I have been able to return to full-time work (even through the challenge of the first year of Type 1 diabetes treatment) • I have improved self-care due to less time spent on daily treatments, meaning I have received treatment for my chronic back problems and am finally addressing ongoing issues experienced since giving birth • I am able to support my elderly father and other family/friends with their health/problems as I now have time for others 9b/ The mental health improvements for me have been the most important as the severity of them before CFTR modulators was so great, exacerbated by the need to campaign for such a long period for access to them, a period during which many people with CF died and suffered irreversible health damage.

Patient expert statement

	9c/ As mentioned, the fact that taking CFTR modulators does lead in most cases to fewer other medications/treatments, compliance with it does mitigate the burden associated with daily treatments. Over time the cost associated with funding the drugs should also be mitigated by fewer patients starting on life-long therapies to treat symptoms, many being able to stop those already prescribed and a reduction in IV stays in Hospital.
10. If there are disadvantages of ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor over current treatments on the NHS please describe these. For example, are there any risks with ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	Opportunity cost is the main concern because there is still a requirement for treatment for people with CF to have specialist care, particularly in the adult service. People with CF can expect to have many more decades of high-quality life now, but as a result of this will, like the general population, develop more other health conditions associated with longer life (e.g. cancer). Sadly, for a minority, CFTR modulators cannot be tolerated and some people are ineligible for current drugs. They will require ongoing support of a fully funded multi-disciplinary CF service.
11. Are there any groups of patients who might benefit more from ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	CF is a progressive condition and cumulative damage to lungs and other organs is often irreparable, with additional therapies added over time (e.g. mucolytics like DNase, Hypertonic saline). Therefore, treatment as young as possible is the most advantageous as it is preventative. To quote another CF parent whose child started Orkambi aged two 'For us it has taken away all of the stress and worry that comes with CF and has been transformational in that sense. We no longer look at him as a boy with a life limiting condition that needs protecting, but just a normal kid who needs a few tablets. It's also reduced the time burden of treatment as he hasn't needed to start DNase, for example'. To fully realise the benefits of CFTR modulators in the patient population, future label extensions that allow access for younger patients must be included in funding.

Patient expert statement

	Older patients with already significantly damaged bodies, may benefit less as the risk to reduce long-term treatments is high, although this does not always appear to be the case with some amazing examples of restorative effects after starting treatment with CFTR modulators. From a carer perspective, having previously noted that the mental health impacts of caring for a young child with CF are the most damaging, not having to experience this with your child is life-changing. Nowadays when parents are given a diagnosis of CF, for those eligible for CFTR modulators, they do not need to be told that there is no treatment. They can be given a hopeful view of their child's future, particularly if the treatment can start in early life potentially before any/substantial CF damage occurs.
12. If you have experience of this treatment during the period of Interim Access please tell us your views on the results from tests and assessments that have been used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	As a child with CF my son was always monitored heavily, because his health was at constant risk – hence these checks and tests have been used in the Interim access data gathering. E.g. lung function, growth via weight and height, sputum results, blood tests, chest x-rays, physical examinations etc. In addition, specifically for the interim access scheme his pancreatic enzymes were checked and a repeat sweat test was carried out. The sweat test result came back as normal, which married with all the other evidence that suggest his body is functioning as if it no longer has CF. Hence, in my son's instance I would say that the effectiveness of the treatment is complete and the evidence collected to demonstrate that is compelling. However, I am aware that Covid significantly impacted the ability of clinics to do tests and feel that this needs to be taken into consideration. Also, it must be noted that the impact of modulators takes some time to be fully realised, particularly in patients with significant existing damage and conversely in patients with no damage, as no-one will ever know how poorly they would have become, a wide view of comparator untreated patient groups should be taken. The length of time of the Interim access is undoubtedly not enough to fully demonstrate impact of CFTR modulators on current patients and to assess future generational change.

Patient expert statement

13. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Not in my opinion nor have I been supplied any examples by other CF carers.
14. Were patients experiences captured adequately in the Interim Access tests and assessments? **If not please explain what was missing.**	Covid may have impacted the number of tests and assessments collected for the Interim Access scheme. In addition, many of the ways in which CFTR modulators have positively changed my life and that of other CF carers (outlook, optimism etc) are not ones that can be easily measured in clinical terms, and this may also apply to patients. Also, the understandable caution of CF teams to withdraw drugs from patients currently using them (e.g. mucolytics) without clinical trials evidence that this can be done safely has likely impacted the reduction in treatment burden. Over time, this effect may be greater and to fully realise the benefit of young patients not starting on additional treatments, a longer period of assessment is required.
15. What outcomes (if any) do you think have not been assessed or captured during the Interim Access period Please tell us why	As a carer group, CF Voices would argue that the impact on carers of treatment with CFTR modulators should have been captured fully as part of the Interim Access data collection.
16. Are there any potential equality issues that should be taken into account when considering cystic fibrosis and ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

Patient expert statement

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.	
17. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- As the first and only drugs to tackle the root cause of the condition, CFTR modulators are essential in the treatment pathway of CF - there are no comparators.
- CFTR modulators have dramatically improved the lives of the majority of patients and their carers in the CF community and will have an even greater impact on future generations.
- CFTR modulators have changed the nature of CF from a progressive, life limiting condition to a manageable chronic illness and have the greatest, preventative, effect on patients started young before damage occurs.
- CFTR modulators do incur opportunity cost and are sadly not suitable for all CF patients.

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- CFTR modulators have brought hope for the future to thousands of CF families for the first time – a hope that must be sustained by a move to routine NHS funding
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Guidance review following a period of managed access

Clinical expert statement

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Thank you for agreeing to give us your 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	
1. Your name	**Prof Andrew M Jones**

2. Name of organisation	**NHSE Respiratory CRG**
3. Job title or position	**Consultant Physician in Adult Cystic Fibrosis**
4. Are you (please tick all that apply):	☐**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐**x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain • Member, NICE/NHSE Vertex CF modulator therapies Interim Access Oversight Committee 2019-2022 • Local site sub-investigator on Vertex clinical studies • Accepted invitation to speak at Czech CF meeting September 2023 – this meeting is sponsored by Vertex and they provide speaker fees • Vertex Independent Medical Grant for Investigator Initiated Study 2017 - The Effect of Gastro-oesophageal Reflux on Cystic Fibrosis Lung Disease (GOR-CF)
7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
8. What is the main aim of treatment?	To restore function of the defective CFTR protein – the underlying cause of this condition

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

9. 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 pulmonary exacerbations by 30% An improvement in Fev1 of 5% An improvement in QOL eg. CFQR of >4 points
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Increased survival - this will take time to assess, and may not be apparent in short term data; however, there has been a reduction in need for lung transplantation Increased time to progression Yes – progression of lung disease, as assessed by %predicated FEV1 Improved QOL Yes Does the new technology provide other substantial health related benefits not included in the QALY calculation? Increased in weight gain for those who are underweight - CF leads to malnutrition and this is associated with decreased survival Improvements in sub-infertility for females with this condition Improved glycaemic control Non-health benefits.:

	Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y/N, please explain: yes, less exacerbations and hospitalisations will allow less disruption to schooling Implications for delivery of the NHS service Yes, decreased hospitalisations and hospital bed days. Decreased frequency of need for outpatient review appointments
11. Are there any recognised side effects of the technology?	There are reports of struggles with mental health issues In a small number of patients hepatic side-effects, including rarely hepatic necrosis Transient skin rashes are sometimes encountered at initial commencement of therapy
12.Are there any important outcome data that were not collected during the managed access period?	

13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Prior to CFTR modulator therapies there were no treatment for patients that addressed the basic cause of the condition; all treatments were for managing downstream effects (organ damage) of CFTR dysfunction There are still patients who have a rare genotype where there is a lack of evidence of benefit as the medications have not been tested on these due to their rarity; these patients are not eligible as they do not fall into the licensed indication but may still be responsive to the treatments. A trial of therapy in those people with CF outside of the approved list of mutations could reduce the number of people not receiving this highly effective treatment, reducing the burden to the NHS.
14. 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?	This is the only therapies that address restoring the function of the defective CFTR protein – the underlying cause of this condition. All other previous therapies have addressed the secondary downstream effects of CFTR function – the organ damage
15. Are there any groups of patients who might benefit more or less from the technology than others?	Those with CF genotypes that are associated with 'classical' cystic fibrosis that leads to underlying lung damage and those with CF genotypes that are associated with exocrine pancreatic insufficiency There are some patients who are established on Ivacaftor as a monotherapy. They also show further improvement on kaftrio but to a generally lesser extent than modulator naïve patients

What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CF clinical guidelines NHSE service specifications for managing cystic fibrosis in children, and NHSE service specifications for managing cystic fibrosis in adults Cystic Fibrosis Trust standards of care
17. Are there other clinical pathways used in England other than those recommended in the guideline?	See answer to q16
18. Would the new technology require a change in the clinical pathway?	no
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	no

20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	The treatment is for patients who have a confirmed diagnosis of cystic fibrosis and an eligible CF genotype. There is an age specifications to commencing therapy based on available drug safety studies – currently 6 years or older for ivacaftor–tezacaftor–elexacaftor. It is lifelong therapy.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: Reduced hospitalisations and need for intravenous antibiotics A decrease in number of malnourished patients An improvement in lung function Patients on the lung transplant waiting list demonstrated an improvement in their clinical condition such that they were removed from active waiting Easier for females to conceive

	Patients report positive effects on their general well being Negative: Development of liver side-effects with raised transaminases and liver biopsy evidence of hepatic necrosis (<1%) Some patients have reported side-effects on mental health
22. Did any people decline treatment? What were their reasons why?	Yes some patients have reported side-effects on mental health and a small proportion have stopped therapy (approx 1%)
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	The clinical benefits have replicated those seen in the phase 3 studies

24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	no
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: Yes for the comparator, please give link:

Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are still patients who have a rare genotype where there is a lack of evidence of benefit as the medications have not been tested on these due to their rarity; these patients are not eligible as they do not fall into the licensed indication but may still be responsive to the treatments. A trial of therapy in those people with CF outside of the approved list of mutations could reduce the number of people not receiving this highly effective treatment, reducing the burden to the NHS. These CF mutations occur more frequently in non-Caucasian people with CF.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Multiple Technology Appraisal

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Clinical expert statement

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Andrew Lilley**

NICE National Institute for Health and Care Excellence

2. Name of organisation	**Alder Hey Children's Hospital and NPPG**
3. Job title or position	**Pharmacy Clinical Service Lead and Lead for Respiratory**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain **Nil**
7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes
The aim of treatment for this condition	
8. What is the main aim of treatment?	To restore function of CFTR leading to improvement of QoL and Life expectancy
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Restoration of the CFTR leading to increased (or no decline) in FEV1 and other markers of lung function. Additionally prevention of further decline in pancreatic function leading to better growth. Reduction in the number of chest infections.

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x cm, or a reduction in disease activity by a certain amount.)	
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival Y Increased time to progression Y Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? N, please explain: Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y Leads to a somewhat 'normal' life without hospital visits and chance to have children in some patients who may not have been able to previously. Improved accessibility to patients N Implications for delivery of the NHS service Y however already in use

11. Are there any recognised side effects of the technology?	Questions around mental wellbeing still to be answered Some mild side effects such as rash which can be managed
12.Are there any important outcome data that were not collected during the managed access period?	
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Availability of a modulator for all CF gene mutations
14. 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	Yes – only drugs of their type

improve the way that current need is met?	
15. Are there any groups of patients who might benefit more or less from the technology than others?	Those whose genes are not on the approved and tested list
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	
17. Are there other clinical pathways used in England other than those recommended in the guideline?	

18. Would the new technology require a change in the clinical pathway?	Already in use within clinical practice
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	no
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	Would have to ensure patient is on approved list of genes for comissioning
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering	Positive:

the technology during the period of the MAA?	Negative:
22. Did any people decline treatment? What were their reasons why?	
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	

25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: Yes for the comparator, please give link:

Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	Those not on approved list do not have alternative treatment at this time

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Guidance review following a period of managed access

Clinical expert statement

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Thank you for agreeing to give us your 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 expert statement

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- 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.

About you	
1. Your name	**Dr Don Urquhart**

2. Name of organisation	**Royal Hospital for Children and Young People** **NHS Lothian**
3. Job title or position	**Consultant in Paediatric Respiratory Medicine** **CF Centre Director**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. Do you have a conflict of interest that you wish to declare[1]?	**Direct – financial** I have previously received speaker fees from Vertex Pharmaceuticals I have received fees for taking part in advisory boards for Vertex Pharmaceuticals and AbbVie Pharma. **Direct – non-financial** None **Indirect** I have been a principal investigator on a number of clinical trials undertaken by Vertex Pharmaceuticals
7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes **N/A**

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

The aim of treatment for this condition	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: curative / stop progression / palliative Other, please describe **CFTR Modulator Therapy** The aim of CFTR modulator therapies is to increase function of the Cystic Fibrosis Transmembrane Regulator protein in order to normalise the transport of chloride ions at epithelial cell surfaces in teh airway, gut, pancreas and biliary tree. By normalising chloride transport, more chloride (and also sodium and water) leave cells providing improved hydration of airways, gut and other cell surfaces. The implication of this is that a number of health benefits ensue including: a) Improved airway clearance leading to reduced infections/lung damage and as a result reduced infective exacerbations of CF and improved lung function b) Improved gut hydration reducing gut complications of CF e.g. DIOS c) Possible partial restoration of pancreatic function with improved absorption contributing to improvements in weight

9. 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.)	Treatment responses can be assessed in a number of ways a) Lung Health i) Improvements in lung function Improvements of 10-14% in FEV_1 were noted in trials of Kaftrio/Kalydeco that are mirrored by real-world experience **10% change in FEV_1 from baseline = clinically significant** ii) Reduction in exacerbation frequency Having less respiratory flare-ups of CF noted in trials of all modulator treatments Also our experience in clinical practice **30% reduction in exacerbations = clinically significant** iii) Reduction in antibiotic requirements I guess a consequence of the improved lung function and reduced exacerbations This is also our experience in clinical practice **30% reduction in antibiotic use = clinically significant** b) Nutrition Weight gain of 2kg or more noted on initiation of treatments Also our experience in clinical practice
10. What are the benefits that you expect the technology to provide compared with	Health benefits. Please delete as appropriate: Increased survival Yes Real-world data is now modelling survival for CF patients on Kaftrio/Kalydeco to be a median of >70 years

routinely commissioned care?	Increased time to progression Yes The accepted 'rate of decline' for FEV_1 in CF prior to modulators used to be around 2%/year for people with CF. Most recent real-world registry data has shown stable lung function e.g. no decline in those on highly-effective modulator therapy though accepted these data are limited to short follow-up durations to date due to the recent introduction of these therapies. Improved QOL Yes Improved quality of life is a clearly demonstrated outcome from clinical trials of highly-effective modulator therapies (HEMT). Again this mirrors our clinical experience. (One note of caution is that some people have experienced adverse mental health side-effects when starting HEMT that have been reversed by dose reduction or cessation of HEMT). Does the new technology provide other substantial health related benefits not included in the QALY calculation? Yes i) Improved nutrition/weight. An important health-benefit in a group of patients that have often required nutritional supplementation. ii) Improved airway clearance/reduced sputum An important benefit is the reduction in sputum production. There is a reduced burden in terms of reduced chest physiotherapy requirements There may be improvement in confidence in social situations due to reduced sputum production. Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc…

	Yes: a) Less time in hospital and more time at work/school People with CF are 'living their life' instead of 'living their life in hospital'. b) Improved QoL for carers People with CF being healthier is a huge weight lifted off the shoulders of parents and carers Improved accessibility to patients N/A Implications for delivery of the NHS service Yes A healthier more stable CF population require: a) Less in-patient admissions We are seeing this already b) Less medications i) Withdrawal trials (CF-STORM, SIMPLIFY) already being undertaken to look at stoping some longer-term therapies in people with CF ii) Reduced antibiotics in both in-patient and out-patient settings c) Reduced out-patient contacts Again, we are seeing this already

	d) Reduction in referrals for lung transplantation This is evident in UK centres. A huge reduction in CF patients being referred for lung transplantation was also reported in International Society of Heart and Lung Transplantation (ISHLT) registry data.
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life Side-effects of highly-effective modulator therapies are well-described 1. Liver dysfunction These are well-recognised and screened for with testing of transaminases/LFTs at regular intervals. 2. Cataracts Very rare side-effect. Annual eye tests recommended in children 3. Rash Relatively common side-effect especially in female patients Hopefully can resolve with dose interruption and restarting Short-term detrimental effect on quality of life 4. Mental Health Effects Anxiety and mood disturbance reported Clear detrimental effect on quality of life May require dose interruption, dose reduction or dose cessation

12.Are there any important outcome data that were not collected during the managed access period?	N/A
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Unmet need for people with CF - Development of new therapies for those (10-15%) people with cystic fibrosis who either a) do not tolerate OR b) do not qualify (non-eligible genotype) for highly-effective modulator therapies RE: Highly-effective modulator therapies If ongoing treatment with highly-effective modulator therapies (HEMT) were not supported going forward then that would leave an unmet health need for people with CF that have been on HEMT for several years with demonstrable health benefits as above. This would leave unmet needs in regards to physical health, as well as the effect of withdrawal of a life-improving therapy on mental health and quality of life.
14. 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?	Highly-effective modulator therapy can be expected to have significant and substantial health-related benefits for people with CF with beneficial effects including improvements in lung function, reduced chest infections, improved nutrition as well as quality of life improvements. Highly-effective modulator therapy is currently available. This MTA is re-appraising the benefits of treatment.
15. Are there any groups of	Possibly

patients who might benefit more or less from the technology than others?	One might argue that those with worse lung function may gain most benefit by having improvement. The treatment certainly appears life-extending in those with more severe lung disease. Another argument would be that impacting early (and before lung disease is advanced) allows for the best outcome – extension of life that is high-quality life. With this in mind, highly-effective modulator treatment is licensed down to age 6 (Kaftrio/Kalydeco), and aged 1 month (Ivacaftor). A 2-5 year application for Kaftrio/Kalydeco is currently under consideration.
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes Examples would include: Brompton CF guidelines Clinical guidelines: Care of children with cystic fibrosis, 2023 | Royal Brompton & Harefield hospitals (rbht.nhs.uk)
17. Are there other clinical pathways used in England other than those recommended in the guideline?	Approach would be similar across all UK CF centres (Our site is in Scotland)
18. Would the new technology require a change in the clinical pathway?	No Already part of current approach to care of people with CF

19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	Not new costs Costs of monitoring liver function and eye health are indirect costs of treatment with highly-effective modulator therapies. This monitoring is already taking place.
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	Yes Starting – eligible genotype, careful patient (+/- parent) counselling along with shared decision-making on whether to start. Stopping – side-effects as outline as above e.g. elevated transaminases/bilirubin, severe rash, mental health issues.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: Improvements in lung function in our patient cohort (FEV_1 and also lung clearance index) Dramatic reduction in number of CF in-patients/those requiring intravenous antibiotics

	Reduced exacerbations for most with consequent reduction in need for oral antibiotics Improved weight across the clinic cohort Reduction in numbers of patients requiring nutritional supplementation Negative: Excessive weight gain in some (Highlights importance of health eating and exercise in the era of modulator therapy) Mental health effects have not been an issue in our patient cohort though I am aware of thse issues in other clinics Liver dysfunction We have had three patients with significantly raised liver function tests. Two patients had a temporary cessation of treatment and then restarted (one at a lower dose), whilst the third patient has only recently been advised to stop treatment. We are awaiting on liver function normalising before planning to restart at a lower dose. Rash Our experience has been that rash has not been a major issue in our childhood cohort.

22. Did any people decline treatment? What were their reasons why?	Only 1 patient has declined treatment. The family in question have distinct health beliefs (e.g. declined COVID vaccinations, etc.) and do not want to expose their (currently well) child to new treatments.
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	Treatment monitoring has been straightforward We have a clear algorithm for monitoring of eyes, liver function and lung function. Our nurse specialists utilise a spreadsheet to ensure we have oversight of who is due what and when, and any monitoring that is overdue. All results come back via an electronic workbench and are signed off.
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	No I don't think so. The monitoring is in keeping with the SmPC advice, and we and our adult colleagues are each aiming to stick to this.
25. Are there other points of learning arising from the period of the managed access	Providing psychological support to patients and families would be important. Highly-effective modulator therapy is perhaps reframing life goals from being quite limited to 'the sky's the

agreement that you would like considered?	limit'. The adjustment for those that have perhaps underachieved at school (due to being in hospital) and have not been working is particularly hard as they contend with viewing life differently due to improved health and stability, but also the prospect of losing some of the financial benefits of ill-health. In paediatric practice, some parents have found the 'letting go' aspect hard – having been involved in a daily run of therapies and frequent hospital admissions with their child, the prospect of additional freedom for their child can be quite daunting. The other key group that require psychological support are the families of people with CF that are not eligible for a CFTR modulator treatment. Being in a clinic where 85% of your peers are getting what is billed as a 'wonder drug' by the media has clearly been very difficult for several of our families, in particular two or three where inexorable decline has occurred against the backdrop of CF optimism driven by new therapies.
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: None that I am aware of Yes for the comparator, please give link:

Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	Potentially a) Much of the trial data comes from Europe and North America Patients of Asian and African origin may therefore be potentially under-represented in trials b) The true prevalence of CF in some parts of the developing world is not known Probably not an issue in regard to the treatment - just that need to recognise the condition (CF) across persons of all ethnicities - perhaps closer monitoring for side-effects in non-Caucasian populations due to potential under-representation in trials

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Thank you for agreeing to give us your 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. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Yasmin Stammers**
2. Name of organisation	**NHS England (Specialised Commissioning National Team)**

3. Job title or position	**Senior Programme of Care Manager**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not	☐ yes

have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE NG78
9. 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	Yes

experience is from outside England.)	
10. What impact would the technology have on the current pathway of care?	It is already having a positive impact through a reduction of hospital admissions, bed days, antibiotic use etc.
The use of the technology	
11. To what extent and in which population(s) is the technology being used in your local health economy?	Take up across England of up to around 96% of eligible populations.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Agree with statement provided
• How does healthcare resource use differ	Appears to be requiring less inpatient use. Unclear as to longer-term outcomes and disease trajectory for patients receiving modulator therapy.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Technology is taken at home.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
13. What is the outcome of any evaluations or audits of the use of the technology?	Awaiting analysis of the Managed Access Scheme.

Equality	
14a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. There are a total of over 2000 different gene variants and only a small proportion have been tested for CFTR responsiveness though it is highly likely that many of these patients will respond. There is a systematic bias that has been applied because the variants tested so far are those expressed mainly in European populations. There are patients with origins outside Europe who clearly have CF with diagnostic sweat tests, two CF genes identified and a phenotype often of severe CF disease. These non-European populations are less likely to have been tested for ETI responsiveness and so will be discriminated as their variant will not be on the list of responsive variants.
14b. Consider whether these issues are different from issues with current care and why.	Current CF care outside modulator therapy is available to all patients with CF through both NICE guidance and NHS England commissioning policies regardless of genetic mutation.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **19 September 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Vertex Pharmaceuticals
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**NA**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Abbreviations

Abbreviation	Definition
AE	Adverse event
CarerQoL	Care-Related Quality of Life measure
CEA	Cost-effective analysis
CEM	Cost-effectiveness model
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R-8D	Cystic Fibrosis Questionnaire-Revised-8 dimensions
CFTRms	Cystic fibrosis transmembrane conductance regulator modulators
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID	Coronavirus disease
DCA	Data collection agreement
DID	Difference in difference
EAG	External assessment group
ECM	Established clinical management
ELX	Elexacaftor
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
FE	Fixed effects
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
HRQoL	Health related quality of life

HTA	Health technology assessment
IAOC	Interim access oversight committee
ICER	Incremental cost-effectiveness ratio
IV	Intravenous
IVA	Ivacaftor
LUM	Lumacaftor
NA	Not applicable
NCCTEs	Negative-control-corrected treatment effects
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OKB	ORKAMBI
OLE	Open label extension
PAS price	Patient access scheme
PEx	Pulmonary exacerbations
ppFEV1	Percentage of predicted forced expiratory volume in 1 second
pwCF	People with cystic fibrosis
QALY	Quality adjusted life year
QoL	Quality of life
RE	Random effects
RF	Residual function
RWE	Real-world evidence
SE	Standard error
SwCl	Sweat chloride
TEZ	Tezacaftor
UK	United Kingdom

US	United States

Comments on External Assessment Report

Summary and introduction:

The EAG's model and analysis has a number of technical errors as well as inappropriate assumptions. As such, the results reported by the EAG are not suitable for decision-making. While the structure of the model is in line with published literature and is largely consistent with Vertex's model structure, the model contains several inaccuracies, miscalculations, and programming errors.

Moreover, the EAG's approach to consideration of the evidence is unreasonable in light of the body of real-world data that is available and was developed specifically for this appraisal. This includes the EAG's approach to consideration of key clinical assumptions (e.g., long-term clinical benefits) and utility estimation disregarding the disease-specific tool used in CF (CFQ-R), and the fact that CFQ-R data was collected specifically to inform this appraisal. All parties to the data collection agreement (NICE, NHS England, Vertex and UK Cystic Fibrosis Trust) gave their consent to the study protocol, and EQ-5D data was not requested to be collected.

Therefore, use of ALL relevant evidence currently available and an alternative peer-reviewed model is required to inform committee decision-making. We summarise this in the table below, which compares the EAG approach with the Vertex proposed approach using an alternative peer-reviewed and published model.

Table 1. Key settings for the economic analysis: EAG's and Vertex's approach

Issue	EAG approach	Vertex proposed approach	Rationale
Technical errors	EAG has created a *de novo* own model. We have identified technical/programming/mathematical errors, including lack of modelling best practices, poor programming implementation and an unquantifiable level of uncertainty on its estimations.	Use of Vertex model which has been thoroughly QC'd, peer-reviewed, published and accepted by other reputable HTA bodies.	The Vertex model has received favourable feedback from several HTA organizations, including NICE (TA398), for its design and internal validity in modelling the disease pathway. Most recently the model was reviewed and gained successful appraisals from reputable HTAs in Canada, Ireland and Australia. The modelling framework and underlying survival approach has also been presented in a peer-reviewed

			publication [1-3] (Rubin et al., 2019, Lopez et al 2023, Mc Garry et al 2023).
IVA/TEZ/ELX rate of change in lung function (ppFEV$_1$)	IVA/TEZ/ELX rate of change in lung function assumed to be 37.7% based on ivacaftor methods paper by Newsome et al. 2022 [4]	100% rate of change in lung function as shown by IVA/TEZ/ELX real-world evidence [5, 6]	Use of evidence from studies ofIVA/TEZ/ELX is most appropriate, particularly given the abundance of data available for this product, including UK-specific data collected as part of the data collection agreement for this appraisal
TEZ/IVA rate of change in lung function (ppFEV$_1$)	10.6% rate of change in lung function	61.5% rate of change in lung function [7]	Use of evidence from studies in TEZ/IVA are most appropriate, given they are available.
LUM/IVA rate of change in lung function (ppFEV$_1$)	0% (i.e., no long-term clinical benefit vs ECM)	42% rate of change in lung function decline [8]	Use of evidence from studies in LUM/IVA are most appropriate, given they are available – equally, the large body of long-term evidence for LUM/IVA shows a clear benefit vs ECM which the EAG does not account for.
PEx	The EAG applies a pulmonary exacerbation treatment effect (rate ratio) for only the duration of trial period	Pulmonary exacerbation treatment effect (rate ratio) applied for patients' lifetime	Vertex has submitted a comprehensive evidence package containing pivotal trial data, OLE data and real world DCA data to evidence the long-term decline on PEx beyond the trial period.
Baseline mortality hazard	Keogh (2018) [9] paper used to predict CF baseline mortality using 2011-2015 registry data: Median survival of 46.8 years.	Vertex had previously used UK CF Registry data from 1985–2008, reporting a median survival of 40.8 years. Vertex accepts the EAGs alternative approach for this variable.	Despite lack of transparency on how these data were derived from Keogh et al., [9] Vertex accepts that this study could be used as an alternative input.
Compliance	100%	Previously Vertex had assumed 80% compliance but have now revised this in our base case to [redacted]%.	Evidence suggesting compliance is [redacted]% is now available from the DCA; we therefore believe this is a reasonable estimate [6].
ECM rate of lung function decline	The ECM rate of lung function decline used by EAG was derived from genotype- and age-specific	Vertex approach used genotype- and age-specific rates of lung function decline for F/F and F/RF	. The assumption made by the EAG indicate that F/RF patients are declining faster than what was observed by Sawicki. This assumption biased the ICER

	rates from Szczesniak et al 2023 [10] in which decline rates for F/F patients was used for F/MF and F/Gating. The reported decline rate for the overall population (which included F/F patients) was applied for F/RF patients. Decline rates were capped based on Sawicki et al 2022 [11] decline rates for F/RF.	from Sawicki et al 2022 [11]. Rate of lung function decline for F/F was applied to F/MF and F/Gating.	estimations for F/RF as the rate of lung function decline is directly associated with survival and other parameters in the model (e.g., costs, QALYs). In addition, Sawicki et al 2022 [11] estimates of lung function decline were derived based on patients who were not on a CFTR modulator treatment, different than Szczesniak et al 2023 [10] which did not have an exclusion criterion for patients on a CFTR modulator treatment.
Disease specific utilities	The EAG *de novo* model uses utility inputs based on TRAFFIC/TRANSPORT EQ-5D-3L data . $ppFEV_1$ >=70: 0.91 $ppFEV_1$ 70-40: 0.88 $ppFEV_1$ <40: 0.85	Vertex believes the correct utility data should be from the CFQ-R data derived from real world data collection agreement, converted to utilities using a validated preference-based algorithm: $ppFEV_1$ >=70: [redacted] $ppFEV_1$ 70-40: [redacted] $ppFEV_1$ <40: [redacted]	The CFQ-R is a validated CF-specific tool, and has a preference-based scoring algorithm (the CFQ-R-8D), according to published guidelines by NICE, which enables estimation of CF-specific health-state utilities based on the CFQ-R. EQ-5D-3L is insensitive to CF, hence the omission of the EQ-5D data which shows CF patients with severe lung disease to have a utility (0.85) higher than that of the general population (0.84) [12].
IVA/TEZ/ELX treatment specific utility	The EAG has not included this in its *de novo* analysis and has not given a rationale for this approach.	The 0.08 IVA/TEZ/ELX treatment specific utility should be applied	Assigning utility scores based only on $ppFEV_1$ and PEx would fail to capture the extra-pulmonary benefits of IVA/TAZ/ELX, including benefits to other organ systems and general improvements in functioning, well-being, and quality of life unrelated to respiratory outcomes. In all Phase 3 trials of IVA/TAZ/ELX, treatment provided substantial benefit across multiple non-respiratory domains of the CFQ-R. The model captures these benefits by incorporating a treatment-specific utility increment – that is, an increase in the utility above that predicted based on $ppFEV_1$ for patients treated with IVA/TAZ/ELX. The magnitude of this utility increment 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 the IVA/TAZ/ELX trial conducted in patients age ≥12 years with F/MF genotype, Study 445-102 [13]
Disease management costs	The EAG has used a resource use questionnaire as part of a trial to assess adherence to inhaled medications, to inform disease management costs (Tappenden 2023 et al) [14].	Vertex used a retrospective chart review of patients with CF aged ≥6 years old across eight specialist CF centres in the UK. (Ramagopalan et al.) [15]. Full 24-month data were extracted for each patient, including patient characteristics, pharmacotherapy, and healthcare resource use	The retrospective chart review provides a comprehensive and accurate source of data using medical record data to inform costings. Using questionnaires inherently introduces inaccuracy into the data given recall bias, memory bias, incomplete data trends, inaccurate estimations, and response burden.
Severity	No severity modifier is applied in the EAG's *de novo* model.	A severity modifier should be applied.	Cystic fibrosis is a severe respiratory disease, which leads to a significant shortening of life. In 2021, the median age at death in the UK was 38 years [16]. The fact that the EAG used EQ-5D utilities for $ppFEV_1$-defined health states which lack face validity due to values being higher than the UK general population norms, contributes to overestimation of QALYs accrued by the CF patients treated with established clinical management during the EAG's model time horizon. This in turn diminishes their QALY shortfall relative to the UK general population, and results in severity modifier threshold not being reached.
Discount rate	3.5% for costs and outcomes	3.5% for costs, 1.5% for outcomes	Vertex has submitted a comprehensive evidence package containing pivotal trial data, OLE data and real world DCA data to evidence the long-term value that CFTRms provide to patients and the healthcare system, justifying a differential discount rate. NICE has shown flexibility by accepting differential discount rates in prior appraisals for severe paediatric conditions. [17]

Executive summary

Long-term clinical outcomes

a) The EAG proposes that using an estimate from a methods paper on ivacaftor is the most appropriate source to estimate the long-term rate of change in lung function ($ppFEV_1$) for IVA/TEZ/ELX – this estimate is 37%. Vertex proposes using the data from the IVA/TEZ/ELX OLE studies as well as the mandated UK registry as the most appropriate estimate of long-term effect – this data shows no decline in lung function. Using recent UK data on IVA/TEZ/ELX is more appropriate than a methods paper on another medicine.

b) The EAG concludes that COVID-19 related restrictions preserved lung function in CF patients, and that this leads to an overestimation of the clinical benefit of IVA/TEZ/ELX. The evidence for this is derived from two studies, one of which is a systematic review in COPD. The other is a study from Australia, with a third of patients aged below 6 years, leading to uncertain lung function results [17, 18]. This evidence is insufficient to argue that CF patients' lung function would have been preserved in the absence of treatment during the COVID-19 pandemic, particularly considering evidence to the contrary (detailed below).

c) The EAG has disregarded the data from Study 445-105 (192-week Phase 3 open-label extension study) and deemed the estimates of the long-term rate of $ppFEV_1$ decline and reductions in pulmonary exacerbations (PEx) for IVA/TEZ/ELX to be unrobust due to COVID-19 confounders. The EAG's position is not evidence-based.

d) The real-world evidence from the UK CF Registry collected under the data collection agreement, which was set up solely to collect outcomes to inform the appraisal, should provide the fundamental source of data on the long-term effectiveness of IVA/TEZ/ELX. The methods applied in the UK CF Registry study, conducted as part of the data collection agreement, were agreed with NICE and the UK Cystic Fibrosis Trust, with ongoing monitoring which supports the validity of its results. The EAG has disregarded evidence on long-term effectiveness in favour of less appropriate sources (e.g., EAG preference for Newsome et al 2022 [4] to suggest 37.7% rate of change in lung function, rather than the 100% from the real world evidence).

e) The EAG has taken an assumption-based approach for the estimates of rate of decline of ppFEV1 for people treated with LUM/IVA and TEZ/IVA, which is not substantiated by the robust clinical evidence. The EAG proposed a rate of change in lung-function decline for LUM/IVA of 0% (no benefit vs. ECM) and for TEZ/IVA of 10.6%. This runs contrary to the available clinical evidence which shows that the rate of change in lung-function is 42% for LUM/IVA and 61.5% for TEZ/IVA.

Utilities and application of the treatment specific utility increment for IVA/TEZ/ELX

The CFQ-R is a validated CF-specific tool and has a preference-based scoring algorithm (the CFQ-R-8D) according to published guidelines by NICE, which enables estimation of CF-specific health-state utilities based on the CFQ-R. This is the appropriate tool for capturing QoL in CF. EQ-5D-3L is insensitive to CF (there are only 5 questions with 3 potential answers), hence the omission of the EQ-5D data which shows severe CF patients to have a utility (0.85) higher than that of the general population (0.84) [12]. Application of a treatment-specific utility increment captures the additional non-respiratory benefits of treatment with IVA/TEZ/ELX.

Discount rate

Vertex believes that the use of a differential discount rate (1.5% for health benefits, 3.5% for costs) is appropriate for decision-making. This is on the basis that uniform discounting undervalues medicines which incur health gains far into the future, particularly in chronic paediatric diseases. We note that NICE has in the past accepted use of differential discounting in an appraisal for a rare paediatric condition [19].

Severity modifier

Based on the EAG analysis, CF is not a severe disease. The use of EQ-5D utilities which overestimate the health-related quality of life of CF patients treated with established clinical management without CFTR modulators in EAG's *de novo* model leads to the failure to meet the QALY shortfall threshold at which severity modifier can be applied. However, given that patients in the UK currently have a median age of death in their 30s, Vertex maintains that this is an unreasonable suggestion [16].

1. **The EAG's model has a number of errors, and therefore the analysis and results are not suitable for decision-making**

A number of technical errors were identified in the EAG model. These have a significant impact on the ICER, and the fact these errors were not identified by the EAG prior to finalisation is concerning. Vertex agrees with the general structure and principles of the model, however, Vertex has uncovered a significant number of errors in the short consultation period and believe there may be others which would become apparent if more time could be spent checking the EAG model. We will continue this work beyond the consultation period. There are also issues with the EAG reporting of the model results in the report itself, which further reduce confidence in the EAG's work.

Taken together these errors had a significant impact across all elements of the EAG model such a clinical (e.g., PEx events), economical (e.g., ECM costs) and utilities (e.g., PEx disutility). Overall, the impact of these errors has significantly impacted the ICERs (up to 15%).

The errors listed below are those identified by Vertex during the consultation period:

1) Costs of ECM (e.g., the costs of inhaled antibiotics, hypertonic saline solution, etc.) were labelled as “drug costs” in the NICE EAG model and should be applied to all treatment arms. However, in the EAG model, the costs were only applied to CFTRm arms but not to ECM (i.e. the treatment costs were not included in the total costs in the model engine). This significantly underestimates the total costs in the ECM arm and overestimates the ICERs of CFTRm vs. ECM. This is a major error and has a significant impact on the reported ICERs. Vertex asked NICE to raise this with the EAG several times during the consultation period, but NICE declined to pass Vertex questions to the EAG.

2) The calculation of PEx costs in the CFTRm arm were estimated based on the total number of PEx events of the ECM arm, leading to an overestimation of the disease management costs in the CFTRm arm and entailing a significant impact on the ICERs reported.

3) There should be no PEx in patients aged 2-5 years. However, when running a cohort with 2 years old with a 3-year time horizon, the results reflect PEx outcomes, thus indicating that PEx were counted in patients aged 2-5 years. This is a significant error and indicates poor understanding of the clinical course of CF and the available evidence.

4) The calculation of PEx events in the ECM arm was implemented incorrectly, resulting in no PEx events for ECM in F/Gating, which in turn affects the total costs and QALYs in the ECM arm. This is a significant error that substantially underestimates PEx costs and QALYs in the ECM arm, resulting in an overestimated ICER for IVA/TEZ/ELX in F/Gating.

5) The discontinuation rates are not transformed into probabilities before comparing to a random number, which resulted in much higher discontinuation in the acute period. This is very much standard practice when dealing with probabilities and further reduces confidence in the EAG model.

6) The back-end calculation of the baseline mortality hazard is incorrectly implemented. The mortality inputs are already mortality hazards but were treated as probabilities in the model calculations. This impacts the survival estimates and the CE results.

7) The EAG model incorrectly applies a reduction in the rate of $ppFEV_1$ decline for IVA/TEZ/ELX, TEZ/IVA and LUM/IVA when there is a positive change in $ppFEV_1$, leading to a slower decline rate in $ppFEV_1$ for ECM when compared with the rate of decline in $ppFEV_1$ for IVA/TEZ/ELX, TEZ/IVA and LUM/IVA.

Misalignments around the model inputs and reported results were also identified:

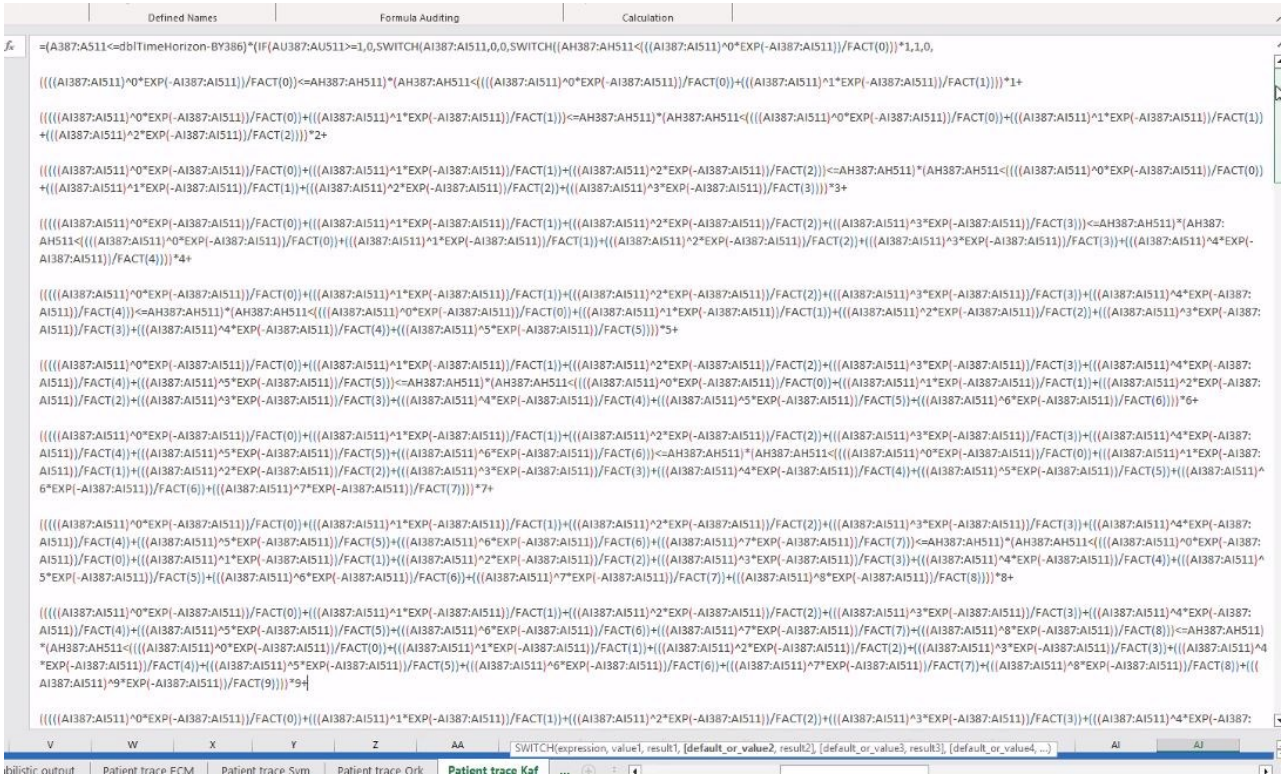
1) The results for F/Gating generated with the base case EAG model were different from the results reported in the EAG report.

2) In the scenario with Vertex base case inputs, several incorrect inputs were identified. One such example is the utility increment for IVA/TEZ/ELX and TEZ/IVA, which was incorrectly linked to the OKB utility increment value (which is 0) and resulted in no utility increment being applied to IVA/TEZ/ELX and TEZ/IVA.

3) Discontinuations are modelled by the EAG such that the acute increase in ppFEV$_1$ and weight-for-age z score are lost immediately upon discontinuation. There is a lack of data to confirm this assumption from the EAG.

Vertex would like to highlight that the overall complexity of the equations and programming used by the EAG are not in line with general good practices expected in health economic modelling. This has led to the model being slow and unresponsive to scrolling and editing, and extremely long run times often taking up to 90 minutes for a single analysis (see example below). This has severely impacted our capacity to properly analyse the model within the short consultation period, which is both unfair and unreasonable.

Figure 1 : EAG calculations model sample



Due to the errors and potential quality considerations outlined above, we suggest an alternative peer-reviewed and published modelling approach is used. We outline this alternative further in section 3.

2. The EAG's approach is unreasonable in light of the evidence available

The EAG has not appropriately appraised the evidence on clinical effectiveness or quality of life which informs the model. The CFTRms, LUM/IVA, TEZ/IVA and IVA/TEZ/ELX, were all made available through an unprecedented interim access agreement between Vertex and NHSE. The intention of the access agreement was that real world evidence be collected on the medicines in a UK real-world setting. This data collection agreement (DCA) was designed and executed in close collaboration with NICE, Vertex, the clinical community and the CF Trust. The *sole* purpose of the agreement was that data be collected to inform the future appraisal of the CFTRms, along with other real-world evidence (RWE) and data available through open-label extension studies (OLE). The data collected illustrate the considerable impact these medicines have had on clinical outcomes and quality of life (QoL) for patients living with CF and their caregivers.

Therefore, it is concerning that the EAG disregards, without proper justification, the body of evidence gathered in the real world on the effect of these medicines on clinical outcomes and QoL. The EAG fails to acknowledge or discuss 11 of the 13 objectives of the Registry Study (major component of the DCA) and fails to adequately consider other real-world evidence from the DCA and OLE studies on 1) rate of change in lung function ($ppFEV_1$) and 2) QoL. On the change in lung function parameter, the EAG suggests there is confounding by COVID-19 pandemic, which is refuted in our response below. Through the DCA, (over the last 3 years) regular meetings and presentations were held between NICE, Vertex and the wider interim access oversight committee (IAOC). Therefore, NICE and the broader IAOC have had reasonable opportunity to comment on the research methods and interim data analysis while there has been full awareness of the data informing the real-world evidence outcomes report. No major concerns were raised that would lead to the Registry Study not to be a main real-world data source informing the effectiveness of the CFTRm in UK patients.

Furthermore, it is well established that reported utilities in patients with CF are better captured using the CFQ-R (which includes 8 domains and is validated according to NICE methodology) than the generic EQ-5D-3L which asks patients 5 generic questions to which they can only respond with 3 answers. This is demonstrated by the fact that, using EQ-5D, the EAG suggests patients with the most severe CF have a quality of life (QoL) of 0.85. Other CF patients have a QoL score higher than 0.9. General population QoL is around 0.84 in the UK [12]. It is clear that the EAG's approach to utilities is not suitable.

We respond below to a number of the most important shortcomings in the EAG's choice of evidence considered in its analysis.

Rate of change in $ppFEV_1$

a) The EAG proposes that using an estimate from a methods paper on ivacaftor is the most appropriate source to estimate long-term rate of change in lung function ($ppFEV_1$) for IVA/TEZ/ELX – this estimate is 37%. Vertex proposes using the data from the

IVA/TEZ/ELX OLE studies as well as the mandated UK registry study as the most appropriate estimate of long-term effect – this data shows no decline in lung function. Using recent UK data on IVA/TEZ/ELX is more appropriate than evidence from another medicine.

Vertex's estimates of long-term ppFEV1 rate of change for IVA/TEZ/ELX, TEZ/IVA and LUM/IVA are informed by the direct real-world evidence from the UK CF Registry as per the DCA and the OLEs for the corresponding medicines. However, the EAG-adopted assumption is unsupported, and the methodology is inconsistent. Specifically, Vertex does not agree with the EAG approach of using the Newsome et al [4] methodology to provide an estimate of the long-term treatment effect of IVA on $ppFEV_1$ decline. This analysis is a methods paper exploring how to apply negative control outcomes/difference in difference (DID) approach in a new way to estimate negative-control-corrected treatment effects (NCCTEs). This methodology is not appropriate for "correcting" the treatment effect of IVA/TEZ/ELX.[1]. Furthermore, it is not appropriate to compare different estimates of rate of change from differently designed studies that vary on data availability, data sources, follow-up time, modelling approaches, or other factors (Szczesniak et al. 2023) [10].

As described in our response to the EAG clarification question A3, Vertex has evidence on the long-term durability of IVA on reduction of change in lung function over up to 5 years in pwCF aged 6+ years, which was explored in a longitudinal study from the US Cystic Fibrosis Foundation Patient Registry [20]. This analysis supported the previous Sawicki et al. [21] analysis with a difference in annual change of $ppFEV_1$ between IVA and a comparator cohort of +0.80 over 5 years of follow-up. This annual change estimate is also mentioned by the Keogh et al. [9] study as unbiased estimate. The EAG's rationale of using the Newsome et al estimate of long-term treatment effect of IVA on $ppFEV_1$ decline instead of this data is unclear.

Vertex does not agree with the EAG's approach to apply the estimated relative reduction in $ppFEV_1$ decline from data based on IVA monotherapy for IVA/TEZ/ELX. It is inappropriate to assume similar response to IVA in patients with F/G mutation and to IVA/TEZ/ELX in patients with an F/any genotype, simply based on a comparison of sweat chloride responses in different IVA and IVA/TEZ/ELX studies. In fact, the EAG assumption of similar response to IVA and IVA/TEZ/ELX based on similar sweat chloride results is not supported by their NMA (see page 135 of the EAG report), which shows that the acute treatment effects in changes in ppFEV1 for IVA/TEZ/ELX is relatively higher than IVA (FE: 5.80; RE: 5.82) in the F/G 12+ population.

The inconsistency in the EAG methodology in the estimates of relative reduction in $ppFEV_1$ decline for IVA/TEZ/ELX and TEZ/IVA is also noted. To estimate the long-term treatment effect of TEZ/IVA on ppFEV1, the EAG's approach is to scale the effect estimate for IVA/TEZ/ELX

[1] The "parallel trend assumption" is necessary for the DID analysis to ensure internal validity of the DID model. It requires that in the absence of treatment, the difference between IVA/TEZ/ELX and established clinical management (ECM) is constant over time. Vertex believes that the effect of the COVID-19 pandemic over time cannot simply be considered as a confounding factor but violates this critical assumption for DID because of the dynamic of the pandemic over time. The +0.49 value as negative-control-corrected treatment effect (NCCTE) is derived by subtracting an adjusted negative control effect (NCE) of 0.2 from an adjusted naïve treatment effect (NTE) of 0.68.

by a ratio of the TEZ/IVA to IVA/TEZ/ELX acute treatment effect in the F/F population (i.e. 4/14.2 = 0.282), based on the EAG base case NMA. However, the EAG has not adopted a similar approach in scaling the effect estimate up for IVA/TEZ/ELX based on the relative magnitude of acute effect of IVA/TEZ/ELX compared to IVA in the F/G population as reported in EAG NMA for absolute change from baseline in ppFEV1 (see Table 41 in the EAG report; FE: 15.18/9.38 = 1.62; RE: 14.60/8.77= 1.66). This inconsistency in the EAG's preferred assumption-based approach is not justified.

b) The EAG concludes that COVID-19 related restrictions preserved lung function in CF patients, and that this leads to an overestimation of the clinical benefit of IVA/TEZ/ELX. The evidence for this is derived from two studies, one of which is a systematic review in COPD. The other is a study from Australia, with a third of patients aged below 6, leading to uncertain lung-function results [17, 18] **This evidence is insufficient to argue that CF patients' lung function would have been preserved during the COVID-19 pandemic without IVA/TEZ/ELX treatment, particularly considering evidence to the contrary, set out below.**

Vertex disagrees with the conclusion that the Final Analysis of 445-105 underestimates the rate of decline in lung-function for patients on IVA/TEZ/ELX. In fact, sensitivity analysis testing for different types of data included in the model suggests that due to the treatment there is no change in lung function over time, in line with other studies, including Lee at al [5], 445-102 [13], 445-103 [22], 445-105 [23]).

Part of the Lee et al. analysis [5] relied on clinical data collected during the time period before the start of the COVID-19 restrictions, i.e. 445-102 (completed April 2019), 445-103 (completed December 2018), and the early part of 445-105 (started October 2018). A portion of the IA3 data cut in study 445-105 was data collected from October 9, 2018 to March 25, 2021, partly overlapping with the COVID-19 pandemic when social distancing and mask use likely led to a decline in pulmonary exacerbations.

The Final Analysis of study 445-105, which was completed on January 9, 2023, included an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, and demonstrated that participants treated with IVA/TEZ/ELX continued to have on average no loss of lung function and pulmonary exacerbation rates remained low, which strongly suggests that IVA/TEZ/ELX is the primary driver behind these results and not the COVID-19 pandemic. Study 445-105 and the Lee et al. [5] analysis show a flat rate of change regardless of the COVID-19 pandemic. [redacted] [23].

Adjusting the analysis for the potential confounding effect of shielding/lock-down interventions during the COVID-19 pandemic needs to be further investigated when longer-term real-world data beyond 2022 on patients initiated on IVA/TEZ/ELX are available (outside of the

pandemic). Further research is needed to understand the specific impact that social shielding during the COVID-19 pandemic may have had on lung function outcomes.

c) The EAG has disregarded the data from Study 445-105 (192-week Phase 3 open-label extension study) and deemed the estimates of the long-term rate of ppFEV$_1$ decline and reductions in pulmonary exacerbations (PEx) for IVA/TEZ/ELX to be unrobust due to COVID-19 confounders. The EAG's position is not evidence-based.

Pre-pandemic clinical trial data (e.g. Study 445-102) has clearly demonstrated that the treatment with IVA/TEZ/ELX resulted in significant reductions in PEx and unprecedented improvements in lung function. Patients with F/MF genotype treated with IVA/TEZ/ELX experienced a 78% and 71% reduction in annualised PEx requiring treatment with IV antibiotics and PEx leading to hospitalisation, respectively [13]. There is a large body of evidence highlighting that PEx are significant clinical events in the lives of CF patients and are associated with a greater rate of lung function decline and decreased survival [24]. The study by Waters et al took place outside of the pandemic therefore provides direct, unconfounded evidence of the clinical benefits of IVA/TEZ/ELX in reducing the rate of decline in lung function.

The rapid improvements in ppFEV$_1$ achieved in the pivotal studies (445-102 and 445-103) for F/MF and F/F patients were maintained throughout the 192-week OLE (445-105), which covered the time period before, during and after the pandemic (Figures 1a and 1b). Given studies 445-102 and 445-103 completed in April 2019 and December 2018, respectively, all patients entering the OLE Study 445-105 would contribute at least 12 months of pre-pandemic data. A portion of the IA3 data cut in study 445-105 was data collected from October 9, 2018 to March 25, 2021, overlapping with the COVID-19 pandemic when social distancing and mask use likely led to a decline in pulmonary exacerbations. The Final Analysis of study 445-105, which completed on January 9, 2023 and included an additional 96 weeks of data collected largely during a time period when restrictions related to the COVID-19 pandemic were relaxed, demonstrated that participants treated with IVA/TEZ/ELX continued to have on average no loss of lung function and pulmonary exacerbation rates remained low. This finding strongly suggests that IVA/TEZ/ELX is the primary driver behind these results and not the COVID-19 pandemic. Study 445-105 and the Lee et al. analysis show a flat rate of change regardless of the COVID-19 pandemic. The 192-week data in study 445-105 [redacted]

This data is complemented by the sweat chloride (SwCl) results from the same studies. As shown in Figures 1c and 1d, [redacted]. The EAG (Section 3.2.2.1.1 of the report) agrees that SwCl data is at low risk of bias due to a) the lack of a plausible mechanism by which the COVID-19 pandemic could confound this outcome and; b) the low likelihood of spontaneous improvement in SwCl without CFTR modulators. An association between CFTRm-induced restoration of CFTR activity, as measured by sweat chloride concentration, and other clinical responses including ppFEV$_1$ [25] and PEx has been reported [26].

Given this, the sustained improvements in SwCI observed in Study 445-105 support the long-term clinical benefit of IVA/TEZ/ELX in lung function preservation.

Given the similar trend of $ppFEV_1$ and SwCI data, both of which showed sustained improvements through week 192 of the OLE, Vertex considers the data from Study 445-105 to provide robust estimates of the long-term effectiveness of IVA/TEZ/ELX on $ppFEV_1$ progression. As included in the initial submission (Doc B Section B.3.3.4.1), comparing the estimated annualised rate of change in $ppFEV_1$ (based on Study 445-105) vs the corresponding matched control group, a reduction of 117.3% and 135.6% in the rate of $ppFEV_1$ decline was reported for the F/MF and F/F genotype treated with IVA/TEZ/ELX, respectively [5]. These data support the durability of IVA/TEZ/ELX effect on lung function preservation.

Vertex does not agree with the EAG's comments that the estimate of the annualised rate of change in $ppFEV_1$ from study 445-105 is biased by the missing data at Week 192. The by-visit absolute changes from baseline in ppFEV1 and the sample sizes for each visit are provided in Figure 1a and 1b. As shown in the figures, [redacted].

Table 2: Treatment period subject disposition in OLE Study 445-105 [23]

d) The real-world evidence from the UK CF Registry collected under the data collection agreement, which was set up solely to collect outcomes to inform the appraisal, should provide the fundamental source of data on the long-term effectiveness of IVA/TEZ/ELX. The EAG has disregarded evidence on long-term effectiveness and quality of life, in favour of less appropriate sources (EAG preference for Newsome et. al (ivacaftor methods paper) to suggest a 37% rate of change in lung function, rather than the 100% from the real-world evidence).

The data from the UK registry represent the largest set of data analysing the impact of IVA/TEZ/ELX on patients with CF in the UK, and are supportive of the positive benefit-risk profile of IVA/TEZ/ELX established in the Phase 3 clinical trials, confirm observations found in other large real-world studies, and further support the positive impact of IVA/TEZ/ELX on the lives of people with CF. When analysing progression of ppFEV1 after IVA/TEZ/ELX initiation, pwCF aged 12 years and older showed improvements in ppFEV1 of [redacted] [6]. Improvements of [redacted]

[redacted] A lower annualised rate of PEx (proxied by IV antibiotic treatment episodes) was observed in pwCF treated with IVA/TEZ/ELX, with a [redacted] in the annual rate of PEx. In the IVA/TEZ/ELX cohort there was a low number of deaths reported with a rate significantly below the historical value reported for all individuals in the UK CF Registry, and an unprecedented low number of lung transplants across the entire IVA/TEZ/ELX study follow-up period. Other analyses, including nutritional outcomes, and prevalence of lung infections all showed improvements after initiation with IVA/TEZ/ELX.

In Section 3.2.2.6.2, the EAG has only reported one sensitivity analysis for the estimated mean annual rate of change in $ppFEV_1$ (i.e. excluding the Managed Access Program patients) from the UK CF registry data. It should be clarified that when using annual reviews only (i.e. excluding encounter data), the annual rate of change in ppFEV1 was [redacted] for IVA/TEZ/ELX, and [redacted] for the matched controls, amounting to a [redacted] in the rate of lung function decline vs ECM. As stated in the final analysis report, the sensitivity analysis based on annual reviews only may be more representative of outcomes due to the difference in data availability for patients treated with IVA/TEZ/ELX compared to the historical CFTRm-naïve group.

A reduction in prevalence for the four bacterial chronic lung infections was observed at first and second annual review post-initiation of IVA/TEZ/ELX (see Table 29 of the UK CF Registry June 2023 report) [6]. As reported in Liou et al. 2001 [27], infection with Burkholderia capacia is a major negative predictor of survival that is associated with accelerated pulmonary disease. Therefore, reduction in B. capacia infection following IVA/TEZ/ELX treatment would contribute to the reduced rate of lung function decline. Pseudomonas aeruginosa is generally the predominant infection in pwCF, which, when present chronically was virtually impossible to eradicate prior to the CFTR modulators being available [28]. Pseudomonas leads to impaired lung function and structural abnormalities [29] and is associated with failure to recover from a PEx to baseline levels of lung function [30]. The significant reduction is pseudomonas infection in patients treated with IVA/TEX/ELX is further evidence of the long-term benefits of treatment. It should be noted that the prevalence of chronic infection is unlikely to be impacted by the pandemic as these infections were present prior to COVID-19 and the restrictions and shielding would have no impact on clearing of chronic infection.

e) The EAG has taken an assumption-based approach for the estimates of rate of decline of $ppFEV_1$ for people treated with LUM/IVA and TEZ/IVA which is not substantiated by the robust clinical evidence. The EAG proposed the rate of change in lung-function decline for LUM/IVA is 0% (no benefit vs. ECM) and TEZ/IVA is (10.6%). This runs contrary to the available clinical evidence which shows that the rate of change in lung-function is 42% for LUM/IVA and 61.5% for TEZ/IVA.

As per our response to Questions A4a & 4b in the clarification response, preclinical data and prior experience with CFTRm support that acute improvement in $ppFEV_1$ likely represents improvement in mucociliary clearance and removal of mucus plugs; and after the acute phase, further improvement may indicate improvements in structural changes other than mucus accumulation in the airways. We would like to

reiterate that the LUM/IVA and TEZ/IVA rate of change estimates are based on clinical trial data (LUM/IVA: 24-week TRAFFIC/TRANSPORT and the 96-week PROGRESS OLE study [8]; TEZ/IVA: 24-week EVOLVE and the 96-week EXTEND OLE study) [7]. Patients in both trials had an acute improvement in lung function. The rate of improvement in ppFEV$_1$ has reached its maximum after 2 weeks of treatment, and the further numerical increase is much less prominent. Therefore, it is appropriate to exclude the spirometry measurements in the first 21 days and 22 days for LUM/IVA and TEZ/IVA, respectively, after treatment initiation to exclude the acute lung function improvements observed from the slope estimation. Patients who received LUM/IVA experienced a mean annual decline in ppFEV$_1$ of -1.33 (95% CI: -1.80 to -0.85), which was a 42% reduction vs the decline of -2.29 (95% CI: -2.56 to -2.03) observed in the untreated matched controls. Patients (F/F) who received TEZ/IVA experienced a mean annual decline in ppFEV1 of -0.80 (95% CI: -1.31 to -0.30), which was 61.5% lower than the decline of -2.08 (95% CI: -2.34 to -1.82) observed in the untreated matched controls [7].

With regards to the EAG critique of the use of registry data for propensity matching against the clinical trial data for LUM/IVA and TEZ/IVA, it should be noted that propensity score matching is a well-established statistical technique in the medical literature [31]. It serves to balance covariates among the clinical trial patients with registry patients to ensure the groups in comparison are well matched on the known predictors of disease progression [21]. To ensure the baseline characteristics are well balanced in the matching cohorts, a wide range of variables that are known predictors of lung function decline including demographics, nutritional measures, CF-related diabetes, pre-study medications, lung function measures and bacteriology were applied in our propensity scoring model. In addition, the inclusion criteria for the historical control included at least one stable encounter in the baseline year, which is indicative of no material change in lung function or routine medications from the prior encounter and no evidence of a care episode. This would have avoided the inclusion of patients with unstable control of CF to be included in the matching set. Moreover, the annual rates of change in ppFEV1 observed in the historical control cohorts (-2.29 and -2.08) are very much in line and consistent to what has been reported in the literature. The VOICE study [32] evaluated disease progression measured by ppFEV1 in a cohort of European CF patients prior to initiation of CFTRm therapy and estimated an annual rate of change of -2.17 (SE 0.30) for individuals ≥6 years. Therefore, we believe that comparing the clinical trial and registry data is unlikely to underestimate the relative rate of decline for LUM/IVA and TEZ/IVA compared to ECM.

Utilities and application of the treatment specific utility increment for IVA/TEZ/ELX

The CFQ-R is a validated CF-specific tool and has a preference-based scoring algorithm (the CFQ-R-8D) according to published guidelines by NICE, which enables estimation of CF-specific health-state utilities based on the CFQ-R. This is the appropriate tool for capturing QoL in CF. EQ-5D-3L is insensitive to CF (there are only 5 questions with 3 potential answers), hence the omission of the EQ-5D data which shows CF patients with severe lung disease to have a utility (0.85) higher than the general population (0.84) [12]. Application of a treatment-specific utility increment captures the additional non-respiratory benefits of treatment with IVA/TEZ/ELX.

Cystic fibrosis is a chronic severe disease experienced from birth. As such, and as has been recorded in CF and other similar conditions, patients may score unrealistically high on generic tools which are sometimes used to derive patients' quality of life. This is due to a phenomenon called response shift, where patients score highly on insensitive generic measures as they have never known a general population health state. Equally, there is a ceiling effect due to this response shift, which means that there is little or no room for improvement in the QoL scores if the patient becomes better, or their disease burden is reduced (i.e. if a CF patient scores 0.9 using EQ-5D, then any new therapy is limited in the additional utility it can deliver for that patient – limited by 0.1 given the upper limit of 1 denoting perfect health).

The EQ-5D tool, preferred by the EAG, is not appropriate for capturing the impact these medicines have in cystic fibrosis. The EQ-5D has been used in previous CFTR modulator clinical trials, but the data clearly demonstrate that this measure is insensitive: people with CF self-report a mean utility of 0.923 and 0.870 for mild and severe lung function impairment, respectively, which is considerably higher than the UK population norm of 0.856. For reference, patients with severe lung disease typically have trouble climbing a flight of stairs, often require supplemental oxygen, etc, which does not reconcile with higher HRQoL than the general population.

The CFQ-R is a validated, reliable, and more sensitive measure of HRQoL widely used in CF. Vertex developed a CF-specific, preference-based scoring algorithm (the CFQ-R-8D) according to published guidelines by the National Institute for Health and Care Excellence (NICE), which enables estimation of CF-specific health-state utilities based on the CFQ-R. The EAG even acknowledge the validity of this tool across multiple CF patient cohorts and carers.

The EAG have provided no justification for the exclusion of the treatment-specific utility applied to the ELX/TEZ/IVA cohort and TEZ/IVA (R/RF only) which was demonstrated by the CFQ-R real world data. Analysis of the real-world DCA study TRAJECTORY demonstrated that ELX/TEZ/IVA substantially improved CFQ-R utility values compared to study baseline providing further support to the treatment-specific utility increment.

The EAG also excluded the real-world DCA study MAGNIFY, which quantified the impact CF has on CF patients' caregivers. Day-to-day care of people with CF imposes a considerable burden on their caregivers and families. Collecting and analysing QoL from caregivers was included as part of the DCA agreement. The caregiver QoL was assessed using the Care-Related Quality of Life measure (CarerQoL), a validated questionnaire which showed an improvement in their QoL in addition to QoL improvements in the children they were caring for.

Furthermore, the DCA that is in place between NICE, NHSE, the Cystic Fibrosis Trust, and Vertex clearly outlines the collection of CFQR to address QoL uncertainties. This data was collected in our DCA report, as well as studies TRAJECTORY and MAGNIFY, to inform utilities used in our model to capture QoL improvements, carer utilities and a treatment-specific utility.

Discount rate

Vertex believes that the use of a differential discount rate (1.5% for health benefits, 3.5% for costs) is appropriate for decision-making. This is on the basis that uniform discounting undervalues medicines which incur health gain far into the future, particularly in chronic paediatric diseases. We note that NICE has in the past accepted use of differential discounting in an appraisal for a rare paediatric condition [19].

There are strong economic and ethical arguments in support of differential discounting [33-36]. It has been shown that if the monetary value of health benefits, such as QALY, is expected to grow, future additional costs will displace less health and a lower discount rate for outcomes would account for the future increase in the value of health, thus invalidating the consistency argument for the use of uniform discounting [37].

Ethically, uniform discounting risks undervaluing long-term health gains in decision making as it works against some treatments for chronic diseases characterised by accrual of health benefits for into the future [35, 38]. CFTR modulators are examples of such interventions which generate health benefits over long periods of time due to the lifelong and progressive nature of CF. Uniform discounting of costs and effects of CFTR modulators disproportionately impacts health benefits because costs are incurred from the first day of treatment initiation, when the impact of discounting is less while most health benefits accrue later and are therefore more heavily discounted.

The strong arguments in favour of differential discounting have shaped the national HTA guidelines of the Netherlands, Belgium and Poland, which recommend a lower discount rate for outcomes (1.5%, 1.5% and 3.5%, respectively) than costs (3%, 4% and 5%, respectively) [39], [40]. In its 2001 Guide to technology appraisal process, NICE was the first HTA agency to recommend differential discounting (6% for costs and 1.5% for effects) based on methodology of Gravelle and Smith [34], but these were later changed to equal discounting (NICE, 2004) [41]. In July 2011, however, NICE accepted differential discounting at 3.5% (costs) and 1.5% (benefits) per annum in the appraisal of mifamurtide for osteosarcoma, a rare disease that mainly afflicts children and young adults [42]. This example illustrates that in the past, NICE has accepted differential discounting to ensure an appropriate ICER for a drug that slows progression of a severe paediatric disease.

Severity modifier

Based on the EAG analysis, CF is not a severe disease. Given that patients in the UK currently have a median age of death in their 30s, Vertex maintains that this is an unreasonable suggestion [16].

3. Use of an alternative peer-reviewed and published model is required in order to inform committee decision-making

Given the concerns and evidence presented in this response, Vertex recommends the use of an alternative peer-reviewed model to inform decision-making. As acknowledged by the EAG, its model follows a similar structure and principles of the Vertex peer-reviewed model, which is deemed appropriate to inform committee decision-making.

Equally, the proposed model has received favourable feedback from several HTA organisations, including NICE (TA398), for its design and internal validity in modelling the disease pathway. Most recently the model was reviewed and gained successful appraisals from reputable HTAs in Canada, Ireland and Australia.

We provide a revised based case. This has been updated based on the EAG feedback, and the change in scope to include patients aged 2-5 years treated with IVA/TEZ/ELX since the original Vertex submission was made. All analyses were run with PAS prices, using active comparators (at PAS prices as well) in the relevant populations. Table 3 below shows the market shares used in the model analysis and Table 4 presents the weighted ICER of IVA/TEZ/ELX compared with the active comparators.

Table 3. Market shares of active comparators

Genotype	Genotype Prevalence	Intervention	Comparators	Market Share
F/F	54.3%	ELX/TEZ/IVA	[redacted]	[redacted]
			[redacted]	[redacted]
F/MF	29.0%	ELX/TEZ/IVA	[redacted]	[redacted]
F/Gating	10.6%	ELX/TEZ/IVA	[redacted]	[redacted]
F/RF	6.2%	ELX/TEZ/IVA	[redacted]	[redacted]

Table 4. Incremental deterministic base case results

VERTEX updated CEM for pwCF aged 2+ with F/Any genotype	ICER (population with F/F, F/MF, F/Gating and F/RF genotypes)
Model settings: • Baseline CF mortality from **Keogh 2018***	[redacted]

• Compliance [redacted]%* • ECM rate of lung function decline per Sawicki et al 2022 • CFQ-R-8D utilities • Differential discounting (1.5% for outcomes, 3.5% for costs) • Severity modifier of 1.7	

*Indicates EAG's preferred model inputs adopted by Vertex in the new analysis presented here, as explained in detail in Table 1.

In conclusion, Vertex does not believe the EAG *de novo* model or analysis is suitable for decision-making and instead proposes an updated base case is considered. Use of the EAG model and its results to guide decision-making is unreasonable and could lead to an unfair outcome from the appraisal. The updated base case analysis is preformed using a published and validated model and as such enables a more reasonable and robust way to estimate cost-effectiveness of the CFTRms in this evaluation.

References

1. Rubin, J.L., et al., *Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor.* Therapeutic advances in respiratory disease, 2019. **13**: p. 1753466618820186.
2. Lopez, A., et al., *Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del.* Journal of Cystic Fibrosis, 2023.
3. McGarry, L.J., et al., *Calibration and validation of modeled 5-year survival predictions among people with cystic fibrosis treated with the cystic fibrosis transmembrane conductance regulator modulator ivacaftor using United States registry data.* Plos one, 2023. **18**(4): p. e0283479.
4. Newsome, S.J., et al., *Using negative control outcomes and difference-in-differences analysis to estimate treatment effects in an entirely treated cohort: the effect of ivacaftor in cystic fibrosis.* American Journal of Epidemiology, 2022. **191**(3): p. 505-515.
5. Lee, T., et al., *Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis.* Journal of Cystic Fibrosis, 2023. **22**(3): p. 402-406.
6. Vertex, *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*. 2023.
7. Flume, P.A., et al., *Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study.* The Lancet Respiratory Medicine, 2021. **9**(7): p. 733-746.
8. Konstan, M.W., et al., *Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.* The lancet Respiratory medicine, 2017. **5**(2): p. 107-118.
9. Keogh, R.H., et al., *Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data.* Journal of Cystic Fibrosis, 2018. **17**(2): p. 218-227.
10. Szczesniak, R., et al., *Lung Function Decline in Cystic Fibrosis: Impact of Data Availability and Modeling Strategies on Clinical Interpretations.* Annals of the American Thoracic Society, 2023(ja).
11. Sawicki, G.S., et al., *Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation.* Pulmonary Therapy, 2022. **8**(4): p. 385-395.
12. Alava, M.H., S. Pudney, and A. Wailoo, *ESTIMATING EQ-5D BY AGE AND SEX FOR THE UK.* 2022.

13. Middleton, P.G., et al., *Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele.* New England Journal of Medicine, 2019. **381**(19): p. 1809-1819.
14. Tappenden, P., et al., *A model-based economic analysis of the CFHealthHub intervention to support adherence to inhaled medications for people with cystic fibrosis in the UK.* International Journal of Technology Assessment in Health Care, 2023. **39**(1): p. e6.
15. MacLachlan, S.R.D.L.J.L.R.A.P.C.S., *Predictors of Healthcare Costs for Cystic Fibrosis Patients in the United Kingdom.* Biennial European Meeting at the Society for Medical Decision Making, 2014.
16. Sokhi, S., *UK Cystic Fibrosis Registry 2021 Annual Data Report* 2022.
17. Doumit, M., et al., *Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic.* Journal of Cystic Fibrosis, 2023. **22**(3): p. 581-586.
18. Alqahtani, J.S., et al., *Reduction in hospitalised COPD exacerbations during COVID-19: a systematic review and meta-analysis.* PLoS One, 2021. **16**(8): p. e0255659.
19. *NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE-Final appraisal determination Mifamurtide for the treatment of osteosarcoma.* 2011.
20. Merlo, C., et al., *Long-term durability of ivacaftor (IVA) treatment benefit in people with cystic fibrosis (PwCF)*. 2022, Eur Respiratory Soc.
21. Sawicki, G.S., et al., *Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data.* American journal of respiratory and critical care medicine, 2015. **192**(7): p. 836-842.
22. Heijerman, H.G., et al., *Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial.* The Lancet, 2019. **394**(10212): p. 1940-1948.
23. Vertex. *A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation*. 2022; Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03525574.
24. Waters, V., et al., *Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis.* European Respiratory Journal, 2012. **40**(1): p. 61-66.
25. Nichols, D.P., et al., *Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: a clinical trial.* American journal of respiratory and critical care medicine, 2022. **205**(5): p. 529-539.
26. Mayer-Hamblett, N., *Greater Reductions in Sweat Chloride with CFTR Modulator Use are Associated with Improved Clinical Outcomes.* 2022.

27. Liou, T.G., et al., *Predictive 5-year survivorship model of cystic fibrosis.* American journal of epidemiology, 2001. **153**(4): p. 345-352.
28. Ramsey, K.A., et al., *Multiple-breath washout outcomes are sensitive to inflammation and infection in children with cystic fibrosis.* Annals of the American Thoracic Society, 2017. **14**(9): p. 1436-1442.
29. Hudson, V.L., C.L. Wielinski, and W.E. Regelmann, *Prognostic implications of initial oropharyngeal bacterial flora in patients with cystic fibrosis diagnosed before the age of two years.* The Journal of pediatrics, 1993. **122**(6): p. 854-860.
30. Bhatt, J.M., *Treatment of pulmonary exacerbations in cystic fibrosis.* European Respiratory Review, 2013. **22**(129): p. 205-216.
31. Rubin, D.B. and N. Thomas, *Matching using estimated propensity scores: relating theory to practice.* Biometrics, 1996: p. 249-264.
32. McKone, E.F., *Disease Progression and Burden in Patients With Cystic Fibrosis Homozygous for F508del Across Europe in an Observational Registry (VOICE study).* European Cystic Fibrosis Conference, 2019.
33. Van Hout, B.A., *Discounting costs and effects: a reconsideration.* Health economics, 1998. **7**(7): p. 581-594.
34. Smith, D.H. and H. Gravelle, *The practice of discounting in economic evaluations of healthcare interventions.* International journal of technology assessment in health care, 2001. **17**(2): p. 236-243.
35. Postma, M.J., M. Parouty, and T.A. Westra, *Accumulating evidence for the case of differential discounting.* Expert Review of Clinical Pharmacology, 2013. **6**(1): p. 1-3.
36. Paulden, M., J.F. O'Mahony, and C. McCabe, *Discounting the recommendations of the second panel on cost-effectiveness in health and medicine.* Pharmacoeconomics, 2017. **35**(1): p. 5-13.
37. Claxton, K., et al., *Discounting and decision making in the economic evaluation of health-care technologies.* Health economics, 2011. **20**(1): p. 2-15.
38. Brouwer, W.B., et al., *Need for differential discounting of costs and health effects in cost effectiveness analyses.* Bmj, 2005. **331**(7514): p. 446-448.
39. Attema, A.E., W.B. Brouwer, and K. Claxton, *Discounting in economic evaluations.* Pharmacoeconomics, 2018. **36**: p. 745-758.
40. Sharma, D., et al., *National healthcare economic evaluation guidelines: a cross-country comparison.* PharmacoEconomics-Open, 2021. **5**: p. 349-364.
41. *Guide to the Methods of Technology Appraisal-NICE.* 2004.
42. O'Mahony, J.F. and M. Paulden, *NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified.* Value in Health, 2014. **17**(5): p. 493-496.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

NICE National Institute for Health and Care Excellence

The deadline for comments is **5pm** on **19 September 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Cystic Fibrosis Trust
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Cystic Fibrosis Trust has received a total of £20,400.00 from Vertex Pharmaceuticals in the last 12 months to support key charitable activity to improve the lives of people with CF: • £6,000.00 for Clinical Trials Accelerator Programme (CTAP) Feasibility Services for VX21-522-001: A Phase 3 study evaluating for the pharmacokinetics, safety, and tolerability of VX121 / Tezacaftor / Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 years of age. • £6,000.00 for sponsorship of the UK CF Registry Annual Meeting 2022 and conference in November 2022 • £8,400.00 for a UK CF Registry epidemiology data request from 2021 cohort Cystic Fibrosis Services Limited, a subsidiary of the Cystic Fibrosis Trust, hosts the UK CF Registry and has received funding for ongoing pharmacovigilance studies and the HTA study agreement. The Trust have received no funding from any of the comparator treatment companies in the last 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Comments on External Assessment Report

Cystic Fibrosis Trust welcome the opportunity to comment on the External Assessment Report (EAR) as part of the Multiple Technology Appraisal (MTA) of Orkambi (lumacaftor–ivacaftor), Symkevi (tezacaftor–ivacaftor) and Kaftrio (ivacaftor–tezacaftor–elexacaftor) for people with cystic fibrosis (CF).

Cystic fibrosis is life-limiting genetic condition with no cure. Before modulator treatments, people with CF and their families faced a future of intense treatment, potential lung transplant and very early death. In October 2019, NHS England concluded a deal for access to Orkambi and Symkevi, extended in June 2020 to include Kaftrio.

Since these life-changing treatments have become the standard of care for CF, the CF community has experienced a huge range of benefits. Key changes identified in the UK CF Registry annual reports include:

- The median age at death has increased from 31 in 2019, to [redacted][1]
- The number of lung transplants performed on people with CF aged 16 and older decreased to less than [redacted][2] compared to 49 in 2019.
- The number of women with CF who had babies increased from 58 in 2019 to [redacted][3].
- The proportion of people receiving at least one course of IV antibiotics has dropped, with only 24.3% reported compared to 39.2% in 2020. This represents 1,418 less people needing IVs in 2021[4].

[1] Annual deaths reported in the UK CF Registry between 2013-2022 are reported in Table 26, p.67 of Study Report v2.0 June 2023, 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) submitted as part of this appraisal.

[2] The 2022 UK CF Registry Annual Report will be published by the end the month. 2022 data is therefore marked as academic in confidence as embargoed until 1st October 2023.

[3] The 2022 UK CF Registry Annual Report will be published by the end the month. 2022 data is therefore marked as academic in confidence as embargoed until 1st October 2023.

[4] UK CF Registry Annual Report 2021 https://www.cysticfibrosis.org.uk/sites/default/files/2023-04/CF%20Trust%20Annual%20Data%20Report%202021.pdf

The managed access programme and collection of real-world evidence makes this a unique appraisal. Cystic Fibrosis Trust encourages NICE to utilise all flexibilities in its decision-making to ensure all those who may benefit from these life-changing treatments can do so, now and in the future.
Cystic Fibrosis Trust is concerned that the EAR does not significantly appreciate the profound impact living with CF has on people and their families. As detailed in our evidence submission, 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 just [redacted][5], well below the UK population median age at death reported by the ONS in 2020 - 81.8 years for males and 85.5 years for females[6]. There is currently no cure for CF. Living with CF has a very high treatment burden, requiring medication and physiotherapy to stay well. Being unwell can interfere with work, education, and social activities – people living with CF describe there being no day off from relentless CF. Due to the build-up of thick and sticky mucus, looking after the lungs and keeping them clear is essential. Physiotherapy, whilst essential, can be a huge daily burden particularly alongside a rigorous regime of medicines and nebulisers. The 2017/2018 Cystic Fibrosis Trust Insight Survey found that on average, the time spent on daily CF care was 2.5 hours. 25% of parents of children with CF spent more than 3 hours per day on treatment. This seriously affects the quality of life for people with CF and their families. In addition to the challenging physical symptoms of living with CF, the condition has significant impacts on mental and emotional wellbeing, as detailed in our evidence submission, as well as the serious financial implications of living with a chronic, life-limiting disease. We are pleased to see recognition of recent research by the University of Bristol and Cystic Fibrosis Trust in the EAR which found that 59% of adults with CF surveyed noted that they had incurred loss in income due to needing to reduce work hours, attend routine

[5] The 2022 UK CF Registry Annual Report will be published by the end the month. 2022 data is therefore marked as academic in confidence as embargoed until 1st October 2023.
[6] Mortality in England and Wales - Office for National Statistics (ons.gov.uk) https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/articles/mortalityinenglandandwales/pastandprojectedtrendsinaveragelifespan#:~:text=The%20median%20age%20at%20death%20was%2081.8%20years%20for%20males,die%20in%20a%20given%20year.

appointment or leave employment completely. This research estimates that a typical family with a member with CF will lose £6,768 a year due to the additional costs associated with travel for medical appointments, prescription costs, dietary requirements, and higher energy bills. There are additional important findings which are not included in the EAR. For example, over half (59%) of adults with CF have incurred some form of income loss due to their CF in the past two years (including unpaid leave to attend frequent hospital appointments, reducing working hours due to exacerbations, and receiving a lower level of pay whilst sick), and that more than 70% (71%) had decided not to pursue training, education, or employment opportunities due to their CF. Over three-quarters (77%) of parents of children with CF had lost income (including taking unpaid leave, reducing working hours and giving up work) to manage the burden of caring for someone with CF. This research highlights that people and families living with CF are more likely to be struggling with their finances than the general UK population, and the high levels of anxiety around money, and the great efforts people with CF and their families make to keep themselves as healthy as possible, which comes at significant financial cost.

We are concerned that the impact of living with CF, an invisible condition, is not adequately appreciated in the EAR. As CF is a chronic, life-long condition, many of the CF community have told us that access to these treatments has, as well as keeping them alive for longer, significantly improved their quality of life. People with CF do not know what it is like to not have CF, and they didn't realise how unwell they had been until they experienced improvements in their health and quality of life after accessing these medicines, and in particular that they *"didn't realise how much CF impacted my life until Kaftrio took it away"* and *"I honestly didn't know people could breathe this deeply, I instantly felt like I was able to take bigger breaths and get more air into my lungs when I took a breath, which was just amazing to know how that actually felt for the first time in a very long time".*

Living with CF has a momentous impact upon quality of life, both for individuals living with the condition, and parents, families and caregivers. Cystic Fibrosis Trust highlighted the huge improvements in quality of life for people with CF and their families in our evidence submission, and we wish to emphasise experiences that we feel have not been adequately appreciated by and taken into account in the EAR: *"Before taking Kaftrio I was unable to work, depressed and had no long-term future. It is impossible to comprehend how psychologically difficult it is to cope with CF and the opportunities in life you must give up. Since taking Kaftrio I have my life back. I feel much healthier, and I am unbelievably grateful for what the NHS has done for me. I am only 32 but now believe I have my whole life ahead of me again."*

"My quality of life has improved out of all recognition: I have much more energy, can play with my kids, do my share of parenting, and even play sport. I can be fully engaged at work without having to worry that I'll need to disappear for weeks or months with zero notice. I

can breathe more easily, don't need to cough up sputum every day or constantly feel like I'm fighting infection. I was starting to feel like I was down to my last few years - now I can think about and plan for the future. It has truly been life changing."

"Within weeks of starting, my health was transformed. I am fitter and healthier than I have been in decades. I have reclaimed hours a day by not needing time consuming physiotherapy or nebulisers. I have been able to increase my work hours, go for a promotion, and provide security for my family. I have also had more time and energy to pursue hobbies, and interests. I can't imagine life without Kaftrio."

The UK CF Registry was amended at the beginning of the access period to include CFQ-R data, which was specified in the data collection agreement as a key data item[7]. Despite only one of the Orkambi clinical trials collecting EQ-5D data, the EAG has applied these values obtained from people with CF during this clinical study to all treatment arms in the model which we believe to be inappropriate. The EAG should recognise the CFQ-R data collected during the interim access period as this will accurately reflect the experiences of people with CF. Research published by Acaster et. al [8] reported that "EQ-5D-3L lacks sensitivity to meaningful differences in lung function and HRQOL among people with CF, with individuals self-reporting mean utility of 0.923 for mild and 0.870 for severe lung function impairment, which are higher than UK (0.856) and US (0.867) population norms. Although the EQ-5D-5L was developed to increase sensitivity, it has also been shown to lack sensitivity to changes in lung function among people with CF during pulmonary exacerbations. Relatedly, a mapping study found that the respiratory dimension of the CFQ-R was not a significant predictor of EQ-5D-3L utility, and utilities estimated from mapping to the EQ-5D-3L showed limited ability to discriminate between groups classified based on lung function in a disease largely characterized by respiratory symptoms". We are concerned that the EAG haven't recognised the limitations with EQ-5D, particularly when comparing scores to the general population.

The EAR later concludes that there is evidence to suggest Orkambi meaningfully reduces the long-term rate of ppFEV1 decline compared to established clinical management and that there is good evidence that Kaftrio reduces the long-term rate of ppFEV1 decline compared to established clinical management, we are concerned that by applying the values from the Orkambi study's EQ-5D, the transformative effect of Kaftrio in the real-world environment has not been captured in the EAR model, as detailed in our evidence submission.

[7] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement

[8] Sarah Acaster, Clara Mukuria, Donna Rowen, John E. Brazier, Claire E. Wainwright, Bradley S. Quon, Jamie Duckers, Alexandra L. Quittner, Yiyue Lou, Patrick Sosnay, Lisa J. McGarry, Development of the CFQ-R-8D: Estimating Utilities From the Cystic Fibrosis Questionnaire-Revised, Value in Health, 2022, ISSN 1098-3015, https://doi.org/10.1016/j.jval.2022.12.002.

Cystic Fibrosis Trust is disappointed that the EAR does not take into account the significant benefits people with CF have experienced since access to Orkambi, Symkevi and Kaftrio was agreed. As well as substantial changes in the UK CF population within the agreed outcomes of the appraisal, detailed within the EAR such as improvements in lung function and the heights and weights of people with CF, there have also been wider benefits experienced, highlighted in our evidence submission. These include increased energy levels and the increased opportunities access to these medicines has given people with CF and their families. Since starting Kaftrio, an adult with CF told us: *"It gives options which were never necessarily there before..."* and others told us *"We're all talking about a future"* and *"I feel positive about my future for the first time ever…which is a wonderful thing."* These options include increased opportunities for education, employment, starting a family and homeownership as well as a feeling of being able to contribute to society. There has been a remarkable increase in the number of women with CF becoming mothers over the past few years and a common theme in our research has been stories from people with CF who never thought they could start a family.

This is particularly poignant for parents of children with CF who told us they *"no longer think in terms of how long they will be able to work or even live. We can see a future for them"* and they are no longer planning funerals for their children. Parents told us how they have *"dreamt of a future"* for their child with CF for years, and that for the first time *"CF was not the first thing we all thought about."* Parents have wished they could *"go back to diagnosis day and tell those two very scared and devastated parents how CF will be significantly different one day and the future will be bright."* We have heard countless examples of parents and carers being able to return to work, children missing far less school and being able to plan holidays without bringing huge amounts of medical equipment with them.

The data collection agreement, agreed in 2019, identified specific areas of uncertainty from the original appraisal of Orkambi and recommendations made by a NICE-commissioned independent EAG. The length of the data collection period was agreed by all parties, including NICE, NHS England and Vertex Pharmaceuticals, to be four years. An Interim Access Oversight Committee (IAOC), including CF clinicians, was formed to oversee all aspects of the agreement, the protocol and to address any issues that arose during the data collection period. As part of the agreement, a series of reports were produced during the term to review the data collected and ensure it was proceeding as anticipated. These reports were reviewed by an external assessment centre at Newcastle upon Tyne Hospitals NHS Foundation Trust, with feedback and clarifications issued upon review. Following the licensing agreement for Kaftrio in 2020, significant revisions were made to the protocol including addition of Kaftrio within the planned analysis as well as additional summary statistics to describe the impact of the COVID-19 pandemic.

Reports provided included:

- An interim summary report in September 2020 to review the impact of the COVID-19 pandemic on the analysis plan and inform amendments to the data protocol.
- An interim analysis of primary outcomes for Orkambi and Symkevi in July 2021, reviewed by the Interim Access Oversight Committee and the Newcastle EAG.
- An interim summary report in May 2022 to determine whether the real-world data collection for Kaftrio was proceeding as anticipated and if the intended matched analysis to compare rate of ppFEV1 decline for people with CF prescribed Kaftrio compared to established clinical management was feasible.
- An interim analysis for all objectives in October 2022 for Orkambi and Symkevi. This report was a final analysis for Orkambi and Symkevi.
- A final analysis of all objectives for Kaftrio in June 2023 based on UK CF Registry data up to December 2022.

Despite intense monitoring by the IAOC and Newcastle EAG, no concerns were raised by NICE to Cystic Fibrosis Trust that the data collection agreement and agreed amended protocol were not acceptable to address the clinical uncertainties following the commencement of the COVID-19 pandemic. Cystic Fibrosis Trust is concerned the EAR does not acknowledge this significant monitoring, and subsequent amendments made by the UK CF Registry to account for the changes in the external environment and CF care landscape, and instead concludes *"Despite the availability of real-world evidence in the UK and elsewhere, analyses of these data were limited due to the uncertain impact of the COVID-19 pandemic on clinical outcomes and lung function of people with CF*". As highlighted by the UK CF Registry Research Committee and clinical members of the UK CF Registry Steering Committee, and referenced in the EAR, analyses to understand the impact of the COVID-19 pandemic on health outcomes for people with CF needs appropriate methodology and should be conducted over an appropriate time frame, of which the 2-year follow up period within the agreed protocol is unlikely to be long enough, particularly when both of those years overlap with the pandemic and government-imposed restrictions. It is concerning that this has only been recognised by NICE at the conclusion of the data collection agreement and not earlier in the process when it may have been possible to adapt the protocol and data collection period.

It is concerning that the whole portfolio of results using the UK CF Registry data (for the above agreement) has been dismissed because of the overlap with COVID-19 pandemic, in favour of, for example, an estimate of rate of decline in ppFEV1 from one Registry-based study on Kalydeco (Newsome et al). Even if the results in the final report are considered an underestimate of the rate of decline in ppFEV1, we feel a sensitivity analysis using a range of values from the final report should have been conducted within the EAR.

The EAR references the results of a data request to the UK CF Registry, to support their opinion that "*it is likely that a sufficient number of people in the UK CF Registry who were not receiving Kaftrio, Orkambi, Symkevi or Kalydeco may have been available to measure the impacts of the COVID-19 pandemic on lung-function decline in people with CF, but notes that such an analysis was not undertaken."* We are concerned that the figures provided have been overinterpreted. For example, the number or people with at least one annual review between 2019 and 2021, aged 12 years and older with no recorded Kaftrio use between 2019 and 2021 will not necessarily be the same number as those with ppFEV1 data available for the whole period of study with well-defined inclusion/exclusion criteria. Cystic Fibrosis Trust is not aware of any published evidence yet from the UK to confirm the assumption that shielding during the COVID-19 pandemic resulted in improvements in lung function for people with CF. The research referenced by in the EAR by Doumit et al. was conducted in an Australian cohort. The government restrictions within Australia differed to the UK, including differences in lockdown restrictions and border control measures only lifted in early 2022[9]. The EAG also reference the changes observed in a CFTR modulator naive cohort, possible in this Australian study as access to these therapies was not available for most at that time. It is unclear how generalisable these results can be to the UK population with the differing lockdown restrictions, but primarily with the numbers receiving a modulator in the UK during this time period, and the resultant improvements in health outcomes that come with that (6208 in by end of Dec 2020 – UK CF Registry Annual Report 2020). It would only be possible to fully understand the impact of the COVID-19 pandemic on people in the UK by undertaking appropriate research on the UK population.
As highlighted in our evidence submission, over many years, CF lungs become increasingly damaged, and the ultimate goal of CF care has been to prevent as much decline as possible. Access to modulator treatments will result in a generation of children and young people with CF growing up healthier than ever before and with a different disease profile to those who have started modulator treatment in later life. Cystic Fibrosis Trust welcomes the view of the EAG's clinical experts, who noted that if Kaftrio is *"initiated in very young patients, such as age 1 to 2, this may avoid long-term lung damage and could potential provide "near normal" lifetime lung function. Therefore, an incident CF population that begins treatment prior to any irreversible lung or pancreatic damage may experience greater benefits in treatment."*
The EAG model does not include data on changes in infection rates over time due a lack of available data on prevalence rates. People with CF and their families highlighted reduced hospital admissions and reduced use of antibiotics as a major change to CF care since they have had access to Orkambi, Symkevi and Kaftrio. The CF community told us: *"Since I've been on Kaftrio, I've been in for other hospital*

[9] Doumit M, Chuang S, Middleton P, Selvadurai H, Sivam S, Ruseckaite R, et al. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic. *J Cyst Fibros* 2023; **22**: 581-6.
Covid-19 in Australia: How did a country that fought so hard for extra time end up so ill prepared? | The BMJ

admissions, but I haven't been in for a chest exacerbation or chest infection. So that's a big difference in that because I would tend to go in probably two to three times a year depending on, you know how things were." *"I went from having IVs sort of every 10 to 12 weeks…It was three years before I needed to have another set of IVs".* This has had a significant impact on health stability and quality of life, and despite not being included in the EAR model due to a lack of available data on prevalence rates, represents a significant benefit of CFTR modulator treatment, as recognised by the EAG's clinical experts.
Cystic Fibrosis Trust believes it is inappropriate to use long-term data from Kalydeco to approximate the long-term rate of ppFEV1 decline for people with CF who are treated with Kaftrio, Symkevi and Orkambi. Single therapy Kalydeco is indicated for different CFTR mutations and therefore the patient populations and long-term outcomes of those receiving Kalydeco or Kaftrio, Symkevi and Orkambi are likely to be very different, not least in the frequency of people with CF with homozygosity or heterozygosity for responsive mutations.
As Cystic Fibrosis Trust have consistently advocated; this appraisal is unique, given the large amounts of real-world data available following the widespread use of modulators. Cystic Fibrosis Trust encourages NICE to consider all types of evidence in its evaluations and utilise all flexibilities in its decision-making to ensure all those who may benefit from these life-changing treatments who are not currently taking them can do so in the future. Without that we will see people with CF experiencing significant deteriorating health and dying knowing there is a treatment that could save them

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Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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The deadline for comments is **5pm** on **19 September 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	CF Voices
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Comments on External Assessment Report
The over-riding comment on this report from a CF Voices perspective is one of disappointment. After fighting so hard for access to these drugs for our loved ones, on the basis that their impact needed to be assessed across a longer period of time than is possible in short-term clinical trials, it is disheartening beyond comprehension that the NICE data collection which involved such a lot of work by clinicians, CF Trust, NICE, Vertex and involved CF Voices on the oversight committee, is hardly apparent. The data from that process is mostly mentioned to be dismissed due to the timing and a conclusion of a 'Covid-19 confounding effect'. Other vital data, such as sweat chloride changes, which cannot be skewed by the pandemic other than in the completeness of the data, are questioned and due to the heavy redaction of this report, a clear picture cannot be seen. It is hoped that the NICE Committee can gain clarification where required and that with full sight of the final data collection analysis will adopt a pragmatic assessment.
Most of this AEG report refers to short-term pre-2020 clinical trials. It bears little resemblance to the impact that access to these medicines is having in real life now and since access was granted – changing the whole nature of living with CF, for the vast majority of patients and their families. Reading this report has been like being transported back in time to when arguments over small percent points of improvement in Fev1 were seen as the primary, almost only, issue and not the current time when lives have been transformed (normalised to a large extent) for thousands of families in ways that we could only have dreamt of and CF care within NHSE has changed forever.
Comments per page/section:
Page 6 – LUM/IVA was available for people aged 6+ years since October 2019 **ELX/TEZ/IVA – states two years – 'since August 2020 2019' – clarify as August 2019 compassionate access, August 2020 marketing authorisation**
Page 8 – Why is the only quality of life data taken from EQ-5D questionnaire taken during a short-term trial of LUM/IVA? Where are results from Vertex QoL research and CF Trust data?
Page 9 – mentions the 'unforeseen COVID-19 pandemic likely had a strong confounding effect on clinical trial data and real-world evidence collected during periods of viral shielding' which is used to suggest a high risk of bias and effectively seems to rule out inclusion of most of the data collection. While no one would argue that there is not a positive effect on Fev1 from fewer viral infections, there is also an unquantified negative impact on Fev1 by lack of exercise, and at times for many, any

opportunity for physical activity by CF patients during shielding. CF patients and their families were advised not to leave their homes during the early period of the pandemic and for those in shared accommodation, this meant hardly leaving their bedrooms for extended periods. CF patients were told not to take the daily exercise that others in the population took to retain an element of physical fitness and actively use their lungs. CF patients, many of whom previously had relied heavily on a high level of exercise to maximise lung function were forced into a sedentary lifestyle during this period and many children and their parent/carers were denied the hands-on tutorage of active breathing and airway clearance techniques that help to improve lung function in young children. Even in the case of having IV treatment, there is evidence to show that the intervention of physiotherapists as available when treatment takes place in a hospital setting, rather than at home, leads to improvements in Fev1 (Bradley et al 1999). The impact of Covid-19 seems to have been considered very one-dimensionally by the EAG in this report.
Page 10 – Additional uncertainty – it's extremely disappointing that these weren't answered by the Data collection agreement which was set up specifically to address the uncertainties identified previously. **Where is the data on 'patient and caregiver quality of life impact, including age-related differences' specified in the collection agreement?** **The rate of co-adherence to non-CFTR modulators is uncertain and should be considered in part due to caution shown in clinician-led reduction of other treatments in lieu of clinical trial evidence to support safety e.g. of stopping DNase (pending results of the STORM study). Patient-led non-adherence to non-CFTR modulator therapies is less easy to monitor but has undoubtedly occurred.** **Adverse events through mental health outcomes that led to discontinuation should be trackable through CF registry data/data collection agreement. In some instances, these adverse symptoms were alleviated through dose adjustment (e.g. not taking evening dose of IVA), something which merits a study in its own right as taking lower doses of ELX/TEZ/IVA has been shown to not negatively impact Fev1 or other clinical measures in many patients in the UK and worldwide.** **Page 35 – why is genotype data redacted?** **Page 37/38 – Comparative nature of reported health-related quality of life between people with CF and healthy controls in 2 x clinical trials shows the EQ-5D asks the wrong questions for patients with a complex, life-long condition such as CF and that short-term collection is inappropriate. CF Voices research, quoted on page 37 explains the multifaceted, often decades-long impact of the condition on CF carers which affects whole families. Long-term pessimism is a major debilitating factor in the mental health for carers of untreated patients and is ill-captured by the EQ-5D questionnaire.**

P55/56 Relevant comparators for IVA/TEZ/ELX: In pwCF aged 6+ homozygous – ECM without IVA/TEZ/ELX – this would presumably be with LUM/IVA or TEZ/IVAfor most patients after October 2019?
P61 – Is Vertex's analyses in response to Clarification question A26 available to the Committee?
P62 – 'The EAG considers that inhaled mucolytics…are therapies that individuals receiving a CFTR modulator would still be eligible for, and would still receive, should their symptoms require' – however, these drugs are still being prescribed whether symptoms are apparent or not because there is no verified data to support their safe withdrawal and most clinicians are waiting for the results of studies such as STORM. The benefit to NHS of cost reductions on these treatments cannot yet have been fully realised because of this. Rather, early savings would be made from younger patients not starting on drugs such as DNase which have traditionally been taken for life after commencement of the therapy. As noted 'CFTR modulator therapies are an addition to all the established clinical management therapies available' and this is why even a two-year data collection period cannot fully reflect the impact on clinical practice and hence savings to NHS from access to modulators, with the drugs initially being given to a population with extensive existing disease and irreparable damage to multiple organs.
P62/63 it is very disappointing and simply wrong in terms of wider costs to the NHS to disregard the impact on carers as an outcome. CF Voices research March 2020 submitted as part of our initial submission for this appraisal details the many ways in which carers physical and mental health is impacted by CF and has been transformed where patients were receiving treatment.
P63 – 'EAG's clinical experts also noted that any reduction in pulmonary exacerbations would be meaningful for a person with CF, given the likelihood that treatment..will require IV antibiotics..' – this is true also for carers, but also not only when flare-ups end in IV's. Without effective modulator treatment every viral episode will result in stress, anxiety, increased need for airway and nasal clearance possibly up to 4-5 times a day for 2-4 weeks (incl. hypertonic saline/nasal douche/steaming) other sinus treatments, anti-inflammatories, pain killers, lack of sleep, upset to insulin needs if diabetic, increased use of supplements, mealtime issues, sputum testing – all of these occur with or without the subsequent need for antibiotics. Only the episodes that eventually lead to drug therapy are recorded by clinicians/trials, but all episodes typify and dominate the life of CF carers and patients leading to a permanent fear of infection (heightened in autumn/winter, at hospital visits, in communal settings such as educational/childcare, at family/group gatherings). The gradual removal of this fear as patients have become so much more resilient and robust through treatment with modulators and are now able to shrug off a mild 'cold' in 2-3 days like healthy people can, is one of the singularly most meaningful changes in living with CF. Marginal changes in Fev1 have a much lesser if any, effect on lived experience.

P64 – Equality – it is noted that socioeconomic status is a predictor of outcomes for people with CF and this is not surprising given that the standard of care given by CF carers from the birth of patients will depend much on the carer's available time/resources and ability to care. Carers who struggle to survive financially without working part or full-time or who have several other children to care for have less time to give to care for patients. If a carer is trying to subsist on a carers allowance they are likely to be mentally much more stressed. Families with less disposable income cannot afford the extra supplements/physio aids including things like trampolines and sports club memberships that more affluent families can which benefit the lung function of their children with CF. Carers with a higher educational level and more time on their hands often spend hours researching non-standard treatment options to discuss with clinicians, they can find the best home treatment regimes and buy, even import non-prescription equipment, supplements and medicines. Living in an area with poor air quality, with less space and opportunity to exercise, will impact people with CF. **Hence, amongst the eligible population, CFTR modulators have a great capacity to improve equality because they massively improve resilience as well as Fev1 and the 'extras' that cost time and money are less important or not needed at all.**
P71 – not sure why the development of CF-related diabetes is not in the NICE scope as the condition has a life-long and substantially negative impact on patient and carers lives. Empirically, modulators appear to have prevented some patients who were on the cusp, from developing CFRD and others with a new diagnosis have been able to stop or reduce insulin.
P89 – as mentioned at the start of comments, the amount of data discounted by this report diminishes the data collection agreement and the single-arm clinical trials from 2020 onwards. This is disheartening and we urge the Committee to assess the data pragmatically with a measured approach to Covid-19 confounding effects.
P91 – we can't see the sweat chloride improvement in some sections but can do for ages 6-11 in Table 21. This massive improvement shows how modulators are making the bodies of children with CF work more normally – in many cases, they are now within normal range and would test negative for CF if diagnosed blind today. In the real world, this translates to people who can live largely normal/regular lives. Despite many needing to maintain existing treatments due to chronic infections or CFRD, they no longer need daily airway clearance as sputum is normal. The interruptions of frequent illness have been taken away and these children and their carers are able to achieve high levels of attendance at school for the first time, keep up with their friends in sport, not be scared of getting a cold or Covid, their Mums and Dads can work full-time (perhaps for the first time), can hope for their kids to complete college/Uni and have a full adult life with aspirations that they previously did not have. Outside of and because of these statistics is the transformation of thousands of lives – the fear has been replaced with hope. Please don't forget what these endless tables and statistics mean in real life, because the impact is amazing.

P112 + 115– important point that the ceiling effect of patients with high Fev1 show that this measure is of limited importance in this subgroup. As noted, 'for people with preserved lung function..the benefit of CFTR modulators..may be more visible in the prevention or delay of lung function decline'. Not only does this mean that patients can hope to live longer but coupled with having normal mucus and the resultant greater resilience to illness gained by modulator treatment, children treated from age 2 will never require the level of CF care that their forerunners have experienced. This will be the case even if some pancreatic insufficiency has occurred by this point. Their carers will never have the care burden, the hopelessness, fear and stress caused by a loved one having untreated CF – it will be a manageable condition. The savings to the NHS will then be fully realised and only then. This is why it's so important that younger patients are not omitted from the NICE recommendations. They and the NHS have the most to gain from starting treatment – a high level of prevention – as noted that with routine commissioning nearly all eligible patients would be taking up treatment before declining to the severe disease state (unlike the current situation whereby 18% of patients had Fev1 lower than 40%)
P132 – 'it is likely that ECM was less optimised in..early ivacaftor trials' however also states that inhaled hypertonic saline use was substituted by DNase use – where is the evidence that one is more effective than the other to inform the assumption that ECM was less optimised?
P141 – 143 – 'currently the EAG considers all available sources of rate of decline in Fev1…to be at high risk of bias…covid-19 pandemic' while this is understandable we urge that the Committee not just dismiss all data and take a balanced view. Other data is stated as plausibly 'not missing at random' – precisely what does this comment allude to?
P144 – why is this registry data redacted? The use of people with gating mutation treated with IVA since 2012 to guess responses in people with at least one F508Del seems strange and without a firm basis.
P159 – Key issues and uncertainties – again this is very disheartening given that the NICE data collection agreement was set up to provide certainty and now appears to be disregarded by the EAG. We urge the Committee to take a more enlightened and pragmatic viewpoint on the results in the final analysis of the data collection. The reason these drugs were supplied through managed access – aside from the extremely high acquisition costs - was to evidence the longer-term impact of CFTR modulators through the data collection agreement, because of the obvious limitations of short-term trial data for life-long therapies. While it is imperative that Vertex is realistic in its pricing, it is also vital that NICE and NHS recognise the full impact on patients, families and the long-term changes to CF care that have already begun in response to the widespread health gains from treatment of the current population, many of whom had substantial disease. Most

importantly, to appreciate that the full value of prescribing CFTR modulators to all parties will come in the future with earlier intervention.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Quest for a CF Cure
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**NIL**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**NIL**

Comments on External Assessment Report

We have read the EAG report and have the following 4 points to make and comment on.

Whilst the data is very thorough and complete it does not reflect the real-life quality of life improvements. The difference that these drugs, in particular the triple therapy drug, has made to patients' lives is incomparable to any other drug or combination of drugs on the market. It is the difference between a disease where the patients are struggling with the effects of the symptoms which the patients will succumb to and die AND having a disease that you can modify to greatly reduce and in a lot of cases switch off the symptoms making it a manageable disease. Cystic Fibrosis becomes manageable with these drugs instead of terminal. They are nothing short of 'miraculous' to those who live with this disease. In case studies and surveys, we have gathered the following comments:

It's completely life changing. Finally, I can start thinking about what I am going to do with my life instead of the next hospital stay – and whether I will survive it and get out.

I can look forward to a future instead of worrying about dying.

I now have an opportunity that I didn't think was possible, I can plan for a future, I now have the motivation to stick in at school, go to university and get a good job.

Without access to these drugs, we will die.

I would love to have had these drugs when I was younger and to have been able to prevent and stop the deterioration and impact of the progression of CF

With regard to this last comment, it is most important that all children born with cf have access to these drugs and have the best treatment available. It is necessary that those children who have little lung and organ damage are given access and start these drugs without delay.

The data in the report has not taken into account the transformational positive impact on quality of life due to a significant increase in fertility and family planning. There has been a huge increase in fertility among females and pregnancies within the CF community. As stated in the report, there is a 'psychological burden of disease for people with CF, including burden associated with infertility'. 'Infertility can be associated with stress, anxiety and depression'. In one specialist CF clinic alone, there has been over 500% increase in pregnancies since these modulators became more accessible. The increase in female fertility and being able to have a 'normal' life with a manageable disease and a future to look forward to, has allowed patients, male and female, to plan to have families. This has not been expanded upon in the report but we do feel it is a hugely important factor in quality of life.

The established methods of cost saving measures cannot and do not show the knock on / “ripple” effect on the quality of life obtained by not only the patient but their care givers, their siblings and wider families. The savings to their community and their contributions to society are not taken into account. (Many caregivers and family members of those with CF are also given a greater quality of life. They have new opportunities both at work and at home as a result of not having the huge burden of caring for someone with CF or having parents/partners who are absent due to CF caring responsibilities.) We do accept that due to shielding in COVID, the collection of data and those results may not be as valid as they would be. Many clinicians would have been wary and would not have reduced the other many medicines prescribed to patients. It is likely, based on the patients we have been in contact with over the last year and since COVID, that most patients have now had a huge reduction in treatment burden and medicines. Some examples are: the prescribing of prophylactic antibiotics; prescribing of DNase and mucus thinning meds; removal of port-a-caths due to regular in patient and home IVs being discontinued; removal of feeding tubes as result of being able to maintain a healthy body weight. (The reduction of the outpatient care the latter two involve, has been removed) etc. In summary, whilst the effects of COVID could have appeared to have produced a more positive result, the cost savings now will be much greater than actually reported.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

External Assessment Group Report consultation response form

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	ACPCF
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Educational grants received to support annual ACPCF educational study days; Grants received from; Mylan/Viatris, Vertex, Chiesi, PARI, Aerogen and Trudell Medical (£1,800) and £1000 from TEVA. All sponsors in turn received an educational stand for the duration of the event where they could engage and network with the membership. Non-Medical Prescribing consortium of funding has also been formed with grants of £2,000 (each) from PARI and Gilead. Grants have been agreed but are currently outstanding from Zambon and Vertex. [redacted] has received honorarium/expenses from: · Insmed for advisory boards and speaking at educational meetings · Chiesi for speaking at educational meetings · Zambon for travel and accommodation for meetings · PARI medical for travel and accommodation for meetings [redacted] has received honorarium/expenses from: · Vertex Pharmaceuticals for creating educational content and speaking at educational meetings · Chiesi for advisory boards, creating educational content and speaking at educational meetings · Gilead Sciences for creating educational content and speaking at educational meetings

	· Zambon for consultancy work · PARI medical for travel and accommodation for meetings.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	NA

Comments on External Assessment Report

The MTA Process

- We do not feel that the process outlined by NICE regarding this consultation has been followed;
- We have concerns that, although ACPCF was registered as a stakeholder and received an invitation to the meeting held on the 22nd of February, we did not receive and information about the draft remit and draft scope consultation and were not able to comment on the protocol.
- We are aware that a number of other key stakeholder groups were also not involved in the process until this late stage.
- Stakeholder engagement throughout this process is crucial to ensuring a fair and comprehensive review, and we feel that this opportunity has been missed.

The MTA protocol

Had we have been given the opportunity to comment on the protocol we would have suggested the following:

- Inhaled antibiotics and airway clearance are not included within the scope or protocol as a comparator or as part of best supportive care. Both of these important aspects of care are clearly established and, particularly for inhaled antibiotics, evidence based clinical practice.
- Quality of life is an incredibly important outcome measure for this review and should have been considered a key outcome measure. Our clinical experience has shown that this is where some of the greatest gains have been made, both in and out of the respiratory domain.
- The reliance on EQ-5D (rather than CFQ-R) means that a substantial amount of literature and data will have been missed as the majority of work in this area will use CFQ-R.

Timing of the review

- With the Covid-19 pandemic rendering real-world data difficult to interpret, with such an important treatment, we firmly believe it would be safer and more sensible to delay this review, for a short time, to allow post-pandemic, real-world data to be collected and utilised.
- By only using trial data, and not using real-world data in this review, the outcomes analysed are for a highly engaged population who participate in and adhere to clinical trial protocols, and therefore do not represent the wider CF population and their potential outcomes. This further supports delaying this review.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Cystic Fibrosis Dietitians Specialist Group of the British Dietetic Association
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Nothing to disclose**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Nothing to disclose**

NICE National Institute for Health and Care Excellence

Comments on External Assessment Report
Whilst it has been well documented about the improvement in weight and BMI, there is no discussion about the benefits we are seeing in real life terms and the cost implications. Due to improved weight gain, patients are using less prescribed oral nutritional supplements. There have also been patients who have had gastrostomy tubes removed. This all has a cost saving to the NHS. These reductions in numbers have already been acknowledged if you look at the UK CF registry data on pt use of nutritional support over the last few years. There is also savings being made had these drugs not been available and more pts requiring more aggressive nutritional support. **It is also documented that vitamin supplements are part of standard CF treatment. Again, in real lif and some studies now published, some patients have been able to reduce vitamin supplements. This is also true of pancreatic enzymes. Both will have a cost saving within the NHS.**

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Cystic Fibrosis Nursing Association (CFNA)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Comments on External Assessment Report
It is important to note that despite being listed as a stakeholder, the CFNA was not included in the initial process, missing important opportunities to provide feedback. This is the first opportunity the group has had to provide input. We have approached this on a patient focussed basis with our response reflecting our lived experiences in practice. Also, of note this is a very large document, limited time was given for review, with no opportunity for the wider CFNA committee to comment. Redacted data limits opportunity to fully review. Primary outcome identified as FEV^1, weight and exacerbation is of concern as it does not give priority to quality of life (QoL). Although weight is recognised as important, and there is recognised link between weight and FEV^1, this does not however make it a priority within this review where the wider effects of weight are far less than that of QoL. There are many recognised formats for measuring QoL and this is done regularly within CF. This has been one of the areas of the greatest impact for people with Cystic Fibrosis (CF),and has wide socio-economic impact. Data is available to reflect this, yet not included in this review? Patient case example: FEV^1 30-40%, requiring intravenous antibiotics, Poor QoL. Unable to work, living in social housing, approx. 40 CF hospital apts per year 2022- FEV^1 58-63%, no requirements for intravenous antibiotics, reduced insulin requirements, working full time, mortgage and house purchase, approx. 8 CF appointments per year The wider socioeconomic effects of this one patient leads to a reduced demand on social housing, reduced unemployment and reliance on benefits. Seen throughout adult practice, yet not reflected in this report. Reference was made to the increased unemployment within parents of people with CF, yet this was not reviewed further after the introduction of modifiers. As above, employment rates within those with Unemployment rate in 2020 847 (14.1), 2021 791 (12.6) (CF Trust, 2022, Annual Report 2021)

References made to reduced adherence to other medications are misrepresented. Within practice reduction in nebulised therapies is a result of reduced need, not a reflection of adherence. This is also seen with reductions in the need for other medications such as pancreatic enzymes and insulin, which are not included in this report.

Patient case examples:

[redacted]

Omitted from this study is any reference to the increase in pregnancy rates from 56 in 2020 to 103 in 2021 (CF Trust, 2022, Annual Report 2021)
Reference is made to transplant costs (page 228, Table 73), however there is no reference to the reduction in double lung transplant rates from 175 in 2020, to 78 in 2021. 2022 data suggests there were only 5 transplants for people with CF.
We have seen increased numbers of removal of totally implantable venous access devices (TIVAD) and other central venous access devices (CVAD). Decreased numbers of patients having new TIVAD/CVAD inserted.

Concerns over clinical information vs practice, danse is used regularly in children under 5's years old. Many treatments and medications within CF used off-licence/label.

In summary, despite a robust systematic review process, we do not feel this is reflective of our lived experiences within both adult and paediatric CF care and omits areas of clinical significance.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK CF Medical Association
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**No Conflict of Interest**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Comments on External Assessment Report

The CFMA executive committee has reviewed the draft EAG.
We acknowledge that it is a comprehensive review and that overall the methodologies are robust, especially the systematic review of RCT data.
We have several comments,

1) The conclusions do not appear to be consistent with clinical trial data and the real-world experience of our patient population
2) The authors have chosen the following primary outcomes, change in FEV1, PEx rate and Weight for their systematic review. Change in FEV1 is an extremely valid measure of respiratory condition and a good primary outcome. Pulmonary exacerbations are important to people with CF, but difficult to measure precisely and prone to misinterpretation. The rate of PEx is an important secondary outcome. Nutritional well being is a key metric in the outlook for people with CF, and weight provides an insight into this, but needs to be considered in context. It is an important secondary outcome, but complex, in that excessive weight gain has been experienced by some patients on ELX-TEZ-IVA, which may be an undesirable outcome.
3) Quality of life is the most important outcome for people with CF and the one that best reflects changes in their lived experience. This outcome is virtually ignored in this review, despite being measured in all the RCTs. This likely reflects the use of a CF-specific tool (CFQR). Whilst disease specific tools do not sit comfortably within HE assessments, they provide a valuable insight for our population. The change in CFQR score reported in the ELX-TEZ-IVA trials is of a magnitude not seen previously in CF trials (except the smaller trials of IVA for eligible patients more than ten years ago). Generic QoL measures, such as EQ-5D, do not represent accurately the lived experience of our patients, this reflects their resilience and ceiling effects.
4) Modelling for longer term impact should consider real world data regardless of the pandemic. These data, some requested by NICE, provide a valuable insight. We do not agree with the assertion that it is “impossible” for FEV1 not to decline year on year, especially when the underlying CF defect has been corrected.
5) The final model presented should be exercised with the current NHSE price for ELX-TEZ-IVA, rather than the market price. We appreciate the upcoming sensitivities of price negotiation, but that calculation would give a truer reflection of costs for our patient population. We agree with the disease modifier used (1.2) and the reduced discount (1.5) employed in the final model, although this is complex given the potentially very long term impact of ELX-TEZ-IVA.
6) The report notes the difference in efficacy between dual and triple modulator therapy, but the structure of the summary and some of the content tends to conflate these analyses. It is important that the report clearly presents the results of these agents separately, especially when it is published to avoid confusion for the lay reader (for example in the plain English summary).
7) The report should be more critical of the trial data in pre-school children and the fact that these interventions have only been assessed with observational (albeit intense) studies in this age group, which leads to bias in the assessment of efficacy. The authors classify these trials as “high risk of bias” but do not reinforce this in the summary statements.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	United Kingdom Cystic Fibrosis Pharmacy Group
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

NICE National Institute for Health and Care Excellence

Comments on External Assessment Report
Page 223 – "One of the EAG's clinical experts (senior dietician) advised that the costs and dosages associated with supplementary feeding is extremely variable between both patients and centres within the UK. Due to this, the EAG is unable to apply an average cost of supplementary feeding and therefore has excluded this from the overall ECM costs." We understand the rationale for this, but do wonder if that might be a not insignificant cost for e.g. those with a PEG. Plus presumably the cost of inserting a PEG in the first place. So excluding these costs will likely reduce the cost effectiveness of modulator therapy and these costs should be considered.
Page 226 - IV drug costs are quoted as approx. £27 per day. While this may be accurate for the quoted antibiotic regimen it is noteworthy that this is one of the first line, simplest and least expensive regimens. Given the availability of newer more expensive agents, while their use is restricted to complex resistant organisms with the approval of microbiology colleagues, the average costs of intravenous antibiotics in the CF population is likely to be higher than that quoted. With regard to these drug costs, we would also suggest there needs to be some clarity about the costs of the episode of care vs the costs of drugs administered during the episode of care, which will be a cost to the admitting Trust but contained within the overarching year of care tariff the Trust receive.
Page 10, 231 – The document refers to the EAG preference to assume a 37.70% reduction in $ppFEV_1$ decline compared to ECM. We as a group don't recognise that figure and how the EAG came to that conclusion. We also don't agree with the company assumption of 100%.
Page 11 – States "If multiple treatments are made available in clinical practice, it is unknown if patients may switch between CFTR modulators once they reach the age at which a more effective treatment holds marketing authorisation". We have managed this situation in clinical practice for some time in younger patients and have found that there is variation in what people with CF choose to do, but that there is a general movement towards ELX/TEX/IVA in those people for whom it is available (and who were previously on LUM/IVA particularly).
General Comment – While we appreciate the confounding situation with respect to the Covid pandemic, it seems impossible to ignore that there is clearly an effect of widespread modulator therapy on the need for treatments for PEx and hospitalisation. It may be impossible to truly separate the two causes, but that doesn't mean that there has been no effect of the treatments, which appears to be implied as the reason for disregarding any possible effect.
General Comment – One significant change we have noted in clinical practice is a remarkable increase in people with CF having children since the introduction of modulator therapies which is not considered within the report. Specifically on the rate of pregnancy within female people with CF.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

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Thank you for your time.

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK Psychosocial Professionals in CF (UKPPCF) Committee
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
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Comments on External Assessment Report
We were disappointed to see that the impact of modulators on quality of life was not given more weight within the current document. Even when it was considered, the tools used may not capture the improvements that have been seen in this population. This is an area of clinical complexity as highlighted by these qualitative studies (Keye et al, 2022, Chronic Illness, The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy; Aspinall et al, 2022, International Journal of Environmental Research and Public Health, Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis) and the themes reported in these studies are not captured within tools such as the EQ5D or CFQR. Our clinical experience is that for many people with CF, modulators have led to an unprecedented paradigm shift for them in terms of their perceptions and beliefs about their health, themselves and the future. With increased stability in people's health and therefore improved access to school, further education, employment opportunities etc one could hypothesise that these positive impacts could cumulatively build over time. The nuance of these psychosocial impacts of these treatments do not seem to be adequately captured in the current report. It will be very important for future studies and real world data to capture this information using measures which are sensitive to change in CF.
As noted in the document there are some concerns around mental health side effects of modulators (specifically depression) and it will be important to capture real world data on this going forward to better understand the incidence and mechanisms of this. For both direct and indirect (e.g. adjustment to wellness, existential issues etc) mental health effects the clinical community needs further data to consider the best way of monitoring and minimising these difficulties including dose adjustments and treatment with psychological therapy and/or antidepressant medication.
Finally the issue of adherence to modulators (and adherence to other treatments when on modulators) is very important. Adherence difficulties to all treatments for CF and other chronic health conditions are well documented. Further studies are needed to understand the long term adherence data, the obstacles to adherence to modulators (which may be the same or different to the obstacles to taking other CF treatments) and the best ways to support people to adhere to these medications.

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Response to stakeholder comments on MTA report

September 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135829.

1 Introduction and stakeholder comments from the Company

The external assessment group (EAG) received nine stakeholder comments on the External Assessment (EA) report, including one from the Company. In this Section, the EAG responds to the stakeholder comments from the Company, and in Section 2, the EAG responds to other stakeholder comments.

Following the comments of the Company and the other stakeholders, the EAG has made the following changes to its base case model and scenarios:

- The EAG has corrected the programming errors identified in the EAG model;
- The EAG has updated its base case assumption regarding the long-term rate of $ppFEV_1$ decline relative to ECM for ELX/TEZ/IVA (from 37.7% to 61.0%) and for TEZ/IVA (from 10.8% to 17.2%);
- The EAG has provided the following additional scenario analyses:
    - Using CFQ-R utility values from the Company Submission as the measure of health-related quality of life;
    - Including a caregiver utility benefit for people treated with ELX/TEZ/IVA;
    - Assuming two different reductions in the use and costs of ECM medications (23% and 40%) for people treated with CFTR modulator therapies;
    - Applying a long-term compliance rate for all CFTR modulators of [redacted]%.

The EAG replies to each of the Company's comments on the key settings for the economic analysis in Table 1, and provides further context to its replies following Table 1.

Table 1. Stakeholder comments from the Company, along with a comment from the EAG.

Issue	EAG approach	Vertex proposed approach	Rationale	EAG comment
Technical errors	EAG has created a *de novo* own model. We have identified technical/programming/mathematical errors, including lack of modelling best practices, poor programming implementation and an unquantifiable level of uncertainty on its estimations.	Use of Vertex model which has been thoroughly QC'd, peer-reviewed, published and accepted by other reputable HTA bodies.	The Vertex model has received favourable feedback from several HTA organizations, including NICE (TA398), for its design and internal validity in modelling the disease pathway. Most recently the model was reviewed and gained successful appraisals from reputable HTAs in Canada, Ireland and Australia. The modelling framework and underlying survival approach has also been presented in a peer-reviewed publication [1-3] (Rubin et al., 2019, Lopez et	Technical errors identified by the Company and by the EAG have been corrected, with a log of any changes made in the model provided in Appendix 6.1. The EAG notes that the incorporation of model fixes did not have a substantial impact on any of the ICERs. The Company notes that the published model has received favourable feedback on its design and internal validity in modelling the disease pathway, including from the Canadian HTA body. The EAG doesn't consider the published feedback of the Company's model to be exclusively favourable. For example, the CADTH review of ELX/TEZ/IVA states that, "*[the Company] model was programmed with limited transparency, with many inputs and outputs being the result of Visual Basic for Applications coding rather than formula-based*

			al 2023, Mc Garry et al 2023).	*operations*".[4]The EAG notes that a *de novo* model was required in order to implement the EAG's own assumptions and scenarios as the Company models did not incorporate all modulator treatments in one model or age groups required for the MTA. The EAG model uses the same underlying structure of that used by the company but with updates to key clinical parameters such as a non-linear rate of decline in $ppFEV_1$. The EAG model recovers key features of CF that the company model does not, namely median age of death for patients on ECM.
IVA/TEZ/ELX rate of change in lung function ($ppFEV_1$)	IVA/TEZ/ELX rate of change in lung function assumed to be 37.7% based on ivacaftor methods paper by Newsome et al. 2022 [5]	100% rate of change in lung function as shown by IVA/TEZ/ELX real-world evidence [6, 7]	Use of evidence from studies of IVA/TEZ/ELX is most appropriate, particularly given the abundance of data available for this product, including UK-specific data collected as part of the data collection agreement for this appraisal.	The EAG agrees with the Company that use of evidence from studies of ELZ/TEZ/IVA would be the most appropriate source of data, if unbiased estimates from these data sources were available. As outlined in the EA report, the EAG considers the two estimates of the reduction in rate of change for patients on ELX/TEZ/IVA (77% from

				the data collection agreement [DCA] and 100% from the trial open label extension studies) to be at very high risk of bias. The EAG further notes that these estimates, derived from studies with follow-up lengths of 192 weeks (Study 445-105 OLE) and 17.12 months (mean follow-up, DCA), are then applied for a person's lifetime in the economic model. In the EA report, the EAG accepted the estimate of 37.7% was potentially conservative, but notes that because these estimates are applied for a person's lifetime, this estimate has a lower decision risk. In response to a Company comment which identified a reasonable method of adjusting the 37.7% value, the EAG has updated its base case assumption to be a relative reduction of 61.0%. The EAG describes this further in Section 1.1.

TEZ/IVA rate of change in lung function ($ppFEV_1$)	10.6% rate of change in lung function	61.5% rate of change in lung function [8]	Use of evidence from studies in TEZ/IVA are most appropriate, given they are available.	The EAG agrees with the Company that using evidence from studies in TEZ/IVA and LUM/IVA would be the preferred source of long-term effectiveness evidence for these interventions. However, as outlined in Section 3.2.2.6.3 of the EA report, the EAG considers the Company analyses of long-term rate of decline for TEZ/IVA and LUM/IVA to be at very high risk of bias. The EAG requested the Company update these analyses to mitigate this bias, but the Company declined to do so. In the absence of reasonable estimates from TEZ/IVA and LUM/IVA studies, the EAG: • TEZ/IVA: Updated its base case in-line with the updated base case for ELX/TEZ/IVA, providing an estimate of 17.2%; • LUM/IVA: Retained its base case of 0% relative reduction, based on the
LUM/IVA rate of change in lung function ($ppFEV_1$)	0% (i.e., no long-term clinical benefit vs ECM)	42% rate of change in lung function decline [9]	Use of evidence from studies in LUM/IVA are most appropriate, given they are available – equally, the large body of long-term evidence for LUM/IVA shows a clear benefit vs ECM which the EAG does not account for.	

				placebo-controlled data from TRAFFIC/TRANSPORT
PEx	The EAG applies a pulmonary exacerbation treatment effect (rate ratio) for only the duration of trial period	Pulmonary exacerbation treatment effect (rate ratio) applied for patients' lifetime	Vertex has submitted a comprehensive evidence package containing pivotal trial data, OLE data and real world DCA data to evidence the long-term decline on Pex beyond the trial period.	The EAG notes that the effect on PEx does contribute beyond trial period in EAG model, through changes in $ppFEV_1$. The EAG did not feel sufficient evidence was provided of an additional treatment effect outside of the effect through $ppFEV_1$ on PEx. It is also noted the rate ratio was derived by calibrating data to the trial period from which the data was observed and therefore the EAG does not deem it appropriate to apply this rate for a lifetime.
Baseline mortality hazard	Keogh (2018) [10] paper used to predict CF baseline mortality using 2011-2015 registry data: Median survival of 46.8 years.	Vertex had previously used UK CF Registry data from 1985–2008, reporting a median survival of 40.8 years. Vertex accepts the EAGs alternative approach for this variable.	Despite lack of transparency on how these data were derived from Keogh et al., [10] Vertex accepts that this study could be used as an alternative input.	Survival curves were extracted from the equations presented in Keogh *et al.* appendix, using R software. The cumulative log hazards were then produced, and from this, converted into approximate hazard rates to be applied in the economic model.

Compliance	100%	Previously Vertex had assumed 80% compliance but have now revised this in our base case to [redacted]%.	Evidence suggesting compliance is [redacted]% is now available from the DCA; we therefore believe this is a reasonable estimate.[7]	The EAG has provided an additional scenario analysis with [redacted]% compliance, but notes the uncertainty around applying this for a lifetime horizon, with an unknown impact on efficacy.
ECM rate of lung function decline	The ECM rate of lung function decline used by EAG was derived from genotype- and age-specific rates from Szczesniak et al 2023 [11] in which decline rates for F/F patients was used for F/MF and F/Gating. The reported decline rate for the overall population (which included F/F patients) was applied for F/RF patients. Decline rates were capped based on Sawicki et al 2022 [12] decline rates for F/RF.	Vertex approach used genotype- and age-specific rates of lung function decline for F/F and F/RF from Sawicki et al 2022 [12]. Rate of lung function decline for F/F was applied to F/MF and F/Gating.	The assumption made by the EAG indicates that F/RF patients are declining faster than what was observed by Sawicki. This assumption biased the ICER estimations for F/RF as the rate of lung function decline is directly associated with survival and other parameters in the model (e.g., costs, QALYs). In addition, Sawicki et al 2022 [12] estimates of lung function decline were derived based on patients who were not on a CFTR modulator treatment, different than	The EAG notes an error in the EA report in relation to the cap applied based on Sawicki *et al.* for F/RF. This was originally explored in the EAG model but not applied in the base case as the EAG did not feel it was appropriate to apply decline rates from different sources that will have been calculated based on different populations. Therefore, the cap to decline rates is not applied in the EAG analyses. The use of the overall population curve applied to F/RF patients applies a slower rate of decline to that applied to the other genotypes, which applied the decline of the homozygous population. Although at some younger ages this applies a faster rate of decline for F/RF patients than that measured by Sawicki *et al.*, this still applies a much lower rate of decline for individuals aged

			Szczesniak et al 2023 [11] which did not have an exclusion criterion for patients on a CFTR modulator treatment.	over 29 than the Company's model does using the linear decline model. The EAG notes that applying this cap increases the ICER
Disease specific utilities	The EAG *de novo* model uses utility inputs based on TRAFFIC/TRANSPORT EQ-5D-3L data . ppFEV$_1$ >=70: 0.91 ppFEV$_1$ 70-40: 0.88 ppFEV$_1$ <40: 0.85	Vertex believes the correct utility data should be from the CFQ-R data derived from real world data collection agreement, converted to utilities using a validated preference-based algorithm: ppFEV$_1$ >=70: [redacted] ppFEV$_1$ 70-40: [redacted] ppFEV$_1$ <40: [redacted]	The CFQ-R is a validated CF-specific tool, and has a preference-based scoring algorithm (the CFQ-R-8D), according to published guidelines by NICE, which enables estimation of CF-specific health-state utilities based on the CFQ-R. EQ-5D-3L is insensitive to CF, hence the omission of the EQ-5D data which shows CF patients with severe lung disease to have a utility	The EAG analysis follows the NICE Reference Case and has provided alternative scenarios using lower EQ-5D values (Acaster 2015) and an additional scenario has now been added using utility values form the Company's model. The utility values applied in the EAG model were taken from the LUM/IVA clinical trial but scaled to account for the general population average HRQoL at the average age of the model, such that the values applied are lower than those obtained directly form the LUM/IVA trial. The EAG notes that the utility values applied in the EAG model are also age-adjusted throughout a patient's lifetime so that utility declines with age. This was not applied in the Company's models.

			(0.85) higher than that of the general population (0.84) [13].	Despite an available mapping algorithm for CFQ-R to EQ-5D being available, the Company have not provided any alternative utility values which use this. Instead utility values were derived using the CFQ-R-8D preference-based scoring algorithm to calculate utilities from [redacted] The EAG also notes they were not provided with any utility values estimated from CFQ-R data collected as part of the DCA. The EAG notes that the relative difference between moving between $ppFEV_1$ categories, which impacts cost-effectiveness modelling, is similar between both the EAG and Company base case values.
IVA/TEZ/ELX treatment specific utility	The EAG has not included this in its *de novo* analysis and has not given a rationale for this approach.	The [redacted] IVA/TEZ/ELX treatment specific utility should be applied	Assigning utility scores based only on $ppFEV_1$ and PEx would fail to capture the extra-pulmonary benefits of IVA/TAZ/ELX, including	The Company models applied a treatment-specific utility benefit to both ELX/TEZ/IVA and TEZ/IVA (F/RF population only). The EAG does not believe sufficient evidence has been provided to justify an additional utility benefit

			benefits to other organ systems and general improvements in functioning, well-being, and quality of life unrelated to respiratory outcomes. In all Phase 3 trials of IVA/TAZ/ELX, treatment provided substantial benefit across multiple non-respiratory domains of the CFQ-R. The model captures these benefits by incorporating a treatment-specific utility increment – that is, an increase in the utility above that predicted based on $ppFEV_1$ for patients treated with IVA/TAZ/ELX. The magnitude of this utility increment was derived from a post-hoc analysis in which the CFQ-R-8D preference-based scoring algorithm was	associated with a treatment beyond its observed impact on outcomes. An additional treatment benefit is already captured in the model indirectly through reduced PEs, which have an associated disutility applied.

			used to calculate health-state utilities from the CFQ-R data collected in the IVA/TAZ/ELX trial conducted in patients age ≥12 years with F/MF genotype, Study 445-102 [14]	
Disease management costs	The EAG has used a resource use questionnaire as part of a trial to assess adherence to inhaled medications, to inform disease management costs (Tappenden 2023 et al) [15].	Vertex used a retrospective chart review of patients with CF aged ≥6 years old across eight specialist CF centres in the UK. (Ramagopalan et al.) [16]. Full 24-month data were extracted for each patient, including patient characteristics, pharmacotherapy, and healthcare resource use	The retrospective chart review provides a comprehensive and accurate source of data using medical record data to inform costings. Using questionnaires inherently introduces inaccuracy into the data given recall bias, memory bias, incomplete data trends, inaccurate estimations, and response burden.	The retrospective chart review data used by the Company was collected in the years 2007–11. Standard practice and the use of specific therapies for disease management of CF has changed since this time. As the data used by the Company was only available in abstract and poster form, the EAG was unable to assess the specific treatments and resource use included in the pharmacotherapy costs to be able to apply updated prices. The source used by the EAG to inform disease management costs has been published in a peer-reviewed article and as part of a NIHR HTA report.

				Additional scenario analyses have now been included, which apply lower ECM drug costs for patients on CFTR modulator treatments.
Severity	No severity modifier is applied in the EAG's *de novo* model.	A severity modifier should be applied.	Cystic fibrosis is a severe respiratory disease, which leads to a significant shortening of life. In 2021, the median age at death in the UK was 38 years [17]. The fact that the EAG used EQ-5D utilities for ppFEV$_1$-defined health states which lack face validity due to values being higher than the UK general population norms, contributes to overestimation of QALYs accrued by the CF patients treated with established clinical management during the EAG's model time horizon. This in turn	As noted above, the EAG utility values are age-adjusted in the model to account for general population decline in utility with age, which is not applied in the Company's model. The application of the severity modifier is a consequence of the modelling assumptions applied and not specific to the use of EQ-5D values. The EAG notes that when the Company's utility values are used in the EAG model, a severity modifier if still not applicable. The qualification of the severity modifier in the Company's model is instead largely due to the use of a 1.5% discount rate for HRQoL outcomes.

			diminishes their QALY shortfall relative to the UK general population, and results in severity modifier threshold not being reached.	
Discount rate	3.5% for costs and outcomes	3.5% for costs, 1.5% for outcomes	Vertex has submitted a comprehensive evidence package containing pivotal trial data, OLE data and real world DCA data to evidence the long-term value that CFTRms provide to patients and the healthcare system, justifying a differential discount rate. NICE has shown flexibility by accepting differential discount rates in prior appraisals for severe paediatric conditions. [17]	The EAG analysis follows the NICE Reference Case.

Abbreviations: AR, assessment report; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CFQ-R, cystic fibrosis questionnaire revised; EAG, external assessment group; ECM, established clinical management; ELX, elexacaftor; EQ-5, EuroQol five dimensions; DCA, data collection agreement; HTA, health-technology assessment; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; NICE, The National Institute for Health and Care Excellence; MTA, multiple technology appraisal; OLE, open-label extension; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; QALY, quality-adjusted life year; QC, quality control; TEZ, tezacaftor

1.1 Updated EAG base case: long-term rate of decline for ELX/TEZ/IVA

In the External Assessment report (EA report), the EAG considered rate of decline estimates for $ppFEV_1$ for ELX/TEZ/IVA from open label extension studies of ELX/TEZ/IVA clinical trials, and from data collected as part of the Data Collection Agreement within the UK CF Registry. The EAG did not have access to the individual patient data from these analyses, and instead only had access to analyses provided by the Company. As stated in the EA report, the EAG considered these analyses to be at risk of overestimating the long-term effectiveness of ELX/TEZ/IVA due to these analyses:

- Having an unknown degree of confounding from factors, such as reduced viral transmission, during the COVID-19 pandemic;
- Not adequately removing the acute effects of ELX/TEZ/IVA from the analysis;
- A contemporary control group not being available.

The EAG agrees with comments from various stakeholders, including the CF Trust, that analyses to understand the full impact of the COVID-19 pandemic on lung function in CF will require longer-term data collection.

In the absence of unbiased estimates using ELX/TEZ/IVA data, the EAG considered an independent estimate of the long-term rate of decline of $ppFEV_1$ for patient eligible for ivacaftor treatment to be a reasonable alternative. The EAG noted that the estimate derived for ivacaftor, a 37.7% reduction in the rate of $ppFEV_1$ decline relative to ECM, was potentially conservative, but notes that because this rate of decline is applied for a patient's lifetime in the economic model, it is associated with lower decision risk than more optimistic estimates.

In the Company's stakeholder comments, the Company noted that the EAG's method of estimating the long-term treatment effect of TEZ/IVA on $ppFEV_1$ – scaling the ELX/TEZ/IVA effect by the ratio of the TEZ/IVA to ELX/TEZ/IVA acute treatment effect – could also be applied to the initial estimate for ELX/TEZ/IVA by scaling the ivacaftor treatment effect by the ratio of the ELX/TEZ/IVA to ivacaftor acute treatment effect in F/Gating patients. The EAG considers this approach to be a reasonable alternative method of estimating the treatment effect, albeit no longer a conservative approach. Using this approach, the estimate for the relative reduction in the long-term rate of $ppFEV_1$ decline for ELX/TEZ/IVA is 61.0% (37.7*[15.18/9.38]).

Following stakeholder comments, the EAG has updated its base case to this 61.0% relative reduction in the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA. The resulting TEZ/IVA assumption has also been updated to 61.0*(4/14.2) = 17.2%. The EAG notes that, when applied for a lifetime horizon, it confers a higher decision risk than the EAG's original estimate of 37.7%.

1.2 Updated Company base case

In the comments on the EAG report, Vertex provided a revised base case, "based on the EAG feedback, and the change in scope to include patients aged 2-5 years treated with IVA/TEZ/ELX since the original Vertex submission was made." The EAG notes that very limited information about this revised base case was provided, and neither was a revised economic model provided, nor were model outcomes provided beyond the ICER. As such, the EAG was unable to critique or validate the Company's revised base case. However, the EAG notes that:

- The Company did not provide the full range of settings for the updated model, including key features such as the assumed rate of ppFEV$_1$ decline. The EAG assumes these are the same as the Company's original base case, but has not been able to validate this.
- The Company has retained non-NICE reference case differential discounting (1.5% for outcomes, 3.5% for costs);
- An ICER was provided, but only for ELX/TEZ/IVA:
  - Only a single deterministic ICER was presented;
  - This ICER was an incremental deterministic ICER, weighted against a range of comparators. As such, the ICER is very difficult to interpret and is dependent on the chosen (PAS) prices of the active comparators;
- The Company states this model included patients aged 2 to 5 years, but it is unclear how the active comparators were modelled in these age groups, when their marketing authorisations do not cover these age groups, e.g. for TEZ/IVA in people under 6 years.

As such, while the EAG notes the Company has updated its analysis to include patients aged 2 to 5 years, and included active comparators, the EAG has not been provided with a complete description of the model, or the model itself, to validate. The EAG highlights that an ICER has only been provided for ELX/TEZ/IVA compared to a weighted average of active comparators and ECM, with no fully incremental analysis undertaken.

2 Other stakeholder comments

In addition to the stakeholder comments received from the Company, the External Assessment Group (EAG) received eight stakeholder comments on the External Assessment report (EA report). The EAG is grateful for the constructive comments it has received, which have resulted in the EAG updating its base case model, as well as providing several scenario analyses in response to these comments, as outlined in Section 1. The EAG now replies to each of the stakeholder comments in Table 2. Where the stakeholder comments were too lengthy to reproduce in full, the EAG has abridged the comments and responded to the more critical issues raised by the stakeholder.

Table 2. Stakeholder comments on the External Assessment report and the EAG's reply

Stakeholder	Comments	EAG reply
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	**MTA protocol** • Inhaled antibiotics and airway clearance are not included within the scope or protocol as a comparator or as part of best supportive care. Both of these important aspects of care are clearly established and, particularly for inhaled antibiotics, evidence based clinical practice. • Quality of life is an incredibly important outcome measure for this review and should have been considered a key outcome measure. Our clinical experience has shown that this is where some of the greatest gains have been made, both in and out of the respiratory domain. • The reliance on EQ-5D (rather than CFQ-R) means that a substantial amount of literature and data will have been missed as the majority of work in this area will use CFQ-R. **Timing of the review** • With the Covid-19 pandemic rendering real-world data difficult to interpret, with such an important treatment, we firmly believe it would be safer and more sensible to delay this review, for a short time, to allow post-pandemic, real-world data to be collected and utilised. • By only using trial data, and not using real-world data in this review, the outcomes analysed are for a highly engaged population who participate in and adhere to clinical trial protocols, and therefore do not represent the wider CF population and their potential outcomes. This further supports delaying this review.	The EAG thanks ACPCF for these comments. • The EAG would like to clarify that inhaled antibiotics and airway clearance were highlighted by the EAG's clinical experts and have been considered as part of best supportive care in the EA report. Best supportive care/established clinical medication (ECM) is included in the EAG model as all resource use patients would receive when not on CFTR modulators, albeit with simplifying assumptions when certain cost/resource use data were not available; • The EAG recognises that CFTR modulator therapy has a substantial impact on the quality of life of people with CF. While the EAG base case uses EQ-5D data, the EAG has supplied a scenario analysis using the CFQ-R data provided by the Company in response to stakeholder comments. The EAG notes that the main driver of cost-effectiveness due to HRQoL in the model is the relative difference between utility scores at different $ppFEV_1$ levels, which are similar between the EQ-5D and CFQ-R data sources; • The EAG agrees with the ACPCF that real-world data collection post-pandemic has the potential to substantially

		reduce the uncertainty in key parameters in the economic model.
Cystic Fibrosis Dietitians Specialist Group of the British Dietetic Association (BDA)	• Whilst it has been well documented about the improvement in weight and BMI, there is no discussion about the benefits we are seeing in real life terms and the cost implications. Due to improved weight gain, patients are using less prescribed oral nutritional supplements. There have also been patients who have had gastrostomy tubes removed. This all has a cost saving to the NHS. These reductions in numbers have already been acknowledged if you look at the UK CF registry data on pt use of nutritional support over the last few years. There is also savings being made had these drugs not been available and more pts requiring more aggressive nutritional support. • It is also documented that vitamin supplements are part of standard CF treatment. Again, in real life and some studies now published, some patients have been able to reduce vitamin supplements. This is also true of pancreatic enzymes. Both will have a cost saving within the NHS.	The EAG thanks the BDA for these comments. • The EAG recognises that use of CFTR modulators may affect co-adherence to other CF therapies, which is especially true for supplements and therapy around weight gain; • The EAG has highlighted the need for future research to explore the rates of co-adherence to non-CFTR modulator therapies and costs, such that the effects of this on the effectiveness and costs associated with CFTR modulator usage can be modelled; • Although these supplements are not included in the resource use and costs in the model, in response to Stakeholder comments, the EAG has provided additional scenario analyses in which CFTR modulator use is associated with less frequent use of higher cost ECM medications, and the associated cost savings.
Cystic Fibrosis Nursing Association (CFNA)	• Primary outcome identified as FEV_1, weight and exacerbation is of concern as it does not give priority to quality of life (QoL)… There are many recognised formats for measuring QoL and this is done regularly within CF. This has been one of the areas of the greatest impact for people with Cystic Fibrosis (CF),and has wide socio-	The EAG thanks the CFNA for these comments, and the provided patient case examples. • The EAG recognises that CFTR modulator therapy has a substantial impact on the quality of life of people with CF.

	economic impact. Data is available to reflect this, yet not included in this review? • References made to reduced adherence to other medications are misrepresented. Within practice reduction in nebulised therapies is a result of reduced need, not a reflection of adherence. This is also seen with reductions in the need for other medications such as pancreatic enzymes and insulin, which are not included in this report. • Reference was made to the increased unemployment within parents of people with CF, yet this was not reviewed further after the introduction of modifiers. As above, employment rates within those with Unemployment rate in 2020 847 (14.1), 2021 791 (12.6) (CF Trust, 2022, Annual Report 2021) • Omitted from this study is any reference to the increase in pregnancy rates from 56 in 2020 to 103 in 2021 (CF Trust, 2022, Annual Report 2021) • Reference is made to transplant costs (page 228, Table 73), however there is no reference to the reduction in double lung transplant rates from 175 in 2020, to 78 in 2021. 2022 data suggests there were only 5 transplants for people with CF.	While EQ-5D is the NICE reference case for HRQoL data, the EAG has provided an additional scenario using CFQ-R data. As mentioned in the reply to the ACPCF, the main driver of cost-effectiveness due to HRQoL in the model is the relative difference between utility scores at different $ppFEV_1$ levels, which are similar between the EQ-5D and CFQ-R data sources; • The EAG agrees that reduced usage of other medications while on CFTR modulators might reflect reduced need. The EAG uses the term reduced adherence to reflect both the possibility of reduced need and reduced use, as CFTR modulators are indicated for use in addition to ECM therapies. Nevertheless, the EAG considers the ongoing research into the effects of discontinuing ECM therapies while on CFTR modulators to be key to understating the likely clinical and cost-effectiveness outcomes of CFTR modulator therapies. In response to stakeholder comments, the EAG has provided additional scenario analyses in which CFTR modulator use is associated with less frequent ECM use, and therefore lower cost of ECM medications; • The EAG thanks the CFNA for highlighting the effects of CFTR modulators on unemployment and fertility. As the EAG analysis follows the NICE reference case, these additional benefits are not routinely captured. The EAG has highlighted these for NICE, and related comments from other stakeholders, in Table 4The EAG would like to note

		that the EAG model does predict the incidence of lung transplants for those on CFTR modulators vs ECM therapies. In the current EAG base case, the frequency of lung transplants for people treated with ELX/TEZ/IVA is 15.8 times lower than predicted for ECM, which reflects the DCA data.
Cystic Fibrosis (CF) Trust	• Cystic Fibrosis Trust is concerned that the EAR does not significantly appreciate the profound impact living with CF has on people and their families… We are concerned that the impact of living with CF, an invisible condition, is not adequately appreciated in the EAR. As CF is a chronic, life-long condition, many of the CF community have told us that access to these treatments has, as well as keeping them alive for longer, significantly improved their quality of life… The UK CF Registry was amended at the beginning of the access period to include CFQ-R data, which was specified in the data collection agreement as a key data item. Despite only one of the Orkambi clinical trials collecting EQ-5D data, the EAG has applied these values obtained from people with CF during this clinical study to all treatment arms in the model which we believe to be inappropriate. The EAG should recognise the CFQ-R data collected during the interim access period as this will accurately reflect the experiences of people with CF; • We are concerned that the EAG haven't recognised the limitations with EQ-5D, particularly when comparing scores to the general population.	The EAG would like to thank the CF Trust for these comments. Due to the length of the CF Trust reply, the EAG has highlighted and responded to the criticism of the EAG model in this section, but notes agreement with the CF Trust in its other points raised. • In response to the first comment, the EAG wishes to highlight it recognises the profound impact living with CF has on people and their families, which has been highlighted by a variety of stakeholders throughout the process. In the base case analysis, the EAG used EQ-5D data in-line with the NICE reference case. The EAG noted that the changes in utility values between $ppFEV_1$ categories – which influence patients' quality of life in the model – are very similar between the EQ-5D data and the CFQ-R data provided by the Company. As such, changing the data source from EQ-5D to CFQ-R does not change the overall cost-effectiveness conclusions. Despite the EAG's preference for EQ-5D values, the EAG has, i) provided a scenario analysis using CFR-Q data, and ii) provided a

	• Cystic Fibrosis Trust is disappointed that the EAR does not take into account the significant benefits people with CF have experienced since access to Orkambi, Symkevi and Kaftrio was agreed. As well as substantial changes in the UK CF population within the agreed outcomes of the appraisal, detailed within the EAR such as improvements in lung function and the heights and weights of people with CF, there have also been wider benefits experienced, highlighted in our evidence submission… These options include increased opportunities for education, employment, starting a family and homeownership as well as a feeling of being able to contribute to society. There has been a remarkable increase in the number of women with CF becoming mothers over the past few years and a common theme in our research has been stories from people with CF who never thought they could start a family. • It is concerning that the whole portfolio of results using the UK CF Registry data (for the above agreement) has been dismissed because of the overlap with COVID-19 pandemic, in favour of, for example, an estimate of rate of decline in ppFEV1 from one Registry-based study on Kalydeco (Newsome et al). Even if the results in the final report are considered an underestimate of the rate of decline in ppFEV1, we feel a sensitivity analysis using a range of values from the final report should have been conducted within the EAR. • The EAR references the results of a data request to the UK CF Registry, to support their opinion that "*it is likely that a sufficient number of people in the UK CF Registry who were not receiving*	scenario analysis adding a caregiver utility increment for people treated by CFTR modulators; • The EAG agrees with the CF Trust that some benefits resulting from successful treatment of CF are not captured in this cost-effectives analysis, including effects on fertility and employment. As the EAG analysis follows the NICE reference case, these additional benefits are not routinely captured. The EAG has highlighted these for NICE, and related comments from other stakeholders, in Table 4; • The EAG would like to highlight that a sensitivity analysis using alternative values from the final report was provided in the EA report (Section 4.2.2.4); • The EAG thanks the CF Trust for raising their concerns about the limited use of the portfolio of results using the UK CF Registry have been disregarded. The EAG wishes to reassure the CF Trust that data from the CF Registry following the Data Collection Agreement have been considered. In many cases, the limited reference to the DCA data in the EA report are because the DCA data are in-line and supportive of the clinical trial data and predictions from the economic model. To address the comments made by various stakeholders regarding the use of the DCA data, the EAG provides Section 3 of this report to provide a more complete discussion of the DCA objectives and data the EAG were presented with;

	Kaftrio, Orkambi, Symkevi or Kalydeco may have been available to measure the impacts of the COVID-19 pandemic on lung-function decline in people with CF, but notes that such an analysis was not undertaken." We are concerned that the figures provided have been overinterpreted. For example, the number or people with at least one annual review between 2019 and 2021, aged 12 years and older with no recorded Kaftrio use between 2019 and 2021 will not necessarily be the same number as those with ppFEV1 data available for the whole period of study with well-defined inclusion/exclusion criteria. • The EAG model does not include data on changes in infection rates over time due a lack of available data on prevalence rates. People with CF and their families highlighted reduced hospital admissions and reduced use of antibiotics as a major change to CF care since they have had access to Orkambi, Symkevi and Kaftrio. • Cystic Fibrosis Trust believes it is inappropriate to use long-term data from Kalydeco to approximate the long-term rate of ppFEV1 decline for people with CF who are treated with Kaftrio, Symkevi and Orkambi. Single therapy Kalydeco is indicated for different CFTR mutations and therefore the patient populations and long-term outcomes of those receiving Kalydeco or Kaftrio, Symkevi and Orkambi are likely to be very different, not least in the frequency of people with CF with homozygosity or heterozygosity for responsive mutations.	• The EAG accepts that changes in specific infection rates are not captured in the individual patient simulation model, and that this is a limitation of the model, which necessarily is a simplification of CF; • The EAG agrees with the CF Trust that it would be more appropriate to use data from patients treated with Kaftrio®, Symkevi® and Orkambi® to inform the long-term rate of $ppFEV_1$ decline, if robust analyses of these data were available. As detailed in the EA report, the EAG considers the currently available analyses to be at high risk of overestimating the long-term treatment effects of the CFTR modulators. The EAG made a request to the Company to update these analyses to mitigate these biases, but the Company declined to do so. In the absence of robust analyses in Kaftrio® or Symkevi®, the EAG considered an approximation based on ivacaftor data to be the most reasonable approach.

Cystic Fibrosis (CF) Voices	• The over-riding comment on this report from a CF Voices perspective is one of disappointment. After fighting so hard for access to these drugs for our loved ones, on the basis that their impact needed to be assessed across a longer period of time than is possible in short-term clinical trials, it is disheartening beyond comprehension that the NICE data collection which involved such a lot of work by clinicians, CF Trust, NICE, Vertex and involved CF Voices on the oversight committee, is hardly apparent. The data from that process is mostly mentioned to be dismissed due to the timing and a conclusion of a 'Covid-19 confounding effect'; • Why is the only quality of life data taken from EQ-5D questionnaire taken during a short-term trial of LUM/IVA? Where are results from Vertex QoL research and CF Trust data? • While no one would argue that there is not a positive effect on Fev1 from fewer viral infections, there is also an unquantified negative impact on Fev1 by lack of exercise, and at times for many, any opportunity for physical activity by CF patients during shielding… The impact of Covid-19 seems to have been considered very one-dimensionally by the EAG in this report. • Where is the data on 'patient and caregiver quality of life impact, including age-related differences' specified in the collection agreement? • The rate of co-adherence to non-CFTR modulators is uncertain and should be considered in part due to caution shown in clinician-led	The EAG thanks CF Voices for these comments. • As mentioned in the reply to the CF Trust, the EAG has provided Section 3 of this report to specifically address the concerns surrounding the use of the DCA data collection. • In response to these comment and others, the EAG has provided a scenario analysis using the Vertex provided CFR-Q data. • The EAG agrees that the relationship between COVID-19 and lung function for people with CF is complex, and that it is very difficult to adjust currently available analyses to account for this. The EAG would like to thank CF Voices for illustrating the potential confounding of COVID-19 in terms of reducing ppFEV$_1$; • The EAG has provided a scenario analysis including the caregiver quality of life data collected during an interim access study and using the Company's utility values based on CFQ-R. The EAG notes they were not provided with updated utility values based on the final data cut of DCA. • The EAG agrees that the rate of co-adherence to non-CFTR modulators, and the consequences of this, is uncertain and the subject of ongoing research. The EAG recognises that currently people with CF continue to receive ECM medications in addition to CFTR modulators, which forms

	reduction of other treatments in lieu of clinical trial evidence to support safety e.g. of stopping DNase (pending results of the STORM study). Patient-led non-adherence to non-CFTR modulator therapies is less easy to monitor but has undoubtedly occurred. • P62/63 it is very disappointing and simply wrong in terms of wider costs to the NHS to disregard the impact on carers as an outcome. CF Voices research March 2020 submitted as part of our initial submission for this appraisal details the many ways in which carers physical and mental health is impacted by CF and has been transformed where patients were receiving treatment. • Other data is stated as plausibly 'not missing at random' – precisely what does this comment allude to?	the EAG base case. Acknowledging the uncertainty about future co-adherence, the EAG has provided a scenario analysis around a reduction in non-CFTR modulator therapy use for people receiving CFTR modulators; • In response to the comment regarding the impact on carers as an outcome, the EAG has provided a scenario with Company's preferred carer utility gain for ELX/TEZ/IVA; • Data "not missing at random" refers to an assumption in the Company's statistical analysis method that data are missing at random, i.e., that patients not providing measurements is unrelated to their health. The EAG considered it plausible that providing measurements may be related to a patient's health state.
UK Cystic Fibrosis Medical Association (UK CFMA)	• The conclusions do not appear to be consistent with clinical trial data and the real-world experience of our patient population • Nutritional well being is a key metric in the outlook for people with CF, and weight provides an insight into this, but needs to be considered in context. It is an important secondary outcome, but complex, in that excessive weight gain has been experienced by some patients on ELX-TEZ-IVA, which may be an undesirable outcome. • Quality of life is the most important outcome for people with CF and the one that best reflects changes in their lived experience. This outcome is virtually ignored in this review, despite being measured in all the RCTs. This likely reflects the use of a CF-specific tool	The EAG would like to thank the UK CFMA for these comments: • Without further clarification, the EAG is unsure exactly which conclusions the UK CFMA do not agree with. However, the EAG notes that its updated base case for the long-term rate of decline may be more aligned with the UK CFMA real-world experience; • The EAG thanks the UK CFMA for the comment regarding the complexities of nutritional well-being. The EAG accepts the approach in the cost-effectiveness modelling is a simplification of the nutritional outcomes of CF following

	(CFQR). Whilst disease specific tools do not sit comfortably within HE assessments, they provide a valuable insight for our population. The change in CFQR score reported in the ELX-TEZ-IVA trials is of a magnitude not seen previously in CF trials (except the smaller trials of IVA for eligible patients more than ten years ago). Generic QoL measures, such as EQ-5D, do not represent accurately the lived experience of our patients, this reflects their resilience and ceiling effects. • Modelling for longer term impact should consider real world data regardless of the pandemic. These data, some requested by NICE, provide a valuable insight. We do not agree with the assertion that it is "impossible" for FEV1 not to decline year on year, especially when the underlying CF defect has been corrected. • The report should be more critical of the trial data in pre-school children and the fact that these interventions have only been assessed with observational (albeit intense) studies in this age group, which leads to bias in the assessment of efficacy. The authors classify these trials as "high risk of bias" but do not reinforce this in the summary statements.	CFRT modulator therapy and this has been noted in the updated EA report; • As mentioned in replies to previous stakeholders, the EAG recognises the concerns of various stakeholders regarding the suitability of EQ-5D for measuring health-related quality of life in CF. While the EAG considers that sufficient evidence has not been presented to invalidate the use of EQ-5D, it has provided a scenario analysis using the CFQ-R data, and also a scenario analysis incorporating an effect of ELX/TEZ/IVA treatment on caregiver quality of life; • The EAG has considered and included a range of real-world data in the cost-effectiveness modelling. However, the EAG recognises that several stakeholders have raised concerns about the degree of use of the DCA data. The EAG has provided an overview of these data and how they have been used in Section 3; • The EAG does not consider it impossible for $ppFEV_1$ not to decline year on year in an individual with CF, and apologises if the wording the EA report was interpreted in this way. However, the EAG considers that the totality of the available evidence, including the real-world evidence collected in the DCA, to indicate that on a population level, average $ppFEV_1$ does decline over time following ELX/TEZ/IVA treatment;

		• The EAG agrees with the UK CFMA and wishes to highlight the need for higher-quality studies and longer-term follow-up in younger children with CF.
United Kingdom Cystic Fibrosis Pharmacy Group (UK CFPG)	• [on not including an average cost of supplementary feeding] We understand the rationale for this, but do wonder if that might be a not insignificant cost for e.g. those with a PEG. Plus presumably the cost of inserting a PEG in the first place. So excluding these costs will likely reduce the cost effectiveness of modulator therapy and these costs should be considered. • IV drug costs are quoted as approx. £27 per day. While this may be accurate for the quoted antibiotic regimen it is noteworthy that this is one of the first line, simplest and least expensive regimens. Given the availability of newer more expensive agents, while their use is restricted to complex resistant organisms with the approval of microbiology colleagues, the average costs of intravenous antibiotics in the CF population is likely to be higher than that quoted. With regard to these drug costs, we would also suggest there needs to be some clarity about the costs of the episode of care vs the costs of drugs administered during the episode of care, which will be a cost to the admitting Trust but contained within the overarching year of care tariff the Trust receive. • While we appreciate the confounding situation with respect to the Covid pandemic, it seems impossible to ignore that there is clearly an effect of widespread modulator therapy on the need for treatments for PEx and hospitalisation. It may be impossible to truly	The EAG would like to thank the UK CFPG for these comments: • We have noted this in the Table of items missing from the cost-effectiveness modelling and it has also been noted in the updated EA report that this is a potential benefit that is not captured. The EAG notes that this is also not captured in the Company's models. • Thank you for highlighting that more expensive regimes may be given for PEs. The EAG based the costs used on clinical expert opinion and in line with a previous economic model on CF to represent the average costs. Without data on the proportion of patients who may receive these more expensive regimes it is difficult for the EAG to incorporate this. However, the EAG notes that the inclusion of these drugs could reduce the costs for ELX/TEZ/IVA as less PEs are experienced compared to other treatment arms. However, the EAG does not anticipate that this would have a substantial impact on the ICER. • The EAG would like to clarify that it does not interpret the data collected during the COVID pandemic to indicate that there is no effect of CFTR modulators, rather that it is very difficult to assess the magnitude of the effect that is due to

	separate the two causes, but that doesn't mean that there has been no effect of the treatments, which appears to be implied as the reason for disregarding any possible effect. • One significant change we have noted in clinical practice is a remarkable increase in people with CF having children since the introduction of modulator therapies which is not considered within the report. Specifically on the rate of pregnancy within female people with CF.	COVID-19 related factors and the magnitude of the effect that is due to CFTR modulators. This would be a necessary step to incorporate these figures into the modelling. The EAG's model does account for a substantial reduction in the need for treatments for PEx for people treated with ELX/TEZ/IVA. • The EAG thanks the UK CFPG for the comment regarding the remarkable increase in people with CF having children, which was also raised by other stakeholders. The EAG recognises this is not captured in the current appraisal and has highlighted this for NICE in Table 4.
UK Psychosocial Professionals in Cystic Fibrosis (UKPPCF) Committee	• We were disappointed to see that the impact of modulators on quality of life was not given more weight within the current document. Even when it was considered, the tools used may not capture the improvements that have been seen in this population. This is an area of clinical complexity as highlighted by these qualitative studies (Keye et al, 2022, Chronic Illness, The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy; Aspinall et al, 2022, International Journal of Environmental Research and Public Health, Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis) and the themes reported in these studies are not captured within tools such as the EQ5D or CFQR. Our clinical experience is that for many people with CF, modulators have led to an unprecedented paradigm shift for them in terms of their perceptions	The EAG would like to thank the UKPPCF Committee for these comments. • In response to these comments, and from other stakeholders, the EAG has provided a scenario using the CFQ-R data provided by the Company. • Nevertheless, the EAG notes that the UKPPCF comments also highlight that the CFQ-R may not cover psychological implications and health risks of CF pre and post CFTR modulators. The EAG welcomes these comments, but notes that the EAG is limited by the requirements of health economic models to use utility values from validated HRQoL instrument. The EAG has noted the concerns of the UKPPCF in Table 4.

		and beliefs about their health, themselves and the future. With increased stability in people's health and therefore improved access to school, further education, employment opportunities etc one could hypothesise that these positive impacts could cumulatively build over time. The nuance of these psychosocial impacts of these treatments do not seem to be adequately captured in the current report. It will be very important for future studies and real world data to capture this information using measures which are sensitive to change in CF.	

Abbreviations: AR, assessment report; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CFQ-R, cystic fibrosis questionnaire revised; EAG, external assessment group; ECM, established clinical management; ELX, elexacaftor; EQ-5, EuroQol five dimensions; DCA, data collection agreement; HTA, health-technology assessment; ICER, incremental cost-effectiveness ratio; IVA, ivacaftor; NICE, The National Institute for Health and Care Excellence; MTA, multiple technology appraisal; OLE, open-label extension; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; QALY, quality-adjusted life year; QC, quality control; TEZ, tezacaftor

3 Use of the DCA data

A number of stakeholders raised concerns as to the extent to which the EAG had incorporated data collected through the UK CF Registry as part of the Data Collection Agreement (DCA) between The National Institute for Health and Care Excellence (NICE), the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals (Boston, MA, USA), National Health Service (NHS) England, and NHS Improvement.

The EAG received the final report, and associated workbooks, produced by Vertex in July 2023, and had access to an interim report from February 2023. The report and data sheets were prepared by Vertex, and as such the EAG only had access to the data and analyses that were presented by the Company. The EAG is unaware whether or when this report will be made publicly available, but notes that the EAG was limited to viewing the data and analyses presented by the Company from the DCA.

The final report had 13 objectives focusing on ELX/TEZ/IVA, as data for TEZ/IVA and LUM/IVA became progressively less available as people switched to ELX/TEZ/IVA. The majority of the Vertex DCA Report presents descriptive data for ELX/TEZ/IVA patients only, and does not account for the within-person correlation of health outcome measures over time, and does not provide statistical or comparative analyses with uncertainty for most objectives.

Nevertheless, the EAG notes the DCA collected a substantial amount of data that provides context for and validation of many of the economic model's key assumptions. As noted by many stakeholders, the discussion around the rate of change in $ppFEV_1$ for people treated with ELX/TEZ/IVA observed in the DCA compared with a control cohort was the focus of the EAG's comments on the DCA in the EA report. This was because $ppFEV_1$ is a key outcome in the economic model with substantial uncertainty, and one of the only outcomes for which Vertex provided a statistical analysis for in the DCA. The EAG notes that, had the COVID-19 pandemic not occurred, this analysis would have substantially reduced the uncertainty around the long-term rate of $ppFEV_1$ decline in the model, and has still contributed to reducing some of the uncertainty around this.

The EAG now provides a brief summary and comment on each of the DCA objectives, to demonstrate the compatibility of these data with the data in the EAG model, and justifies why the EAG has not used the data directly in the EAG model.

3.1 Objective 1: rate of change in ppFEV$_1$ over time compared to standard of care

The EAG discussed the Company's analyses of rate of change in ppFEV$_1$ over time compared to standard of care at length in the EA report, as the EAG considers this to be a key area of uncertainty in the current appraisal. As outlined in the EA report, the EAG considers the Vertex analysis of the DCA data to be at very high risk of bias due to:

- An unknown degree of confounding from factors, such as reduced viral transmission, during the COVID-19 pandemic;
- Not adequately removing the acute effects of ELX/TEZ/IVA from the analysis;
- A contemporary control group not being available.

Therefore, the EAG preferred to adjust real-world data from ivacaftor treated patients to estimate the likely long-term effect of ELX/TEZ/IVA on ppFEV$_1$. The EAG notes that if an appropriate analysis of the ELX/TEZ/IVA data was possible and available, this could have been the EAG's preferred estimate.

3.2 Objective 2: progression of ppFEV$_1$

The mean increase in ppFEV$_1$ after 1 year of ELX/TEZ/IVA was [redacted] for the overall population [redacted] in people aged 12+ years. The EAG notes this is a less optimistic increase in ppFEV$_1$ than reported in the clinical trials, and this more optimistic figure is used by the EAG in the economic models (i.e., the EAG assumed acute increase in ppFEV$_1$ 12+ years for ELX/TEZ/IVA: F/F, 14.20%; F/MF, 14.30%; F/Gating, 15.18%; F/RF, 8.80%).

The EAG considers it more appropriate to use the data for the acute increase in ppFEV$_1$ from the CF clinical trials in the economic models, rather than the values from the DCA. This is because:

1) [redacted] of patients in the DCA had previously received CFTR modulator therapy, and as such the data from these patients is likely to underestimate the increase in ppFEV$_1$ patients who are naïve to CFTR modulators would experience, and;
2) The patient profiles in the EAG models are taken from the individual participant data from the clinical trials, provided by the Company. As these trials excluded patients with ppFEV$_1$ <40% or >90% at screening, the data collected in the real-world would be unsuitable to use for the acute increase in ppFEV$_1$ due to ceiling effects in people with very high ppFEV$_1$ at

baseline. As stated in the EA report, for these people, avoiding later decline in $ppFEV_1$ is a more relevant clinical outcome than an acute increase in $ppFEV_1$.

3.3 Objective 3: demographics and clinical characteristics

The Company presented the demographics and clinical characteristics at baseline of people with CF treated with ELX/TEZ/IVA. The EAG consider these data important in understanding the characteristics of people treated with ELX/TEZ/IVA during the DCA. The EAG noted that [redacted] of people had baseline $ppFEV_1$ <40% and mean baseline $ppFEV_1$ was [redacted] reflecting the prevalent population of people with CF in the UK at the time of the DCA. The EAG notes that for newly diagnosed children with CF, i.e., the incident population, the results of the DCA cohort are likely not representative of this younger group of patients, who would be able to intimate ELX/TEZ/IVA with less irreversible lung damage, and as such may have more positive outcomes. The EAG notes, however, that irreversible lung, and especially pancreatic, damage can occur at or around birth for people with CF.

The EAG used these data, alongside wider demographic data from the CF Trust annual data reports, to comment on the generalisability of the Vertex clinical trial programme to clinical practice in England and Wales, including highlighting that adults with a $ppFEV_1$ <40% and ≥90% were excluded from most of the clinical trials. The EAG highlighted how these clinical trial results may not be generalisable to people with CF initiating ELX/TEZ/IVA prior to developing significant irreversible lung and/or pancreatic damage. To address this, the EAG performed an exploratory optimistic scenario analysis to assess the cost-effectiveness of ELX/TEZ/IVA in such individuals, who may have the most positive outcomes following ELX/TEZ/IVA treatment.

3.4 Objective 4: pulmonary exacerbations

After a mean follow-up of [redacted] patients treated with ELX/TEZ/IVA experienced a [redacted] reduction in the annual rate of IV antibiotic episodes compared to the year before treatment initiation. The EAG notes that this marked reduction is likely due to, i) the effectiveness of ELX/TEZ/IVA, and ii) reduced viral transmission due to factors associated with the COVID-19 pandemic. The EAG notes the magnitude of this reduction that can be attributed to ELX/TEZ/IVA therapy compared to factors associated with the COVID-19 pandemic is highly uncertain, and considers it likely that both ELX/TEZ/IVA and factors associated with COVID-19 had a substantial contribution. The EAG was not presented with an analysis that attempted to isolate the ELX/TEZ/IVA

effect and agrees with various stakeholder comments that this is unlikely to be possible without large amounts of uncertainty. The EAG would like to note that the EAG's model incorporates a substantial reduction in the rate of PEx for patients treated with ELX/TEZ/IVA.

3.5 Objective 5: discontinuation

Overall, [redacted] of people discontinued ELX/TEZ/IVA at any time. Of these, [redacted] patients discontinued ELX/TEZ/IVA and did not restart any other CFTR modulator therapy. This suggests that discontinuation still continues to occur in the longer-term which is in line with the assumptions made in the EAG base case, i.e., that discontinuations can occur up to 5 years on treatment.

3.6 Objective 6: nutritional outcomes

The EAG was provided with a workbook of changes in weight-for-age and height-for-age z-scores following ELX/TEZ/IVA initiation for those under the age of 18, and changes from baseline in BMI for those over 18. After 1 year, there was a mean increase from baseline of [redacted] (standard deviation [redacted]) for patients greater than 18 years. Baseline mean BMI for these patients was [redacted] The EAG notes that average statistics such as these are of somewhat limited usefulness, given the meaning of changes in BMI depends on a person's baseline BMI, e.g., for some people an increase in BMI is a positive outcome, whereas for others it may not be. Nevertheless, the EAG models include a survival benefit for patients initiating ELX/TEZ/IVA through an improved weight-for-age z-score, which is not assumed to occur for ECM.

In the Vertex DCA workbook, data on weight-for-age z-scores were available at baseline for [redacted] patients under 18 years only ([redacted]). Outcome data were limited at each follow-up. At 3 months, [redacted] of patients had data available, reducing at each subsequent visit to [redacted] at 1 year and [redacted] at 2 years. No analyses were presented accounting for the within-person correlation of weight-for-age z-score, which would be necessary to estimate a change from baseline in weight-for-age z-score from the DCA data. Nevertheless, the EAG notes that if the raw mean at 6 months[redacted] – the highest average weight-for-age z-score reported – is subtracted from the baseline mean (an incorrect analysis), the change from baseline in weight-for-age z score is [redacted], which is less optimistic than the change reported in the clinical trial that the EAG uses in its economic model for ages 6 to 11 years, [redacted] and substantially lower than the assumed change for 12+ years in the F/F and F/MF genotypes[redacted] respectively.

However, the EAG accepts that the EAG model is an oversimplification of nutritional outcomes following ELX/TEZ/IVA therapy. While the EAG model may be conservative as it does not assume a progressive worsening of nutritional outcomes for people with CF, it may also be liberal in that it assumes the changes in nutritional outcomes following CFTR modulator therapy are positive in terms of conferring a survival benefit. The EAG notes that further research into nutritional outcomes and management following treatment with CFTR modulators should be a priority.

3.7 Exploratory objective 7: use of inhaled therapies

The Company presented the change in the number of inhaled and nebulised therapies before and after initiation of ELX/TEZ/IVA. The number of therapies at baseline (number of [n] patients = [redacted], n therapies = [redacted]) [redacted] at Year 1 (n therapies = [redacted]), or at Year 2 (n patients = [redacted], baseline n therapies = [redacted], n therapies at year 2 = [redacted]).

These data appear counter to the suggestion that people taking ELX/TEZ/IVA reduce their use of inhaled or nebulised therapies in the years following ELX/TEZ/IVA. However, the EAG does not consider these data to carry much meaning other than that patients with CF were still being prescribed a similar number of inhaled and nebulised therapies before and after ELX/TEZ/IVA initiation. In-line with stakeholder comments and ongoing clinical trials, the EAG recognises that use of ECM therapies may decline with the use of CFTR modulators. As such, the EAG has provided scenario analyses assuming two different reductions in the use and costs of ECM medications (23% and 40%) for people treated with CFTR modulator therapies.

3.8 Exploratory objective 8: hospitalisation for non-IV antibiotic treatment

There was no meaningful difference in the annualised hospitalisation rate for non-IV antibiotic treatment after initiation of ELX/TEZ/IVA (mean annualised hospitalisation rate for non-IV antibiotic treatment before ELX/TEZ/IVA initiation: [redacted]; after ELX/TEZ/IVA initiation: [redacted]). The EAG model did not assume a difference in the annualised hospitalisation rate for non-IV antibiotic treatment between CFTR modulators and ECM.

3.9 Exploratory objective 9: Overall survival

In the mean 17.24 months of follow-up in the DCA report, [redacted] out of [redacted] people taking ELX/TEZ/IVA died, an annualised death rate of [redacted] The Company contextualised this by providing

the annualised death rate reported in the UK CF Registry from 2013 to 2022, which are reproduced in Table 3 below.

Table 3. Annualised death rate in the UK CF Registry

2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The EAG notes that data from 2022 are subject to updating due to the delayed reporting of some mortality statistics, although the magnitude of this is expected to be small. The EAG notes the annualised death rate decreases after 2019, the time at which ELX/TEZ/IVA was made available. The EAG agrees that these data reflect the large real-world survival benefit of ELX/TEZ/IVA, which is also predicted by the EAG's model. The EAG notes that it is likely that factors associated with the COVID-19 pandemic will have also influence survival in these years.

3.10 Exploratory objective 10: CF related complications

The Company presented data on the incidence and prevalence of CF related diabetes, liver disease, pancreatic insufficiency and allergic bronchopulmonary aspergillosis for patients treated with ELX/TEZ/IVA. No substantial changes in the prevalence of CF related complications were reported, with the prevalence of CF related diabetes, liver disease and allergic bronchopulmonary aspergillosis increasing slightly in the year post ELX/TEZ/IVA initiation. The Company also presented data for the second and third year following ELX/TEZ/IVA initiation which showed considerably larger increases in the absolute prevalence of CF related complications following ELX/TEZ/IVA. However, the EAG does not consider these data interpretable due to the loss of sample size from baseline (n=5841) to year 2 ([redacted]) to year 3 ([redacted]), leading to an overrepresentation of patients treated earlier with ELX/TEZ/IVA – e.g., through compassionate access – in the year 2 and year 3 data.

Overall, these data are not consistent with a large decrease in the prevalence of CF related complications following ELX/TEZ/IVA initiation. However, the EAG notes that:

- Longer term follow-up, and analyses accounting for the within-person correlation of CF-related complications, are likely required to understand the impact of ELX/TEZ/IVA on CF related complications;
- A comparative analysis of outcomes for patients treated with ELX/TEZ/IVA compared to control was not reported;

- An important subgroup analysis, when available, will be people with CF initiating ELX/TEZ/IVA prior to developing irreversible organ damage and prior to developing CF related complications.

3.11 Exploratory objective 11: Lung infections

The Company presented descriptive statistics on the prevalence of four bacterial lung infections, *Mycobacterium abscessus, Staphylococcus aureus, Pseudomonas aeruginosa* and *Burkholderia* from baseline annual review and then at first, second and third annual review post ELX/TEZ/IVA initiation. Again, interpretation of these data were hampered due to the loss in sample size at Year 2 (data available for XXXX% of people with a baseline measure) and Year 3 (data available for XXXX% of people with a baseline measure). There was a reduction in infection prevalence from baseline to first annual review for each bacterial infection (absolute prevalence at baseline compared to prevalence at year 1: *M. abscessus* [redacted] *S. aureus* [redacted] *P. aeruginosa,* [redacted] and *Burkholderia,* [redacted] however, the EAG notes that the analysis does not account for the within person correlation of infection status and that data were only available for [redacted] of individuals at Year 1). The EAG also considers that these reductions in infection prevalence are meaningful, and likely attributable to i) the efficacy of ELX/TEZ/IVA, and ii) factors associated with the COVID-19 pandemic.

The Company also presented graphs on the frequency of IV antibiotic use, which was used as a proxy for pulmonary exacerbations, and hospitalisation rate. The EAG reproduces these graphs in Figure 1 and Figure 2. The EAG highlights that the provided data are absolute rather than relative numbers, and are therefore contingent on the number of entries into the UK CF Registry for each month. The EAG notes that these graphs display a large and immediate reduction in pulmonary exacerbations and hospitalisation following the first COVID-19 lockdown in the UK, and prior to ELX/TEZ/IVA being made widely available. The number of pulmonary exacerbations and hospitalisation rates then stay at a similarly low level until 2022, and from 2022 to 2023 the frequencies appear to converge to 0. The EAG considers this latter convergence to 0 in 2022 is likely to reflect missing data, and the Company itself noted that: [redacted]

The EAG notes that [redacted] in the number of reported pulmonary exacerbations and hospitalisations occurs around October 2020, i.e., shortly after ELX/TEZ/IVA is made available for

those 12 years and older in August 2020. However, the EAG also notes that in September 2020 tighter COVID-19 restrictions, such as the "Rule of 6" for gatherings, a return to homeworking and 10pm curfew for hospitality were imposed, prior to the second national lockdown on 5 November 2020.[18] The EAG therefore considers that the trends represented in Figure 1 and Figure 2 are likely directed, substantially or in part, due to factors associated with the COVID-19 pandemic, and a reduction in data availability across 2022. The EAG also notes that it is likely that the effectiveness of ELX/TEZ/IVA is also having a substantial impact on the shape of the graph, but that this impact is difficult to disentangle from the COVID-19 impact.

Figure 1. The number of IV antibiotic treatment episodes, a proxy for pulmonary exacerbations, recorded each month in the UK CF Registry from January 2018 to December 2022.

Figure 2. The number of hospitalisations for any reason recorded each month from January 2018 to December 2022 in the UK CF Registry.

3.12 Exploratory objective 12: Organ transplant

In the DCA analysis, it is reported that there were [redacted]". The EAG model also predicts a large reduction in the number of lung transplant required for people when treated with ELX/TEZ/IVA, with the frequency of lung transplants for ELX/TEZ/IVA F/F population being 75% lower than predicted for ECM, over a lifetime horizon. The EAG considers its model to be consistent with the data collected as part of the DCA, and further notes that:

- The rate of lung transplant in the short-term post ELX/TEZ/IVA initiation might underestimate the overall long-term rate of lung transplants required for people treated with ELX/TEZ/IVA, due to the large acute increase in $ppFEV_1$ associated with ELX/TEZ/IVA. This is because it would take time, after a large acute increase, for a person's $ppFEV_1$ to drop back down to a level requiring lung transplant;
- The transplant data reported in the DCA are likely confounded to an extent due to COVID-19, although an analysis of lung-transplant rates in the UK post COVID-19 showed a quick re-uptake in lung transplants following an initial decrease in the "first-wave".[19]

3.13 Exploratory objective 13: The impact of COVID-19

The EAG has critiqued the data provided as part of this objective in Figure 1 and Figure 2 for objective 12, and offered commented throughout at EA report on the difficulties of interpreting data collected during the COVID-19 pandemic.

4 Stakeholder comments not incorporated into the cost-effectiveness modelling

The EAG wishes to highlight several stakeholder comments about features of CF and consequences of CFTR modulator therapy that have not been directly incorporated into the cost-effectiveness modelling in Table 4. The EAG wishes to thank the stakeholders for raising these points.

Table 4. Features of CF highlighted by stakeholders as not currently incorporated into the cost-effectiveness modelling.

Feature of CF	Stakeholder comments	EAG comment
Employment, education and finance	Cystic Fibrosis Nursing Association (CFNA) • Reference was made to the increased unemployment within parents of people with CF, yet this was not reviewed further after the introduction of modifiers. As above, employment rates within those with Unemployment rate in 2020 847 (14.1), 2021 791 (12.6) (CF Trust, 2022, Annual Report 2021) CF Trust • These options include increased opportunities for education, employment, starting a family and homeownership as well as a feeling of being able to contribute to society.	The EAG wishes to highlight that successful treatment of CF by ELX/TEZ/IVA will likely have meaningful impacts on employment rates, time at work, opportunities for education and a wider range of societal benefits for people with CF, CF carers and the wider community.
Fertility	Cystic Fibrosis Nursing Association (CFNA) • Omitted from this study is any reference to the increase in pregnancy rates from 56 in 2020 to 103 in 2021 (CF Trust, 2022, Annual Report 2021) CF Trust	The EAG wishes to highlight that it considers the increase in pregnancy rates for people with CF to be attributable to the treatment effect of ELX/TEZ/IVA.

	• There has been a remarkable increase in the number of women with CF becoming mothers over the past few years and a common theme in our research has been stories from people with CF who never thought they could start a family.	
Rates of specific bacterial infections	CF Trust • The EAG model does not include data on changes in infection rates over time due a lack of available data on prevalence rates. People with CF and their families highlighted reduced hospital admissions and reduced use of antibiotics as a major change to CF care since they have had access to Orkambi, Symkevi and Kaftrio.	The EAG considers that treatment with CFTR modulator therapies is likely associated with a significant reduction in pulmonary bacterial colonisation over time, including delaying the acquisition of certain infections. The economic model does not track such changes, and this is likely a conservative assumption. However, the EAG notes that there is uncertainty around the long-term magnitude of these effects across a patient's lifetime, especially for rarer but more severe infections, such as *B. cepacia*. The EAG model does track the number of pulmonary exacerbations predicted for people treated with ELX/TEZ/IVA, TEZ/IVA, LUM/IVA and ECM.

Psychological aspects of cystic fibrosis not covered by EQ-5D or CFQ-R	UK Psychosocial Professionals in Cystic Fibrosis (UKPPCF) Committee • The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy; Aspinall et al, 2022, International Journal of Environmental Research and Public Health, Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis) and the themes reported in these studies are not captured within tools such as the EQ5D or CFQR. Our clinical experience is that for many people with CF, modulators have led to an unprecedented paradigm shift for them in terms of their perceptions and beliefs about their health, themselves and the future. With increased stability in people's health and therefore improved access to school, further education, employment opportunities etc one could hypothesise that these positive impacts could cumulatively build over time. The nuance of these psychosocial impacts of these treatments do not seem to be adequately captured in the current report. It will be very important for future studies and real world data to capture this information using measures which are sensitive to change in CF.	The EAG thanks the UKPPCF Committeee for this detailed comment, and agrees that treatment with CFTR modulator therapies, especially ELX/TEZ/IVA, can lead to "an unprecedented paradigm shift for them in terms of their perceptions and beliefs about their health, themselves and the future.". The EAG agrees with the importance of future studies and real world data capturing this information using measures which are sensitive to change in CF.

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R, cystic fibrosis questionnaire revised; EAG, external assessment group; ECM, established clinical management; ELX, elexacaftor; EQ-5, EuroQol five dimensions; DCA, data collection agreement; IVA, ivacaftor; NICE, The National Institute for Health and Care Excellence; TEZ, tezacaftor

5 References

1. Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. *Therapeutic advances in respiratory disease* 2019; **13**: 1753466618820186.
2. Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. *Journal of Cystic Fibrosis* 2023.
3. McGarry LJ, Bhaiwala Z, Lopez A, Chandler C, Pelligra CG, Rubin JL, et al. Calibration and validation of modeled 5-year survival predictions among people with cystic fibrosis treated with the cystic fibrosis transmembrane conductance regulator modulator ivacaftor using United States registry data. *Plos one* 2023; **18**: e0283479.
4. Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta). *Canadian Journal of Health Technologies* 2022; **2**.
5. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Using negative control outcomes and difference-in-differences analysis to estimate treatment effects in an entirely treated cohort: the effect of ivacaftor in cystic fibrosis. *American Journal of Epidemiology* 2022; **191**: 505-15.
6. Lee T, Sawicki GS, Altenburg J, Millar SJ, Geiger JM, Jennings MT, et al. Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis. *Journal of Cystic Fibrosis* 2023; **22**: 402-6.
7. Vertex. 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. 2023.
8. Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. *The Lancet Respiratory Medicine* 2021; **9**: 733-46.
9. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *The lancet Respiratory medicine* 2017; **5**: 107-18.
10. Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *Journal of Cystic Fibrosis* 2018; **17**: 218-27.
11. Szczesniak R, Andrinopoulou E-R, Su W, Afonso PM, Burgel P-R, Cromwell E, et al. Lung Function Decline in Cystic Fibrosis: Impact of Data Availability and Modeling Strategies on Clinical Interpretations. *Annals of the American Thoracic Society* 2023.
12. Sawicki GS, Konstan MW, McKone EF, Moss RB, Lubarsky B, Suthoff E, et al. Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation. *Pulmonary Therapy* 2022; **8**: 385-95.
13. Alava MH, Pudney S, Wailoo A. ESTIMATING EQ-5D BY AGE AND SEX FOR THE UK. 2022.
14. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine* 2019; **381**: 1809-19.
15. Tappenden P, Biz AN, Alava MH, Sasso A, Sutton L, Ennis K, et al. A model-based economic analysis of the CFHealthHub intervention to support adherence to inhaled medications for people with cystic fibrosis in the UK. *International Journal of Technology Assessment in Health Care* 2023; **39**: e6.

16. MacLachlan SRDLJLRAPCS. Predictors of Healthcare Costs for Cystic Fibrosis Patients in the United Kingdom. Biennial European Meeting at the Society for Medical Decision Making 2014.
17. Sokhi S. UK Cystic Fibrosis Registry 2021 Annual Data Report. 2022.
18. Institute for Government. Timeline of UK government coronavirus lockdowns and restrictions. 2022. Available from: https://www.instituteforgovernment.org.uk/data-visualisation/timeline-coronavirus-lockdowns. Date accessed: 25 September.
19. Hardman G, Sutcliffe R, Hogg R, Mumford L, Grocott L, Mead-Regan SJ, et al. The impact of the SARS-CoV-2 pandemic and COVID-19 on lung transplantation in the UK: Lessons learned from the first wave. *Clin Transplant* 2021; **35**: e14210.
20. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011.

6 Appendix

6.1 Log of model changes following initial EA report and reply to Vertex comments

Costs in the model *– we [Vertex] have identified that there are some potential bugs in the model relating to costs. The costs of best supportive care therapies (e.g., costs of inhaled antibiotics, hypertonic saline solution, etc. labelled as "drug costs" in the NICE EAG model) are contributing to the total costs for CFTRm comparators but not to ECM. Please can the EAG correct this bug in the model, or explain why this approach was taken, if intentional?*

Drug costs in row 1766 to 1768 of the "Data Library" worksheet are calculated in the trace but were not added to the summed discounted costs in error. This has been corrected.

2. ***Calculator of PEx costs in the CFTRm arm used ECM****- The calculation of PEx costs in the CFTRm arm were estimated based on the total number of PEx events of the ECM arm, leading to an overestimation of the disease management costs in the CFTRm arm and entailing a significant impact on the ICERs reported.*

Column CG in all CFTRm treatment traces used ECM to reference column AJ (PEx rate). This has been corrected. None of the errors identified have a significant impact on the ICERs reported as shown by the difference between the corrected and uncorrected ICERs, although this is largely due to the high cost of the undiscounted CFTRm treatments.

3. ***PEx in patients aged 2-5 years*** *- The EAG report states that there are no PEx in patients ages <6 years, however when we run a cohort with 2 years old with time horizon restricted to max age = 5, we could see the ICER reflecting PEx Disutilities. Please can the EAG clarify this?*

Note that restricting the maximum age to 5 is a limit placed on the initial cohort so patients should still experience PEx as they age past 5. However, the restriction of no PEx in patients under 6 was not added in the model and is now added.

4. ***Discrepancies in model results*** *- We were not able to replicate the model results of F/gating reported in the EAG report. Please can the EAG double check if the model inputs in the base case model shared vs. the ones used for the EAG report? The calculation of PEx events in the ECM arm was implemented incorrectly, resulting in no PEx events for ECM in F/Gating, which in turn affects the total costs and QALYs in the ECM arm. This is a significant error that substantially underestimates PEx costs and QALYs in the ECM arm, resulting in an overestimated ICER for IVA/TEZ/ELX in F/Gating.*

This was due to an error in the application of the time horizon limitation in the latest model in ECM. In F/Gating column AJ in the "Patient trace ECM" worksheet used the wrong >dblTimeHorizon sign which made the PEX rate 0 if time was under the time horizon rather than over. This has been corrected, although this does not impact any of the results presented by the EAG.

5. ***Discontinuation rates not transformed to prob*** *- The discontinuation rates are not transformed into probabilities before comparing to a random number, which resulted in much higher discontinuation in the acute period.*

The discontinuation rate has now been converted to a probability but this has very minimal impact on the discontinuations of patients. However, discontinuation was previously adjusted to be per cycle assuming the input value was the rate of discontinuation for the acute period. This has now also been changed to treat discontinuation as an annual rate

6. ***Back end calculation of baseline mortality hazard*** *- The back-end calculation of the baseline mortality hazard is incorrectly implemented. The mortality inputs are already mortality hazards but were treated as probabilities in the model calculations. This impacts the survival estimates and the CE results.*

-LN(1- removed from -LN(1-SWITCH(blPatSexFf,0,VLOOKUP(F6,rngCfMortBlFfgenMale,9,TRUE),VLOOKUP(F6,rngCfMortBlFfgenFemale,9,TRUE))) in column AO of trace

The baseline mortality hazard has been altered so the rate to probability conversion has been removed. This has marginal impacts on survival.

7. ***The EAG model applies a reduction in the rate of ppFEV1 decline for CFTRm when there is a positive change in ppFEV$_1$*** *-leading to a slower decline rate in ppFEV$_1$ for ECM when compared with the rate of decline in ppFEV1 for IVA/TEZ/ELX, TEZ/IVA and LUM/IVA.*

The ppFEV$_1$ decline calculation has been altered so if the untreated population (ECM patients) ppFEV$_1$ improves, the LT change in FEV$_1$ ratio of CFTRm input increases the rate of improvement in ppFEV$_1$. Only patients aged 6 or 7 see improvements in ppFEV$_1$ when on ECM so the impact of this error was relatively minor.

8. ***Treatment specific utility increment*** *- In the scenario with Vertex inputs, several inputs are incorrect and linking for utility increment for TRI and SYM is incorrect (links to LUM/IVA utility increment = 0). Will the EAG correct this error in the model?*

Symkevi® did not have the treatment related utility added to the Vertex inputs scenario, this has now been added. Both Symkevi® and Kaftrio® were referencing Orkambi® as stated by the Company, this has been repaired. However, the EAG also notes that Vertex inputs were used in earlier versions of the model development process and were meant to be removed before the final model. These were not used in the EA report or model. While corrections to these inputs are welcome this will not impact on any results presented by the EAG

9. ***Additional issues:***

The EAG has made a number of new corrections not identified by the company alongside new features related to additional scenarios.

- In the model sent by the EAG PEx cost was added to the total health state costs in the "Data Library" worksheet "Costs" section and added as a per event cost in the trace. It should have just been added as a per event cost therefore it has been removed from the total HS costs in the data library.

- PEx event costs were adjusted by cycle length in the model sent by the EAG. Given these are costs attributed specific events they should not be adjusted and this adjustment has been removed.

- The EAG has added "Reduction in concomitant drug costs for CFTRm treatments" input to dashboard in order to add scenario analysis.

- On "DSA results" worksheet treatments were not updating with genotype selection (row 7, 35, 63 and 91). This has been corrected.

- Update to which values were included in PSA/DSA i.e. long-term WFAZ excluded for all. This is intended to remove values that should not have a significant impact or the values which should not be varied.

- In the model sent by the EAG general population mortality was not converted to per cycle during the acute period in the model, instead keeping the annual rate. This is now adjusted to per cycle probability.

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Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

MTA Report

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Contribution of authors:

Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the clinical evidence; critical appraisal of the economic evidence; and provided feedback on all versions of the report. Guarantor of the report
Ben Farrar	Devised and carried out the literature searches on clinical effectiveness; contributed to study selection and data extraction; critical appraisal of the clinical evidence; carried out network meta-analyses; critique of the Company submission; and writing the clinical sections of the report.
Nicole Downes	Assisted with project co-ordination.
Victoria Wakefield	Assisted with project co-ordination and validated statistical analyses.
Kate Ennis	Devised and carried out the economic literature searches; study selection; data extraction; critical appraisal of the economic evidence; development of the conceptual model; performing economic analyses; critique of the Company submission; and writing the economic sections of the report.
Isaac Mackenzie	Study selection; data extraction; critical appraisal of the economic evidence; development of the economic model; carried out the economic analysis; and critique of the Company submission.
Archie Walters	Study selection and data extraction.
Tracey Jhita	Critical appraisal of the economic evidence; and quality assurance of the economic model.

All authors read and commented on draft versions of the EAG report.

All commercial in confidence data and information are highlighted in [redacted]

All academic in confidence data and information are highlighted in [redacted]

Abstract

Background

Cystic fibrosis (CF) is a life-limiting genetic condition that affects around 9,500 people in England and Wales. CF is usually diagnosed through newborn screening and causes symptoms throughout the body, including the lungs and digestive system. Around 90% of individuals with CF have at least one copy of the *F508del* mutation on the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Objectives

To appraise the clinical and cost effectiveness of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), tezacaftor/ivacaftor (TEZ/IVA) and lumacaftor/ivacaftor (LUM/IVA) within their expected marketing authorisations for treating people with CF and at least one *F508del* mutation, compared to each other and established clinical management (ECM) before these treatments.

Methods

A *de novo* systematic literature review (SLR [search date February 2023]) was conducted searching electronic databases (MEDLINE, EMBASE, CENTRAL), bibliographies of relevant SLRs including a relevant Cochrane review, clinical trial registers, recent conferences and evidence provided by Vertex Pharmaceuticals (Boston, MA, USA). Data on the following key outcomes were summarised: acute change in $ppFEV_1$; change in weight-for-age z-score and; the change in frequency of pulmonary exacerbations. Network meta-analyses were conducted where head-to-head data for comparisons were not available. Data from clinical trials and real-world evidence were examined to assess the long-term effects of ELX/TEZ/IVA, TEZ/IVA and LUM/IVA. A patient level simulation model was developed to assess the cost effectiveness of the three modulator treatments within their expected marketing authorisations. The model employed a lifetime horizon and was developed from perspective of the National Health Service (NHS).

Results

Data from 19 primary studies and seven open-label extension studies were prioritised in the SLR. ELX/TEZ/IVA was associated with a significantly greater increase in $ppFEV_1$, weight-for-age z-score and reduction in pulmonary exacerbations than ECM, LUM/IVA and TEZ/IVA, and also led to a reduction in the rate of $ppFEV_1$ decline relative to ECM, although the magnitude of this decrease was

uncertain. LUM/IVA and TEZ/IVA were also associated with significant increases in ppFEV$_1$ and reduction in pulmonary exacerbations relative to ECM, but with a smaller effect size than ELX/TEZ/IVA. There was some evidence that TEZ/IVA reduced the rate of ppFEV$_1$ decline relative to ECM, but little evidence that LUM/IVA reduced the rate of ppFEV$_1$ decline relative to ECM.

For the F/F population, the ICERs from the fully incremental analysis [redacted] and [redacted] for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, respectively. In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Deterministic results were similar across the two populations when compared to ECM, with ICERs of £[redacted] and £[redacted], respectively. In the F/RF population, the fully incremental results suggest that ELX/TEZ/IVA is the most cost-effective of the two treatments available, with a resulting ICER £[redacted] compared to the TEZ/IVA ICER of [redacted].

Conclusions

Despite the improved clinical benefits observed, none of the CFTR modulators assessed would be considered cost-effective based on the NICE threshold of £20,000–£30,000 per QALY gained. This is largely driven by the high acquisition costs of CFTR modulator treatments.

Abstract Word Count: 484

Study registration

The protocol for the systematic review is registered on PROSPERO (registration number CRD42023399583).

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Scientific summary

Background

Cystic fibrosis (CF) is a life-limiting genetic condition that is most often diagnosed through newborn screening. There are around 9,500 people with CF in England and Wales, and 89% of these people have CF caused by at least one *F508del* mutation on the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. CF affects organ systems throughout the body, including the digestive system and lungs. Lung disease is the primary cause of death for people with CF, and most people with CF experience progressive lung function loss over their lifetime.

Before the availability of CFTR modulator therapies, established clinical management for CF involved treating the symptoms of CF, rather than the underlying cause of the disease. Existing therapies include inhaled mucolytics, bronchodilators antibiotics and enzyme replacement therapy. A multidisciplinary team are involved in care for people with CF which includes physiotherapists, psychologists, dieticians and social workers, in addition to specialist nurses and doctors.

CFTR modulator therapies treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators have been available through the NHS via managed access agreements:

- Lumacaftor/ivacaftor (LUM/IVA) has been available for people aged 6+ years with CF and two *F508del* copies (F/F genotype) since October 2019, and currently is available for people aged 1+ years with CF and an F/F genotype;
- Tezacaftor/ivacaftor (TEZ/IVA) has been available for people aged 12+ years with CF and an F/F genotype or one *F508del* copy and an eligible residual function mutation (F/RF genotype) since October 2019, and currently is available for people aged 6+ years with CF and an F/F or F/RF genotype;
- Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been available for people aged 12+ years with CF and a single *F508del* copy with another eligible mutation (F/F, F/RF, F/minimal function [F/MF] or F/Gating genotype) since August 2019 under compassionate access, and across England and Wales since August 2020. Currently ELX/TEZ/IVA is available for people aged 6+ years with CF and an F/F, F/RF, F/MF or F/Gating genotype. ELX/TEZ/IVA has also been studied in clinical trials for people with an eligible genotype aged 2 to 5.

The clinical effectiveness and safety of CFTR modulator combination therapies has been studies in clinical trials, and through real-world data collection – notably through a Data Collection Agreement between the National Institute of Health and Care Excellence (NICE), the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals (Boston, MA, USA), National Health Service (NHS) England, and NHS Improvement.

Objectives

The objective of this multiple technology appraisal (MTA) is to compare the clinical and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA with each other and established clinical management for treating CF in England and Wales for people with at least one *F508del* mutation.

Methods

A *de novo* systematic literature review (SLR) was conducted to identify relevant studies through searches of electronic databases (MEDLINE, EMBASE, CENTRAL) up to February 2023, from bibliographies of retrieved studies including a relevant Cochrane review, clinical trial registers, relevant conferences and from an evidence submission provided by Vertex Pharmaceuticals. Pre-specified eligibility criteria were used to identify studies to be include in the SLR. Two independent reviewers appraised the titles and abstracts of identified records and performed an evaluation of full-texts. Data from included studies were extracted into a standardised data extraction form by one reviewer and validated by a second. The quality of included studies was assessed by a single reviewer at both the study and outcome level using standard checklists, which was then validated by a second reviewer. Extracted data and the quality assessments were presented in structured tables. Where sufficient data were available for an outcome measure within a genotype and age-group of interest, network meta-analyses (NMA) were performed using Bayesian Markov Chain Monte Carlo simulations. The key outcomes of the clinical effectiveness review were: changes in percent predicted forced expiratory volume in one second ($ppFEV_1$); changes in weight-for-age z-score and; the frequency of pulmonary exacerbations. Additional real-world evidence was obtained through targeted searches of electronic databases, a data request to the UK CF Registry, reviewing the UK CF Registry records, and through an appraisal of the final report of the Data Collection Agreement produced by Vertex Pharmaceuticals.

A *de novo* economic model was developed to assess the cost-effectiveness of the three CFTR modulator treatments, using an individual patient simulation model. The economic model uses a Cox

proportional hazards model developed by Liou 2001 to predict patient survival based on changes in individual characteristics over a patient's lifetime. Individual baseline characteristics are sourced from either patient level trial data, assumptions or population data from the UK CF Registry. The populations modelled are in line with the expected marketing authorisation of each intervention. Therefore, any patients who start the model in each treatment arm before the marketing authorisation age is reached for that specific CFTR modulator receives ECM only.

Estimates of treatment effectiveness, based on change in $ppFEV_1$, weight-for-age z-score and rate of pulmonary exacerbations were taken from the clinical assessment of the evidence. Due to a lack of long-term data available on the treatment effectiveness of CFTR modulators over a patient's lifetime, a number of assumptions needed to be made, based on clinical expert opinion and published evidence.

Utilities based on $ppFEV_1$ severity (<40, 40–69, ≥70) were obtained from the key trial of LUM/IVA; this was the only CFTR modulator trial that collected EQ-5D data. Costs were obtained from standard UK sources, with the costs of CFTR modulator treatments provided by the Company and based on published list price.

The economic model used a lifetime horizon (up to a maximum of 100 years) and the analysis is from an NHS perspective. Costs and QALYs have been discounted at 3.5%, as per the NICE reference case. The impact of uncertainty in key assumptions and model parameters was tested through a range of scenario analyses and probabilistic sensitivity analysis (PSA).

Results

Nineteen relevant studies and seven associated open label extension studies were included for data extraction from the SLR. Sixteen of these were Phase 3 (n=14), Phase 2 (n=1) or Phase 4 (n=1) randomised controlled trials, most of which were assessed to be high quality. Three non-randomised Phase 3 trials of children with CF were also included. The clinical trials were international studies but were assessed to have good generalisability to clinical practice in England and Wales.

Across genotypes, treatment with ELX/TEZ/IVA led to large and statistically significant acute increases in $ppFEV_1$ (F/F 12+ years genotype compared to ECM: +14.20% [95% CrI: 12.07 to 16.31]), weight-for-age z-score (F/F 12+ years genotype compared to ECM[redacted]) and a reduction in pulmonary exacerbations requiring intravenous antibiotics compared to ECM (F/MF

12+ years genotype compared to ECM [redacted] data not reported for F/F genotype) and, where available, LUM/IVA and TEZ/IVA. Clinical experts advised the EAG that the magnitude of these effects with ELX/TEZ/IVA are clinically meaningful, and likely to lead to increased survival relative to ECM, LUM/IVA and TEZ/IVA. LUM/IVA and TEZ/IVA were also associated with acute increases in increases in $ppFEV_1$, (F/F 12+ years genotype compared to ECM: LUM/IVA +2.83% [95% CrI: 1.84 to 3.81], TEZ/IVA +4.00% [95% CrI: 3.15 to 4.85]), and reductions in pulmonary exacerbations requiring intravenous antibiotics (F/F 12+ years genotype compared to ECM rate ratio: LUM/IVA: 0.44 [95% CI: NR], TEZ/IVA 0.53 [95% CI: 0.34 to 0.80]) and LUM/IVA was associated with an increase in weight-for-age z-score relative to ECM (F/F 12+ years genotype compared to ECM: LUM/IVA: [redacted], TEZ/IVA [redacted] The effect sizes for LUM/IVA and TEZ/IVA were smaller than for ELX/TEZ/IVA. Nevertheless, the effects are still expected be clinical meaningful and be associated with better long-term lung-function and increased survival compared to ECM.

The main outstanding uncertainty in the clinical effectiveness evidence is the effect of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the long-term annual rate of $ppFEV_1$ decline for people with CF. No head-to-head comparative effectiveness data are available for these long-term outcomes, and where uncontrolled long-term data are available, follow-up is often limited to 2 to 3 years follow-up. Real world data collection as part of the Data Collection Agreement does not provide robust long-term data for LUM/IVA or TEZ/IVA due to the rapid transitioning of most patients to ELX/TEZ/IVA once it became available. For ELX/TEZ/IVA, the unforeseen COVID-19 pandemic likely had a strong confounding effect on clinical trial data and real-world evidence collected during periods of viral shielding. The EAG considers the magnitude of any effects of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the long-term annual rate of $ppFEV_1$ decline for people with CF to be highly uncertain, but considers there to be:

- Little evidence to suggest LUM/IVA meaningfully reduces the long-term rate of $ppFEV_1$ decline compared to ECM (external assessment group [EAG] preferred assumption: 0% reduction in rate of $ppFEV_1$ decline compared to ECM);
- Some evidence that TEZ/IVA reduces the long-term rate of $ppFEV_1$ decline compared to ECM, with a small effect size (EAG preferred assumption: 17.18% reduction in rate of $ppFEV_1$ decline compared to ECM);

- Good evidence that ELX/TEZ/IVA reduces the long-term rate of ppFEV$_1$ decline compared to ECM, with a highly uncertain magnitude (EAG preferred assumption: 61.00% reduction in rate of ppFEV$_1$ decline compared to ECM).

Additional uncertainty was noted concerning:

- The effects of CFTR modulator therapy on EQ-5D measurements of health-related quality of life in CF;
- The effects of CFTR modulator therapy on the long-term rate of pulmonary exacerbations, which were inconsistently reported across clinical trials;
- Clinically important differences for acute changes in ppFEV$_1$ and weight-for-age z-score;
- The rate of co-adherence to non-CFTR modulator therapies and the effects of reduced co-adherence on CFTR modulator effectiveness;
- The long-term adverse event profile of CFTR modulators, specifically regarding mental health outcomes, hypertension and cataracts and lens opacities.

NICE typically considers interventions a cost-effective use of the NHS resources if the incremental cost-effectiveness ratio (ICER) sits below a £20,000–£30,000 cost per QALY threshold. None of the EAG's base case ICERs (both pairwise versus ECM alone or full incremental results) were lower than £30,000, and were substantially higher than this upper threshold. For the F/F population, all three modulator treatments have marketing authorisation. The ICERs from the full incremental analysis within the population were [redacted] for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, respectively.

In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Base case deterministic results were similar across the two populations when compared to ECM, with ICERs of [redacted] and [redacted], respectively.

In the F/RF population, both TEZ/IVA and ELX/TEZ/IVA have marketing authorisation. The full incremental results suggest that ELX/TEZ/IVA is the most cost-effective of the two treatments, producing both higher costs and higher QALYs than TEZ/IVA, with a resulting ICER of [redacted] compared to the TEZ/IVA ICER of [redacted].

The EAG ran a range of scenario analyses to explore the impact of different assumptions. The key drivers of cost-effectiveness for all genotype populations were the long-term assumptions of the

treatment effect of CFTR modulators on ppFEV$_1$ decline. None of the implemented scenarios resulted in an ICER below £30,000 and were substantially higher than this upper threshold.

The EAG also implemented an additional exploratory scenario to investigate the impact of ELX/TEZ/IVA preventing any long-term lung decline post treatment initiation. This exploratory scenario also assumes that the direct treatment effect of ELX/TEZ/IVA on the rate of pulmonary exacerbations lasts for a lifetime. Although this scenario resulted in lower ICERs for ELX/TEZ/IVA compared to the base case, they were still not below the £30,000 threshold, despite a severity modifier of 1.2 being applied, a 1.5% discount rate and highly optimistic assumptions regarding the long-term effectiveness of ELX/TEZ/IVA.

Conclusions

ELX/TEZ/IVA is associated with large and clinically meaningful acute improvements in lung function and weight-for-age z-score in people with CF, and results in a reduction in the frequency of pulmonary exacerbations. In the long term, ELX/TEZ/IVA reduces the rate of ppFEV$_1$ decline, although the magnitude of this reduction is uncertain. TEZ/IVA and LUM/IVA are also associated with improved clinical outcomes for people with CF relative to ECM, but with a smaller benefit than ELX/TEZ/IVA.

Despite the improved clinical outcomes observed, none of the included CFTR modulators would be considered cost-effective based on the NICE threshold of £20,000–£30,000 per QALY gained. This is largely driven by the high acquisition costs of CFTR modulator treatments.

If multiple treatments are made available in clinical practice, it is unknown if patients may switch between CFTR modulators once they reach the age at which a more effective treatment holds marketing authorisation (i.e. TEZ/IVA or ELX/TEZ/IVA). In addition, if more than one CFTR modulator was available in routine clinical practice, patients may be started on another upon discontinuation. There is currently a lack of both clinical and cost-effectiveness data on sequences of CFTR modulator treatments.

The following areas for future research are recommended:

- Further data collection concerning the long-term effects of CFTR modulators on the rate of ppFEV$_1$ decline, frequency of pulmonary exacerbations and changes in infection status in people with CF;

- The impact of co-adherence to ECM medications for people treated with CFTR modulators, and the effects of discontinuing CFTR modulators;
- The lifetime adverse event profile of CFTR modulators, including regarding liver disease, cataracts, lens opacities, hypertension and adverse effects on a person's mental health;
- Further validation of the Cox proportional hazards model used to model the impact of changes in patient characteristics over time on survival in the UK population.

Scientific Summary Word Count: 2,230

Plain English summary

This project reviewed the medical benefits, risks and costs of three treatments for cystic fibrosis: elexacaftor/tezacaftor/ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor. They correct the underlying cause of cystic fibrosis. in people who have a specific faulty version of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, called *F508del.*

A thorough search of medical journals and other relevant publications was undertaken to identify evidence on how well each treatment works. People treated with elexacaftor/tezacaftor/ivacaftor had large increases in lung function and other markers of overall health compared to people not treated with this medication, and this was expected to make them live longer. People treated with lumacaftor/ivacaftor and tezacaftor/ivacaftor also had increases in lung function, but this was not as large an improvement as with elexacaftor/tezacaftor/ivacaftor. These treatments have only been widely available in the UK since 2019 (lumacaftor/ivacaftor and tezacaftor/ivacaftor) or 2021 (elexacaftor/tezacaftor/ivacaftor), and so there is still uncertainty about their long-term effectiveness.

This project also assessed whether these treatments are likely to be considered good value for money for the NHS. The analysis found that based on the current prices of these treatments, they are unlikely to be considered good value for money for the NHS.

In summary, lumacaftor/ivacaftor and tezacaftor/ivacaftor appear to be effective, and elexacaftor/tezacaftor/ivacaftor appears to be very effective, at improving the health of people with cystic fibrosis, but they are also very expensive.

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List of Abbreviations

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BL	Baseline
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CDR	Common Drug Review
CF	Cystic fibrosis
CFB	Change from baseline
CFRD	Cystic fibrosis related diabetes
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFTR	Cystic fibrosis transmembrane conductance regulator gene
CFTR	Cystic fibrosis transmembrane conductance regulator protein
CFTRm	Cystic fibrosis transmembrane conductance regulator modulator
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance information criterion
DPI	Dry powder for inhalation
DSU	Decision Support Unit
EAG	External Assessment Group
ECFS	European Cystic Fibrosis Society
ECM	Established clinical management
ELX	Elexacaftor
EMA	European Medicines Agency
ESC	Economics subcommittee
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
F	*F508del*

FAS	Full analysis set
FCE	Finished consultant episode
FEV_1	Forced expiratory volume in one second
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Heath Survey for England
HTA	Health technology assessment
HUI	Health utilities index
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
ISPOR	The International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVA	Ivacaftor
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilograms
$LCI_{2.5}$	Lung clearance index 2.5%
LT	Long-term
LUM	Lumacaftor
LY	Life years
LYG	Life years gained
MA	Meta-analysis
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MF	Minimal function
mg	Milligrams
ml	Millilitre
mmol/L	Millimoles per litre
MMRM	Mixed effects model for repeated measures
MTA	Multiple technology appraisal
NA	Not applicable
NC	No change
NICE	National Institute for Health and Care Excellence

NHB	Net health benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NMA	Network meta-analysis
NR	Not reported
OLE	Open-label extension
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PERT	Pancreatic enzyme replacement therapy
PE	Pulmonary exacerbation
$ppFEV_1$	Percent predicted forced expiratory volume in one second
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Service
q12h	Every 12 hours
QALY	Quality-adjusted life year
qd	Once daily
RCT	Randomised controlled trial
RD	Respiratory domain
RF	Residual function
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomised trials
SAP	Statistical analysis plan
SAS	Safety analysis set
SE	Standard error
SD	Standard deviation
SF-6D	Short-Form 6-Dimension
SF-12	12-item Short-Form Health Survey
SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEZ	Tezacaftor
TSD	Technical Support Document
TTO	Time trade-off
USA	United States of America
UK	United Kingdom
VAS	Visual analogue scale
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

WFAZ	Weight-for-age z-score

1 Background

1.1 Description of health problem

1.1.1 Brief statement describing the health problem

Cystic fibrosis (CF) is a life-limiting genetic condition affecting over 9,000 people in England and Wales,[1] and is most often diagnosed through newborn screening.[2] CF is a recessive condition caused by mutations in the *CFTR* gene, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein: an anion transporter expressed throughout the body. CF is associated with symptoms across organ systems, including the lungs, digestive system, skin, and liver. Lung disease is the primary cause of death for people with CF, and most people with CF experience pulmonary exacerbations and progressive lung function decline over their lifetime.[3]

1.1.2 Aetiology, pathology and prognosis

CF is a recessive autosomal condition caused by mutations in the *CFTR* gene. The *CFTR* gene codes for the CFTR protein: an anion transporter expressed in exocrine glands throughout the body.[4] While primarily a chloride ion transporter, CFTR also transports bicarbonate and plays a key role in maintaining osmotic pressure across the cell membranes. In CF, CFTR dysregulation leads to the build-up of thick secretions that affect multiple organ systems, including the lungs, digestive system, skin and liver.

The most common mutation causing CF is a deletion of phenylalanine at residue 508 of the *CFTR* gene (*F508del* mutation). In the UK, 89.0% of genotyped individuals had at least one *F508del* copy.[1] *F508del* leads to the misfolding and subsequent targeting for degradation of the CFTR protein, reducing CFTR expression at the plasma membrane of cells in the body.[5] *F508del* homozygous individuals (F/F genotype) comprise 47.7% of people with CF in the UK, and 41.3% of individuals are *F508del* heterozygous including the following other mutation groups:

- *F508del* heterozygous with a minimal function mutation (F/MF genotype): Patients with one *F08del* copy and another mutation that produces no CFTR protein or one that is unresponsive to CFTR modulators.
- *F508del* heterozygous with a gating mutation (F/Gating genotype): Patients with one *F08del* copy and another mutation that is associated with CFTR expression at the cell membrane but with a reduced open probability of the CFTR ion channel.

- *F508del* heterozygous with a residual function mutation (F/RF genotype): Patients with one *F08del* copy and another mutation that is associated with CFTR expression at the cell membrane but with residual CFTR activity and ion transport. F/RF individuals typically have milder disease progression than other individuals with CF with at least one *F508del* copy.

People with CF without an *F508del* mutation comprise 10.7% of people with CF in England and Wales.[1] These individuals, on average, have milder disease compared to patients with at least one *F508del* copy, having a higher best forced expiratory volume in one second (FEV_1), lower probability of pancreatic insufficiency and lower probability of chronic *Pseudomonas* infection.[6]

Since 2007, all babies born in England and Wales have been screened for CF using a blood spot immunoreactive trypsin test.[2] Serum immunoreactive trypsin can be elevated in babies with CF due to thick secretions preventing trypsinogen from reaching the intestines. Babies with positive immunoreactive trypsin tests will have a confirmatory gene test for CF, covering over 50 different mutations, and a sweat chloride test.[7] The sweat chloride test detects elevated chloride levels on the skin of babies with CF, which builds up due to aberrant chloride ion transportation. If necessary, further genetic testing for a larger number of CF mutations may be conducted. In rare cases, a diagnosis of CF can be made upon clinical manifestations alone.[8]

Many symptoms of CF stem from damage to the pancreas and damage to the lungs. Irreversible pancreatic damage often occurs early in life, with around 83% of adults with CF in the UK being pancreatic insufficient, i.e., requiring pancreatic enzyme replacement therapy (PERT).[9-11] Damage to pancreatic cells is caused by thick secretions clogging the pancreatic ducts,[11] which can lead to the loss of acinar cells and severe impairment to β-cell function and reduced enzyme and hormone availability in the intestines.[12, 13] This produces a host of gastrointestinal symptoms in people with CF, including bloating, cramps and malnutrition.[14] Approximately 35% of adults with CF have CFRD.[1]

In the lungs, CFTR dysregulation leads to thick mucus obstructing the airways, causing difficulty breathing and leading to inflammation and susceptibility to infection. Such respiratory infections are a primary cause of pulmonary exacerbations requiring hospitalisation in CF, with 38.0% of people with CF in the UK received hospital-based intravenous antibiotics in 2019.[15] During the COVID-19 pandemic, this figure was lower: in 2021 18.7% of people with CF in the UK received hospital-based intravenous antibiotics.[1, 16] Lung disease is the primary cause of death for people with CF, and most people with CF experience progressive lung function loss over their lifetime, which can be measured

using the percent predicted forced expiratory volume in one second ($ppFEV_1$). Estimates of the rate of decline in $ppFEV_1$ vary between regions, age-groups, genotypes and studies; however most studies report an annual decline of around 1.5% for patients aged 12 to 30, after which the rate of decline may decrease.[3, 17] The annual rate of decline is also lower in people with milder CF, such as those who are pancreatic sufficient.[10]

In 2020, 101 (1.0%) of people with CF registered in the UK Cystic Fibrosis Registry died, with a median age of death of 36 years. For people born with CF between 2015 and 2019, median predicted survival is 49.1 years, 7.6 years longer than the median predicted survival of individuals born between 2007 and 2011.[15]

1.1.3 Epidemiology

1.1.3.1 Incidence and/or prevalence

The Cystic Fibrosis Registry is a national centralised registry maintained by the Cystic Fibrosis Trust containing data from over 99% of people with CF in England, Wales, Scotland, and Northern Ireland.[1, 18] The registry provides comprehensive and up-to-date data on the incidence and prevalence of CF in England and Wales. The CF Registry manages data submitted by UK CF centres from patient annual reviews, including details on pulmonary function and infections. Since the 2019 Data Collection Agreement between The National Institute for Health and Care Excellence (NICE), the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals (Boston, MA, USA, hereafter referred to as "Vertex"), National Health Service (NHS) England, and NHS Improvement, encounter-based data has been more systematically captured by the CF Registry.[19, 20]

In 2021, 10,908 individuals were registered in the UK CF Registry (people with CF with at least one annual review recorded in the last three years), including 9,044 people with CF in England and 454 people with CF in Wales.[1] Across the UK, there were 188 new diagnoses of CF in 2021. Genotyping was available for at least one mutation for 99.0% of registered individuals, and for both mutations for 96.3% of registered individuals. Of those with both mutations available, 47.7% of people were *F508del* homozygous and 41.3% of people were *F508del* heterozygous, meaning that 89.0% of genotyped individuals had at least one *F508del* copy. In England, 8,072 (89.3%) of patients had at least one *F508del* copy, and in Wales, 405 (89.2%) of patients had at least one *F508del* copy. For people with CF aged ≥6 years, the Company Submission contained data on the prevalence of F/F (*F50del* homozygous), F/MF (*F508del* heterozygous with a minimal function mutation), F/RF (*F508del*

heterozygous with a residual function mutation), and F/Gating (*F508del* heterozygous with a gating mutation), genotypes in England and Wales (Table 1).

Table 1. The prevalence of CF genotypes of people with CF aged ≥ 6 years in England and Wales

F508del genotype	Genotype prevalence ≥ 6 years, n (% of all genotyped individuals with at least one *F508del* copy)	
	England (N total = 7,600) (N genotyped = 7,537)	Wales (N total = 465) (N genotyped = 456)
F/F	[redacted]	[redacted]
F/MF	[redacted]	[redacted]
F/RF	[redacted]	[redacted]
F/Gating	[redacted]	[redacted]
F/*R117H*[a]	[redacted]	[redacted]
F/Other	[redacted]	[redacted]
No recorded *F508del* copy	[redacted]	[redacted]

[a]*R117H* is a non-gating residual function mutation, however is presented separately due to being within the marketing authorisation for ivacaftor monotherapy alongside other gating mutations, but not being within the marketing authorisation for tezacaftor/ivacaftor, unlike other residual function mutations.

Source: Vertex, data on file obtained from the UK CF Registry 2021[21]

Abbreviations CF: cystic fibrosis; UK: United Kingdom

1.1.4 *Impact of health problem*

1.1.4.1 *Significance for patients in terms of ill-health (burden of disease).*

The impact of CF on a person's health includes: a shortened life-expectancy; the clinical symptom burden; the treatment burden; the psychological burden of having CF and a potential lifestyle and financial burden. One of the major clinical burdens of CF is hospitalisation and requirements for IV antibiotics due to pulmonary exacerbations. In 2019, people with CF in the UK spent a median of 14 days (IQR: 12 days to 34 days) receiving hospital-based IV antibiotics, and 18 days (IQR: 12 days to 34 days) receiving home-based IV antibiotics, with a total of 44.5% of people with CF receiving IV antibiotics across the year.[15] In addition, people with CF can experience a host of symptoms

associated with declining lung function and symptoms associated with malabsorption, including but not limited to:[14, 22]

- Cough and wheezing;
- Breathlessness and reduced exercise tolerance;
- Tiredness and fatigue;
- Chest pain;
- Distal intestinal obstruction syndrome;
- Gastro oesophageal reflux disease;
- Meconium ileus;
- Bloating, cramps and malnutrition;
- Pancreatic insufficiency and CFRD.

People with CF are prone to bone conditions such as osteopenia and osteoporosis,[23] and some patients may develop CF-associated liver disease.[24] Such longer-term outcomes can introduce a significant clinical and psychological burden of disease for people with CF, including burden associated with infertility, transplant, and shortened life expectancy:

- Infertility affects around 98% of men with CF, due to obstructive azoospermia caused by the blockage, atypical development, or absence of the vas deferens. In women with CF, fertility issues are less common, but can be caused by thicker vaginal mucus or due to CF-related illnesses.[25] Infertility can be associated with stress, anxiety and depression, although there is limited research regarding the burden of infertility in people with CF in paritcular.[26]
- People with CF with severe organ damage, most commonly of the lungs, may require transplantation. In 2019 in the UK, 241 people with CF were evaluated for transplantation and 96 were accepted, with 49 people ≥ 16 years receiving a bilateral lung transplant.[1]

People with CF have a large treatment burden. According to the Cystic Fibrosis Trust 2017 and 2018 Insight Surveys, adults with CF report spending an average of 150 minutes a day on treatments and physiotherapy,[27] with physiotherapy for airway clearance occurring at least twice daily for 10-30 minutes.[28] The high treatment burden associated with CF care was noted by multiple stakeholder submissions,[28-33] and by the EAG's clinical experts. Such a high treatment burden is often translated into a large caregiver burden for caregivers of children with CF, who often must coordinate, supervise or perform certain therapies. A Vertex-sponsored systematic review of caregiver burden in

CF found publications reporting a lower utility score in CF caregivers in the UK compared to population norms in both Germany and the UK,[34] and a high incidence of anxiety and depression among CF caregivers.[35] In addition, a survey performed by CF Voices in the UK in Spring 2020 highlighted that:[30]

- UK CF caregivers described how the work, life and financial wellbeing of carers and families had been negatively impacted by their care burden;
- The overall mean CarerQol-7D utility score of CF caregivers was 62.8, similar to that reported of carers of people with degenerative cervical myelopathy;[36]
- The carer burden extends beyond the primary carer, with a significant impact on siblings of children with CF.

A UK-wide survey conducted by the CF Trust on the cost of living with CF in Spring 2022[37] reported that 77% of parents, carers and spouses felt their caring responsibilities for family members with CF had an effect on their employment.

Despite the life-limiting nature of CF, the psychological burden of CF is complex. The NICE guideline on the diagnosis and management of CF (NG78) recommends a psychological assessment should occur at each annual review,[8] and the need for a clinical psychologist as a part of an individual's multidisciplinary team is outlined in the Cystic Fibrosis Trust's Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK.[38]

The Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK highlights a diversity of psychological and behavioural burden that a person with CF may experience, including: the psychosocial impact of segregation from others with CF; eating difficulties; issues concerning needle aversion/phobia; the difficulty of adherence to therapies; school problems; anxiety disorders, depression; concerns over infertility; and end of life/transplant issues. Several studies have also found an association between poor clinical outcomes, such as low $ppFEV_1$ and pulmonary exacerbations, and reduced quality of life between people with CF.[39-41] Stakeholder submissions also foregrounded difficulties in psychological adjustment that may be particularly relevant when new, highly effective therapies are introduced.[33]

Despite the clinical, psychosocial, and treatment burden of CF, people with CF often report high-quality of life — similar to healthy controls on generic measures of health-related quality of life (HRQoL). In two clinical trials where the European Quality of Life 5 Dimensions 3 Level Version (EQ-

5D-3L) has been used to measure HRQoL in people with CF, namely TRAFFIC and TRANSPORT, the mean baseline EQ-5D-3L index score of participants was 0.92,[42, 43] and EQ-5D-3L was highest for those with ppFEV$_1$ ≥90% (0.95), followed by 70%–90% (0.93), 40–70% (0.91) and lowest for those with ppFEV$_1$ <40% (0.88). Similar values were reported using the EQ-5D-5L scale in the STRIVE clinical trial.[44] These values are approximately in-line with UK population norms for ages <25 years (0.94) and 35–44 years (0.91).[45]

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a CF-specific HRQoL measure with versions available for adolescents and adults aged ≥14 years, children, and for parents of children with CF.[46, 47] It is comprised of nine HRQoL domains, three symptom scales, and one health status perception scale: HRQoL domains — Physical Functioning, Vitality, Emotional state, Social limitations, Role Limitations/School Performance, Embarrassment, Body Image, Eating Disturbances and Treatment Constraints; Symptom scales — Respiratory, Digestive and Weight. The CFQ-R has been validated across CF cohorts, including parent cohorts, and displays sensitivity to differences in the HRQoL related to lung-function.[48, 49] That CF patients can experience difficulties throughout the domains of the CFQ-R was highlighted across stakeholder submissions, and also by the EAG's clinical experts, especially for those with a high treatment burden.[28-33] Other, system specific CF patient reported outcome measures have also been developed, such as the CFAbd-Score for abdominal symptoms.[50]

The EAG's clinical experts highlighted how chronic diseases with symptom burdens like those with CF may limit earning potential of many patients. The financial burden of CF on patients and their families has been explored in a 2023 report conducted by the University of Bristol and CF Trust,[51] in which 59% of adults with CF surveyed noted that they had incurred loss in income due to needing to reduce work hours, attend routine appointment or leave employment completely. It was estimated that a typical family with a member with CF will lose £6,768 a year due to the additional costs associated with travel for medical appointments, prescription costs, dietary requirements and higher energy bills. Another recent CF Trust report found that 7 in 10 people with CF reported being on benefits, with 25% of those reporting having to use their benefits for prescriptions.[37]

1.1.4.2 Significance for the NHS

There are 30 paediatric and 26 regional CF centres in the UK, four stand-alone clinics and 76 networked clinics in the UK.[1] A multidisciplinary team is involved in care for people with CF, including a medical consultant, clinical nurse specialist, physiotherapist, dietitian, clinical psychologist, social worker and pharmacist.[38] People with CF should have at least two outpatient visits to their CF centre

each year, including an annual review. The recommended frequency of visits is one every 2 to 3 months, and visits may be more frequent for people experiencing clinical problems. Many people with CF will require inpatient visits, most often to receive IV antibiotics to treat infective pulmonary exacerbations. In 2019, people with CF in the UK spent a median of 14 days (IQR: 12 days to 34 days) receiving hospital-based IV antibiotics.[15] Homecare for CF is also offered by most specialist CF services in the UK, often provided by the clinical nurse specialist but may also involve other members of the multidisciplinary team. Homecare for CF can involve many aspects of clinical and social care, from the provision of home-based IV antibiotics and clinical assessments to psychosocial support and health education.

Due to the multidisciplinary nature of CF and wide range of symptoms and associated co-morbidities, the costs to the NHS are substantial. A cost-of-illness study conducted in 2012 estimated that the average direct health care costs for a person with CF in the UK was €20,854 (costs presented in Euros in 2012).[52] In 2019, the confidential commercial arrangement made between NHS England and Vertex, resulted in access to the three CFTR modulator combination therapies for an estimated 5000 patients. While the amount agreed as part of the commercial arrangement is confidential, with the high costs associated with CFTR-modulator therapies it is likely that the cost for the NHS has risen in recent years.

1.1.5 Measurement of disease

An overview of common indicators of CF severity and quality of life in people with CF is detailed in Table 2.

Table 2. Common measurements of the severity of cystic fibrosis.

Measure	Description
Disease severity	
$ppFEV_1$	The percent-predicted forced expiratory volume in one second ($ppFEV_1$) is a measure of a person's lung function, representing the volume of air that can be blown out in the first second following a full inspiration, standardised against the population average for a person of the same age, height, sex, and race. A variety of reference equations for calculating $ppFEV_1$ have been developed, including by Knudson,[53] Wang and Hankinson,[54, 55] Stanojevic,[56] and the Quanjer-Global Lung Function Initiative.[57]

	In 2021, the mean $ppFEV_1$ of people with CF in the UK CF Registry was 92.0% (aged <18 years) and 72.4% (aged ≥18 years). The lowest mean $ppFEV_1$, 62.6%, was observed in the highest age group, ≥60 years, reflecting the progressive loss of lung function observed in CF.[1] A $ppFEV_1$ <40% is considered advanced lung disease,[58] and is a point at which the EAG's clinical experts stated patients would be considered for lung transplant.
$LCI_{2.5}$	The lung clearance index 2.5% ($LCI_{2.5}$) is a measure of relaxed tidal breathing through a multiple-breath washout test. The $LCI_{2.5}$ measures the number of lung volume turnovers required to clear a tracer gas to 2.5% of its starting volume. Without requiring forced expiration, the $LCI_{2.5}$ is suitable for use in young children and infants, where $ppFEV_1$ can be difficult to measure and unreliable.[59] Abnormal $LCI_{2.5}$ aged 3-5 years may be a more sensitive predictor of later spirometry abnormalities than $ppFEV_1$ at the same age.[60] The $LCI_{2.5}$ is therefore a preferred measure of lung function in young children.
Pulmonary exacerbations	Pulmonary exacerbations are both a cause of lung function decline in CF and are associated with reduced quality of life for people with CF.[44] The EAG's clinical experts stated that pulmonary exacerbations are acute worsening of CF symptoms that is usually associated with infection, and often requires the use of IV antibiotics. Pulmonary exacerbations are the primary cause of hospitalisation for people with CF. However, pulmonary exacerbations have been inconsistently recorded in clinical trials, and are not directly recorded in the UK CF Registry. The following definitions of pulmonary exacerbation are available: • Definitions used in clinical trial protocols, such as: "New event or change in antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection";[61] • In the Medical Dictionary for Regulatory Activities (MedDRA) as Infective pulmonary exacerbation of CF, which has been used to recorded pulmonary exacerbations as adverse events in trials; • IV antibiotic use, which is recorded in the UK CF Registry, may be used as a proxy for the rate of pulmonary exacerbations.[62]

Pulmonary bacterial colonisation	Many people with CF will suffer from chronic or intermittent bacterial infections of the lung, which are monitored at each clinic visit through the microbiological surveillance of respiratory secretions. The most common bacterial infections reported in the UK CF Registry are: • *Pseudomonas aeruginosa* • *Staphylococcus aureus* • *Burkholderia cepacia complex* • *Aspergillus* • *Haemophilus influenzae* • Methicillin−resistant *S. aureus* Of these, *B. cepacia* infection is a severe infection predictive of a rapid decline in lung function and subsequently mortality.[63] The EAG's clinical experts also highlighted how the age of *Pseudomonas* acquisition can influence future lung function decline and clinical outcomes.
Pancreatic insufficiency and CF related diabetes	Pancreatic insufficiency is often measured indirectly through the need for pancreatic enzyme replacement therapy (PERT). Pancreatic insufficiency is correlated with a more rapid decline in lung function than pancreatic sufficiency,[10] which is a marker of less severe CF. Damage to the endocrine function of the pancreas can lead to later developing CF-related diabetes, with 8.3% of people with CF in the UK in 2021 age 10 to 15 years and 35.2% of those aged ≥16 years receiving treatment for CF related diabetes.[1]
Weight-, height- and BMI-for-age z-scores	Measurements of weight, height and BMI are markers of the effects of cystic fibrosis on the digestive system, and independent predictors of survival. Standardised z-scores are calculated across ages up to 20 years.
Sweat chloride	A sweat test is used in the diagnosis of CF and is taken in accordance with the Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis. 2nd Version.[7] Due to CFTR dysregulation, chloride can be elevated in the sweat of people with CF, and changes to sweat chloride levels can be indicative of the severity of CF, in addition to the efficacy of CF treatments that aim to improve CFTR function. A sweat chloride concentration of <40 mmol/L is considered normal, whereas a concentration >60 mmol/L is sufficient to support a diagnosis of CF.
Quality of life	

CFQ-R	The CFQ-R is a CF-specific HRQoL measure with versions available for adolescents and adults aged ≥14 years, children, and for parents of children with CF.[46, 47] It is comprised of nine HRQoL domains, three symptom scales, and one health status perception scale: HRQoL domains: Physical Functioning, Vitality, Emotional state, Social limitations, Role Limitations/School Performance, Embarrassment, Body Image, Eating Disturbances and Treatment Constraints; Symptom scales: Respiratory, Digestive and Weight. The CFQ-R has been validated across CF cohorts, including parent cohorts, and displays sensitivity to differences in the HRQoL related to lung-function.[48, 49]

Abbreviations: CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; HRQoL: health-related quality of life; IV: intravenous; $LCI_{2.5}$: lung clearance index 2.5; PERT: pancreatic enzyme replacement therapy; $ppFEV_1$: percent-predicted forced expiratory volume in one second; UK: United Kingdom

1.2 Current service provision

1.2.1 Management of disease

Established clinical management (ECM) for CF involves managing both CF symptoms and symptoms associated with CF treatments. No ECM therapy treats the underlying cause of the disease, i.e., restores CFTR protein function. ECM for CF is coordinated by a multidisciplinary team, which includes prescribing and administering medication, planning diets, coordinating physical therapy such as airway clearance, and social and psychological support. The 2021 UK Cystic Fibrosis Registry Annual Report provides details on the frequency of use of many of these therapies used by people with CF in the UK, and these are provided in Table 3. In addition, people with CF who are pancreatic insufficient will receive PERT, and those with cystic fibrosis related diabetes (CFRD) will receive insulin.

Table 3. Proportion of people with CF receiving non-CFTR modulator treatments reported in the UK Cystic Fibrosis Registry 2021 Annual Report.[1]

Therapy[a]	Percentage of people with CF using each therapy in 2021
Inhaled antibiotics	53.0
Long-term azithromycin	40.9
Prophylactic flucloxacillin	19.3
IV antibiotics	
Home	12.6
Hospital	18.7

Overall	24.3
Inhaled bronchodilators and corticosteroids	
Inhaled bronchodilators	60.2
Inhaled corticosteroids	18.6
Inhaled bronchodilators and inhaled corticosteroids combination	29.1
Mucoactive therapies	
DNase	69.2
Hypertonic saline	37.3
Mannitol	3.0
Non-invasive ventilation and oxygen use	
Non-invasive ventilation	1.4
Oxygen use	4.1
Physiotherapy	
Active cycle of breathing techniques	12.5
Autogenic drainage	17.7
Postural drainage	6.2
Any form of positive expiratory pressure	59.7
High-frequency chest wall oscillation	1.6
Exercise	59.9
Other	17.6
Feeding	
Any supplemental feeding	34.6
Gastrostomy tube/button	4.5

[a]Only therapies used by ≥1.0% of pwCF are reported. Therapies are not mutually exclusive.
Abbreviations: CF: cystic fibrosis: CFTR: cystic fibrosis transmembrane conductance regulator; IV: intravenous
Source: UK Cystic Fibrosis Registry Annual Report 2021[1]

The existing NICE guidance for diagnosing and managing CF recommends (NG78):[8]

- A mucoactive agent for people with CF who have clinical evidence of lung disease;
- Oral pancreatic enzyme replacement therapy for people with exocrine pancreatic insufficiency;

- Use of physical airway clearance techniques;
- A range of eradication therapies, including oral, intravenous (IV) or inhaled antibiotics for treating pulmonary infections;
- Offering oral or IV fluids to ensure adequate hydration (and rehydration if needed) for people with distal intestinal obstruction syndrome, and further treatment if this is unsuccessful;
- Referring liver disease to a liver specialist and seeking specialist advice for people with a bone mineral density standard deviation below –2.0 (z score);
- The off-label use of immunomodulators for people with CF and deteriorating lung function or repeated pulmonary exacerbations.

In addition, two therapies have been approved through NICE Single Technology Appraisals, specifically:

- TA266: Mannitol dry powder for inhalation (DPI) is recommended as an option for treating CF in adults:
    - who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and;
    - whose lung function is rapidly declining, i.e., FEV_1 decline greater than 2% annually and;
    - for whom other osmotic agents are not considered appropriate.[64]
- TA276: Tobramycin DPI and colistimethate sodium DPI are recommended, with conditions, as options for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with CF.[65]

In 2021, mannitol use was 5.0% for people with CF in the UK ≥ 18 years, and 0.1% for those <18 years. Of people with CF who had a chronic *P. aeruginosa* infection, 18.1% were treatment with tobramycin DPI, and 18.0% were treated with sodium DPI.

1.2.2 Current service cost

Treatments used as part of ECM can vary greatly between patients and care is often individualised to manage symptoms and comorbidities. Due to this, there is no set treatment cost for all CF patients. Since the introduction of the managed access agreement between Vertex and NHS England, the majority of patients are currently on a CFTR modulator treatment. The annual cost per patient based

on current list prices for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA are: £200,187; £173,414 and £104,357 respectively. Based on the latest available data from the CF Trust on the number of patients taking each CFTR modulator in December 2021,[1] this results in an annual cost of £1.2 billion.

1.2.3 Variation in services and/or uncertainty about best practice

CF services in the UK follows the Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK,[38] and NG78,[8] which recommend a multidisciplinary team for the care of people with CF, and appropriate treatments for CF symptoms. The UK Cystic Fibrosis Registry Annual Data Reports provide by centre-analyses on clinical, demographic and treatment use statistics by UK CF centre. Overall, these data suggest that the use of antibiotic and mucoactive therapy is consistent between CF centres, with the possible exception of mannitol, which was not reported as being used by five adult centres. Much of the variability that exists between centres may be attributable to the patient needs of those centres, rather than systematic differences between centres.[1, 15] UK CF centres are also consistent in having a doctor, nurse, physiotherapist and dietician available to form part of the CF multidisciplinary team, with 95.7% of surveyed adult centres and 100% of surveyed paediatric centres in 2021 reporting a member of staff available for each position. Pharmacists (adult centres: 56.5%; paediatric centres: 30.8%) and psychologists (adult centres: 65.2%; paediatric centres: 30.8%) were commonly, but not ubiquitously, available, whereas there was an inconsistent availability of social workers (adult centres: 82.6%; paediatric centres: 76.9%) and research staff (adult centres: 82.6%; paediatric centres: 76.9%).[66] The EAG's clinical experts also noted variability across England and Wales in:

- The likelihood of receiving home versus hospital-based IV antibiotic therapy;
- The treatment of first *Pseudomonas* isolation;
- The CF facilities available to patients.

1.2.4 Relevant national guidelines, including National Service Frameworks

Relevant guidelines for the care and treatment of CF are presented in Table 4.

Table 4. Guidelines for the care and treatment of CF.

Publisher	Document
Overall CF Care	
CF Trust	Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK. Second edition. (2011)[38], *currently being updated*.
NICE	Cystic fibrosis: diagnosis and management (NG78) (2017)[8]
NHS England	National Programmes of Care and Clinical Reference Groups Service Specification: A01 Cystic Fibrosis (Children)[67]
	National Programmes of Care and Clinical Reference Groups Service Specification: A01 Cystic Fibrosis (Adults)[68]
Specific CF Care	
CF Trust Consensus Documents	Pharmacy standards in cystic fibrosis care in the UK (2022)[69]
	Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis (2020)[70]
	Nutritional Management of Cystic Fibrosis (2016)[71]
	Mycobacterium abscessus: Recommendations for infection prevention and control (2017)[72]
	Pharmacy Standards of Care (2011)[73]
	Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis (2022)[74]
	Antibiotic Treatment for cystic fibrosis (2009)[75]
	Methicillin-resistant *Staphylococcus aureus* (MRSA) (2008)[76]
	Pseudomonas aeruginosa infection in people with cystic fibrosis. Suggestions for Prevention and Infection Control (2004)[77]
	The *Burkholderia cepacia complex*. Suggestions for Prevention and Infection Control (2004)[78]
	Management of Cystic Fibrosis Diabetes (2022)[79]
	National Consensus Standards for the Nursing Management of cystic fibrosis (2001)[80]
European CF Society Standards of Care	
European CF Society	ECFS best practice guidelines: the 2018 revision[81]
	European cystic fibrosis bone mineralisation guidelines[82]

	Standards of Care for Cystic Fibrosis ten years later[83]
	European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre[84]
	European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis[85]
	ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis (2016)[86]

Abbreviations: CF: cystic fibrosis; ECFS: European CF Society; ESPEN: European Society for Clinical Nutrition and Metabolism; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; NHS: National Health Service; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.

1.3 Description of technology under assessment

1.3.1 Summary of Intervention

Three CFTR modulator combination therapies are being appraised in this Multiple Technology Appraisal (MTA):

- lumacaftor/ivacaftor combination therapy (LUM/IVA);
- tezacaftor/ivacaftor combination therapy (TEZ/IVA);
- elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA).

CFTR modulators treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators have five categories depending on their effect on the CFTR protein: correctors; potentiators; stabilisers; amplifiers; and read-though agents. Each combination therapy includes ivacaftor (Kalydeco®, Vertex), a CFTR potentiator, which itself has marketing authorisation as a monotherapy for the treatment of infants aged 4 months and over weighing 5 kg to 25 kg,[87] and for adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with CF who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene:[88] *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*. Ivacaftor binds to the CFTR protein at the cell membrane, increasing the open probability and ability of the channel to transport chloride. In contrast to ivacaftor, lumacaftor, tezacaftor and elexacaftor are CFTR correctors that improve CFTR protein folding and subsequent cellular processing, preventing the CFTR protein being targeted for degradation in people with an *F508del* mutation, and increasing CFTR expression at the cell membrane.[89-93]

LUM/IVA combination therapy (Orkambi®, Vertex) is a systemic protein modulator, comprising of lumacaftor and ivacaftor. LUM/IVA is administered orally and has a marketing authorisation in the

UK for treating, "cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".[94] For patients aged 6–11 years, two tablets of lumacaftor 100 mg/ivacaftor 125 mg are taken every 12 hours. For patients ≥12 years, two tablets of lumacaftor 200 mg/ivacaftor 125 mg are taken every 12 hours.[94] LUM/IVA granules also have a marketing authorisation for children with CF who are homozygous for *F508del* and who are aged 1 year and older.[95] The dosing recommendations for people with CF <6 years for LUM/IVA are presented in Table 5. LUM/IVA has previously been appraised by NICE. In TA398, LUM/IVA was not recommended within its marketing authorisation for treating cystic fibrosis in people 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.[96]

Table 5. Dosing recommendations for LUM/IVA in people with CF aged 1 to 5 years.

Age	Weight	Dose per sachet	Dose every 12 hours
1 to 2 years	7 kg to < 9 kg	lumacaftor 75 mg/ ivacaftor 94 mg	One sachet every 12 hours
	9 kg to < 14 kg	lumacaftor 100 mg/ ivacaftor 125 mg	
	≥14 kg	lumacaftor 150 mg/ ivacaftor 188 mg	
2 to 5 years	<14 kg	lumacaftor 100mg/ivacaftor 125 mg	
2 to 5 years	≥ 14 kg	lumacaftor 150 mg/ivacaftor 188 mg	

Abbreviations: CF: cystic fibrosis; IVA: ivacaftor; kg: kilograms; LUM: lumacaftor; mg: milligrams

TEZ/IVA combination therapy (Symkevi®, Vertex) is a systemic protein modulator, comprising of tezacaftor, a CFTR corrector, and ivacaftor. TEZ/IVA is administered orally and has a marketing authorisation in the UK, "in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T".[97] Dosing for TEZ/IVA is age and weight dependent, and is presented in Table 6.[97]

Table 6. Dosing recommendations for TEZ/IVA patients aged 6 years and older.[97]

Age and weight	Morning dose	Evening dose
6 to <12 years, <30 kg	One tablet containing tezacaftor 50 mg/ivacaftor 75 mg	One tablet containing ivacaftor 75 mg
6 to <12 years, ≥30 kg	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg
≥12 years	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg

Abbreviations: CF: cystic fibrosis; IVA: ivacaftor; kg: kilograms; mg: milligrams; TEZ: tezacaftor

ELX/TEZ/IVA combination therapy (Kaftrio®, Vertex) is a systemic protein modulator, comprising of elexacaftor, a CFTR corrector, tezacaftor and ivacaftor. ELX/TEZ/IVA is administered orally and has a marketing authorisation in the UK, "in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".[98] Dosing for ELX/TEZ/IVA is age and weight dependent, and is presented in Table 7.[98] The clinical effectiveness and safety of ELX/TEZ/IVA has also been studied in a Phase III clinical trial in children aged ≥2 years.[99]

Table 7. Dosing recommendations for ELX/TEZ/IVA patients aged 6 years and older.[98]

Age and weight	Morning dose	Evening dose
6 to <12 years, <30 kg	Two tablets, each containing ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg	One tablet containing ivacaftor 75 mg
6 to <12 years, ≥30 kg	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg
≥12 years	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg

Abbreviations: CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; kg: kilograms; mg: milligrams; TEZ: tezacaftor

1.3.2 Identification of important subgroups

The NICE final scope included the following subgroups:[100]

- People with CF who are homozygous for the *F508del* mutation;
- People with CF who are heterozygous for the *F508del* mutation and a residual function mutation or a gating mutation in the *CFTR* gene.

The EAG agrees that CF genotype is a clinically meaningful subgroup, and that CF genotype is a key subgroup to consider in this MTA given the marketing authorisation of some of the comparator therapies are limited to certain CF genotypes, and the inclusion criteria of key clinical trials are based on CF genotypes. The EAG considers the following subgroups to be important:

- People with CF who are homozygous for the *F508del* mutation (F/F genotype);
    - LUM/IVA (≥1 year), TEZ/IVA (≥6 years) and ELX/TEZ/IVA (≥6 years) have marketing authorisation for this genotype.
- People with CF who are heterozygous for the *F508del* mutation and a residual function mutation (F/RF genotype);
    - TEZ/IVA (≥6 years) and ELX/TEZ/IVA (≥6 years) have marketing authorisation for this genotype.
- People with CF who are heterozygous for the *F508del* mutation and a gating function mutation or an *R117H* mutation (F/Gating genotype);
    - ELX/TEZ/IVA (≥6 years) and ivacaftor monotherapy (≥4 months) have a marketing authorisation for this genotype.
- People with CF who are heterozygous for the *F508del* mutation and a minimal function mutation (F/MF genotype);
    - ELX/TEZ/IVA (≥6 years) has a marketing authorisation for this genotype.

The EAG's clinical experts noted that there is considerable overlap in the phenotype and clinical outcomes of patients with F/F, F/MF and F/Gating genotypes, but that the F/RF genotype has a less severe CF phenotype, which is supported by real-world data.[3]

The NICE final scope also included the following statement in other considerations: "If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness." The EAG's clinical experts considered it plausible that low baseline lung function may either decrease or increase the potential effectiveness of CFTR modulator therapies for an individual, which may differ between patients with CF. On the one hand, lung damage may be irreversible in people with CF, which would limit the overall potential effectiveness of CFTR

modulator therapies in people with existing lung damage. On the other hand, patients with little existing lung damage may have near ceiling ppFEV$_1$, which may limit the overall acute response they can achieve through CFTR modulator therapy. The EAG's clinical experts highlighted how a key subgroup of people with CF may be those who receive highly effective CFTR modulator therapy prior to developing initial and irreversible lung and pancreas damage. They suggested that the closer to birth that these people initiate CFTR modulator therapy, the more benefit they are likely to achieve, which may include preventing long term ppFEV$_1$ decline. As such, the EAG will consider the following subgroups:

- If data are available, the EAG will present clinical efficacy data by trial-reported lung function subgroups;
- The EAG will consider a scenario analysis in which patients initiating highly effective CFTR modulator therapies early receive a sustained reduction in long-term decline of ppFEV$_1$.

1.3.3 Current usage in the NHS

All three CFTR modulator therapies that are part of this MTA (LUM/IVA, TEZ/IVA and ELX/TEZ/IVA) are currently available on the NHS through a managed access agreement.[101] LUM/IVA and TEZ/IVA have been available on the NHS since October 2019 and ELX/TEZ/IVA has been available since August 2020. Of the 10,175 individuals registered and who had an annual review in 2021 in the UK Cystic Fibrosis Registry, 7,384 (72.6%) were taking a CFTR modulator by December 2021, including:[1]

- 5,321 people (72.1% of individuals on a CFTR modulator) taking ELX/TEZ/IVA;
- 515 people (7.0%) taking TEZ/IVA;
- 942 people (12.8%) taking LUM/IVA and;
- 606 people (8.2%) taking ivacaftor monotherapy.

Following a request by the EAG to the UK CF Registry (Data Request 469),[102] the UK CF Registry provided updated numbers of people taking a CFTR modulator by December 2022:

- [redacted] people taking ELX/TEZ/IVA;
- [redacted] people taking TEZ/IVA;
- [redacted] people taking LUM/IVA and;
- [redacted] people taking ivacaftor monotherapy.

These figures demonstrate a widespread uptake of CFTR modulator therapy, and that this uptake now primarily consists of individuals taking ELX/TEZ/IVA. During 2021, the number of people receiving ELX/TEZ/IVA rose from 4,195 in January 2021 to 5,321 in December 2021, which [redacted] to [redacted] by December 2022. whereas the use of TEZ/IVA and LUM/IVA combination therapies [redacted]. The EAG's clinical experts stated that most patients who started on LUM/IVA and TEZ/IVA have now switched to ELX/TEZ/IVA, and that ELX/TEZ/IVA is the preferred therapy for any person who is eligible, except in the rare cases where their CF is not severe enough to require CFTR modulator therapy.

1.3.4 Anticipated costs associated with intervention

The three CFTR modulator treatments included in this MTA employ flat pricing, meaning that despite the strength of dose for each CFTR-modulator combination therapy varying by age and weight, the pack price of the different strengths available is the same. The list prices for each of the included interventions is shown in Table 8. Both ELX/TEZ/IVA and TEZ/IVA combinations include a separate dose of ivacaftor, therefore costs of ivacaftor monotherapy are also reported below. Each intervention is given in combination with ECM.

Table 8. Intervention costs for the included CFTR modulator treatments

Treatment	Strength*	Pack size	List price (per pack)
LUM/IVA	75 mg / 94 mg sachet	56	£8,000.00
	100 mg / 125 mg sachet		
	150 mg / 188 mg sachet		
	100 mg / 125 mg tablets	112	£8,000.00
	200 mg / 125 mg		
TEZ/IVA	50 mg / 75 mg tablets	28	£6,293.91
	100 mg / 150 mg tablets		
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]
	[redacted]		
	37.5 mg / 25 mg / 50mg tablets	56	£8,346.30
	75 mg / 50 mg/ 100 mg tablets		
Ivacaftor	[redacted]	[redacted]	[redacted]
	[redacted]		
	75 mg tablets	28	£7,000.00
	150 mg tablets		

*The order of the strength of the tablets reflects the order of the associated combination therapy. For example, for the LUM/IVA strength of 100 mg / 125 mg represents lumacaftor 100 mg and ivacaftor 125 mg.

**Proposed list price for ELX/TEX/IVA + IVA granules for the 2 to 5 years age group.

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; mg: milligram; TEZ: tezacaftor

2 Definition of the decision problem

2.1 Decision problem

The decision problem outlined in the National Institute for Health and Care Excellence (NICE) final scope is presented in Table 9. In Table 9, the external assessment group (EAG) highlights any differences between the decision problem outlined in the NICE final scope and, i) the decision problem addressed by the EAG in this Assessment Report and, ii) the decision problem addressed by Vertex in the Company Submission. The EAG provides further critique of the Company Submission throughout the Assessment Report, and highlights where the EAG's approach to modelling the clinical and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA differs from the Company's.

Table 9. The decision problem in the NICE final scope, addressed in the Company submission and the decision problem addressed by the EAG in the Assessment Report

	Final scope issued by NICE	Decision problem addressed in the Company submission	Decision problem addressed in EAG Assessment Report	EAG comment
Intervention	• Ivacaftor, tezacaftor and elexacaftor combination therapy (Kaftrio®) • Tezacaftor and ivacaftor combination therapy (Symkevi®) • Lumacaftor and ivacaftor combination therapy (Orkambi®)	Same as NICE final scope	Same as NICE final scope	NA
Population	People with CF with at least one *F508del* mutation	Same as NICE final scope	Same as NICE final scope	The EAG notes that the majority of trial evidence in people aged 12+ years includes only individuals with $ppFEV_1$ between 40% and 90%. The EAG considers the long-term clinical outcomes of CFTR modulator therapy from the trials to likely generalise to people with $ppFEV_1$ >90%, but may be more limited in people with pre-existing severe lung disease, i.e., $ppFEV_1$ <40%. The EAG notes that such people comprise around 18.3% of people aged 16+ years attending UK specialist adult centres had a $ppFEV_1$ < 40%,[103]
Subgroups	People who are • homozygous for the *F508del* mutation, or • heterozygous for the *F508del* mutation and gating mutation or a residual function mutation	People with CF with at least one *F508del* mutation in the *CFTR* gene are in scope.	People who are • homozygous for the *F508del* mutation; • heterozygous for the *F508del* mutation and a residual function mutation; • heterozygous for the *F508del* mutation and a gating mutation; • heterozygous for the *F508del* mutation and a minimal function mutation.	As described in Section 1.3.2, the EAG considers it appropriate to consider distinct CF genotype subgroups to mirror the differences in the marketing authorisation between the comparators.

Comparator(s)	• Established clinical management (ECM) including
	  ○ best supportive care
	  ○ mannitol dry powder for inhalation
	  ○ inhaled mucolytics
	  ○ nebulised hypertonic saline
	  ○ anti-inflammatory agents
	  ○ bronchodilators
	  ○ vitamin supplements
	  ○ pancreatic enzymes
	• The interventions will be compared to each other
		Relevant comparators for IVA/TEZ/ELX:
		
		In pwCF aged 6 years or older who are homozygous for the *F508del* mutation:
		• ECM without IVA/TEZ/ELX
		
		In pwCF aged 6 years or older who are heterozygous for the *F508del* mutation:
		• ECM without IVA/TEZ/ELX for those heterozygous for the *F508del* mutation with one of the specified licensed minimal function mutations (F/MF) or one of the specified licensed residual function mutations (F/RF) (*P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*)
		• IVA monotherapy in combination with ECM for those heterozygous for the *F508del* mutation with one of the specified licensed gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H*)
		• ECM without IVA/TEZ/ELX for all remaining indicated mutations
		
		Relevant comparators for LUM/IVA
		
		• ECM without LUM/IVA
		
		Relevant comparators for TEZ/IVA
		
		PwCF aged 6 years or older who
			Same as NICE final scope	NA

		are homozygous for the *F508del* mutation: • ECM without TEZ/IVA **PwCF aged 6 years or older who are heterozygous for the *F508del* mutation with one of the specified licensed residual function mutations (F/RF)** *(P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T)*: • ECM without TEZ/IVA		

Outcomes	The outcome measures to be considered include:
	• Mortality
	• Change in the percentage of predicted forced expiratory volume
	• Forced vital capacity
	• Lung function, including transplantation
	• Body mass index
	• Respiratory symptoms
	• Pulmonary exacerbations including frequency and severity of acute infections
	• Sweat chloride
	• $LCI_{2.5}$
	• Pulmonary bacterial colonisation
	• Need for hospitalisation and other treatments including
		The outcome measures to be considered include:
		• Mortality
		• Lung function
		  ○ Change in the percentage of predicted forced expiratory volume
		  ○ Lung clearance index 2.5 ($LCI_{2.5}$)
		  ○ Lung transplantation
		• Body mass index
		• Respiratory symptoms
		• Pulmonary exacerbations including frequency and severity of acute infections
		• Need for hospitalisation & other treatments including antibiotics
		• Adverse effects of treatments
		• Health-related quality of life
			Same as NICE scope	The EAG performed literature searches that would include all clinical trial evidence relevant to the NICE final scope from relevant study designs. These data are presented in Section 3.2.2 where available. Due to data availability, and the structure of the final economic model, the following variables informed the economic model:
				• Mortality
				• Change in the percentage of predicted forced expiratory volume
				• Change in weight-for-age z-score
				• Lung transplantation
				• Pulmonary exacerbations
				• Adverse effects of treatment
				• Health-related quality of life

	antibiotics • Adverse effects of treatment • Health-related quality of life			
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. 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 and cost of biosimilar and generic products should be taken into account.	• Cost-effectiveness results are expressed in terms of ICER • A lifetime horizon is used in the model • Costs are considered from a National Health Service and Personal Social Services perspective • A differential annual discount rate of 1.5% for health outcomes and 3.5% for costs is applied in the base case • QALY shortfall analyses has been conducted to reflect the high degree of the severity of CF • The impact of loss of exclusivity on cost-effectiveness is considered in a scenario analysis	Same as NICE scope	See critique on deviation from NICE Reference Case in Section 4.1.4
Equality and other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the	An appraisal approach of subgrouping the indicated populations according to *CFTR* genotype or baseline lung function may raise equality concerns.	The EAG notes the following subgroups may be relevant for equality and other considerations, although notes the small evidence base of CFTR modulator therapy specifically within these subgroups: • Socioeconomic status	• The EAG's clinical experts noted that socioeconomic status was a predictor of outcomes for people with CF; • The EAG's clinical experts noted that people with CF

	marketing authorisation granted by the regulator. If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.		• People initiating CFTR modulator therapy prior to developing lung and/or pancreatic damage	who initiate highly effective CFTR modulator therapies early in life, or before irreversible lung and/or pancreatic damage, may have the most favourable clinical outcomes. Such age groups may currently be outside the marketing authorisation of CFTR modulator combination therapies; • The EAG's clinical experts and stakeholder submissions also noted the approximately 10% of people with CF who are currently ineligible for CFTR modulator therapy may be a relevant subgroup to consider for equality. However, the EAG notes that this non-F508del subgroup is outside of the scope of this MTA.

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator gene protein; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; EAG: external assessment group; ECFS: European Cystic Fibrosis Society; ECM: established care management; ELX: elexacaftor; FEV: forced expiratory volume; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; IVA: ivacaftor; LUM: lumacaftor; $LCI_{2.5}$: lung clearance index 2.5; NHS: National Health Service; MTA: multiple technology appraisal; TEZ: tezacaftor.

2.1.1 Critique of Company adherence to the NICE Final Scope

The EAG considers the Company to have adhered to the NICE Final Scope in terms of the intervention, population and outcomes. In addition, while the Company (Company Submission, page 19) stated that: "It is not relevant or appropriate to consider subgroups within CF", the EAG notes that the Company has provided separate economic models for each genotype (F/F, F/Gating, F/RF and F/MF), and as such has implicitly followed the NICE Final Scope.

The Company deviates from the NICE Final Scope in the comparators and economic analysis. Specifically, the Company:

- Provided a cost-effectiveness analysis of ivacaftor monotherapy compared to established clinical management (ECM) in the F/Gating population, which is outside of the NICE Final Scope and;
- Deviated from the NICE reference case in using a differential annual discount rate of 1.5% for health outcomes and 3.5% for costs.

2.1.2 Decision problem addressed in the Assessment Report

2.1.2.1 Interventions

The interventions relevant to this multiple technology appraisal (MTA) are:

- lumacaftor/ivacaftor combination therapy (LUM/IVA);
- tezacaftor/ivacaftor combination therapy (TEZ/IVA);
- elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA).

Details of these interventions, including their marketing authorisations, have been presented in Section 1.3.1.

2.1.2.2 Population including sub-groups

The population relevant to this MTA is people with cystic fibrosis (CF) with at least one *F508del* mutation. Relevant genotype subgroups are based the marketing authorisation for each CFTR modulator combination therapy. Only individuals homozygous for the *F508del* mutation are eligible for LUM/IVA, whereas individuals with at least one copy of the *F508del* mutation are eligible for ELX/TEZ/IVA. To be eligible for TEZ/IVA, an individual must either be homozygous for the *F508del* mutation, or have one copy of the *F508del* mutation and one of the following residual function

mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T. The relevant CF genotype subgroups for this appraisal have been outlined in Section 1.3.2 and are presented in Table 10 are:

Table 10. Interventions and comparators relevant to the appraisal by CF genotype.

Genotype	Relevant interventions and comparators
F/F	ELX/TEZ/IVA, LUM/IVA, TEZ/IVA, ECM
F/Gating	ELX/TEZ/IVA, ECM
F/RF	ELX/TEZ/IVA, TEZ/IVA, ECM
F/MF	ELX/TEZ/IVA, ECM

Abbreviations: CF: cystic fibrosis; ELX: elexacaftor; ECM: established clinical management; IVA: ivacaftor; LUM: lumacaftor; TEZ: tezacaftor

As outlined in Section 1.3.2, the EAG will consider the relationship between lung function and clinical effectiveness by:

- If data are available, the EAG will present clinical efficacy data by trial-reported lung function subgroups;
- The EAG will consider a scenario analysis in which patients initiating highly effective CFTR modulator therapies early receive a sustained reduction in long-term decline of ppFEV$_1$.

In addition, the Company stated that: "Vertex is exploring this post-hoc analysis of clinical trial data internally and will share with NICE once this is available" in response to Clarification Question A26, but this was not available to the EAG at the time of the Assessment Report.

2.1.2.3 Relevant comparators

The comparators of interest listed in the NICE final scope are:[100]

- Each of the interventions under consideration in the MTA:
  - LUM/IVA;
  - TEZ/IVA;
  - ELX/TEZ/IVA.
- Established clinical management, including:
  - Best supportive care;
  - Mannitol dry powder for inhalation (DPI);
  - Inhaled mucolytics;

- Nebulised hypertonic saline;
- Anti-inflammatory agents;
- Bronchodilators;
- Vitamin supplements;
- Pancreatic enzymes.

Of the listed established clinical management therapies, only mannitol DPI (Bronchitol®, Pharmaxis Europe Limited, Dublin, Ireland) has been approved by NICE (TA266).[64] The use of mannitol DPI is restricted to adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and whose lung function is rapidly declining and for whom other osmotic agents are not considered appropriate. The EAG considers that inhaled mucolytics, of which mannitol DPI, nebulised hypertonic saline and rhDNase are examples, are therapies that individuals receiving a CFTR modulator would still be eligible for, and would still receive, should their symptoms require. As CFTR modulator therapies are an addition to established clinical management, participants in clinical trials informing this appraisal will have had access to all the established clinical management therapies available at the time of the trial, both in the placebo arms and the CFTR modulator arms.

Overall, the EAG considers the comparators listed in the NICE final scope to be appropriate, but notes that best supportive care also includes some therapies, procedures, and lifestyle changes not explicitly mentioned, such as antibiotics, physiotherapy, supplemental feeding, and exercise, as outlined in Table 3. The EAG also notes that the availability of some established clinical management therapies varies with age. For example, rhDNase is only indicated for people with CF who are over 5 years of age and who have a ppFEV$_1$ >40%, and mannitol DPI is indicated for the treatment of CF in adults aged 18 and over. Although not a relevant comparator in the NICE final scope, the EAG notes that a number of people with CF (n=606) were receiving ivacaftor monotherapy in the CF Trust Register, as of December 2021.[1] The EAG considers ivacaftor monotherapy to be relevant to the appraisal because of the likelihood that evidence from placebo randomised controlled trials of ivacaftor to form a connected evidence network with ivacaftor monotherapy active-controlled trials with ELX/TEZ/IVA.

2.1.2.4 Outcomes

The NICE final scope states the following outcomes should be addressed in this MTA:

- Mortality;
- Lung function, including $ppFEV_1$, forced vital capacity, $LCI_{2.5}$, respiratory symptoms and transplantation;
- Body mass index (BMI);
- Pulmonary exacerbations, including the frequency and severity of acute infections leading to exacerbations;
- Pulmonary bacterial colonisation;
- Need for hospitalisation and other treatments including use of antibiotics;
- Sweat chloride;
- Adverse effects of treatment;
- Health-related quality of life (HRQoL);
- If evidence allows, the relationship between baseline lung function and clinical effectiveness.

For one HRQoL scale used in cystic fibrosis, the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a minimally important difference for the CFQ-R has been reported for the respiratory domain for people with stable CF (4 points), according to a study of 140 people with CF.[104] No minimally clinically important difference has been established for other domains of the CFQ-R.[104] The EAG did not find evidence that a minimally important difference has been established for lung-function outcomes such as $ppFEV_1$ or $LCI_{2.5}$ in cystic fibrosis, although the short-term variability of $ppFEV_1$ has been reported as around 6.3%.[105] The EAG's clinical experts also noted that while patients may not feel a difference of 5% difference in $ppFEV_1$, this may lead to other measurable differences over time, for example less time spent doing physio. The 2012 European Medicines Agency "Report of the workshop on endpoints for cystic fibrosis clinical trials" noted that while no minimal important difference has been defined, any statistically significant difference between an intervention and ECM is potentially important as $ppFEV_1$ is predictive of mortality.[106] The EAG's clinical experts also noted that any reduction in pulmonary exacerbations would be meaningful for a person with CF, given the likelihood that treatment for exacerbations will require IV antibiotics either at home, or in hospital.

2.1.2.5 Treatment effect modifiers

The EAG's clinical experts did not consider any clinical variable to likely be a treatment effect modifier of CFTR modulators. The EAG's clinical experts outlined that ceiling effects for some outcome measures in some individuals, e.g., $ppFEV_1$ and $LCI_{2.5}$ in younger children may limit the sensitivity of such measures in these groups, and also noted the difficulty in obtaining reliable

measurements of ppFEV$_1$ in younger children. In addition to age-related ceiling effects, disease severity and prior treatment history may modify the magnitude of the treatment effect a patient could gain from CFTR modulator therapy.

2.1.2.6 Equality

The following issues that may be relevant for equality were identified by the EAG:

- The EAG's clinical experts noted that socioeconomic status was a predictor of outcomes for people with CF;
- The CF Voices submission provided survey data that suggests caregivers of people with CF are predominantly female, although it was noted that this is observed across caregivers more generally and is not specific to CF;[30]
- The EAG's clinical experts and stakeholder submissions noted the approximately 10% of people with CF who are currently ineligible for CFTR modulator therapy. People with CF in the UK who are not eligible for CFTR modulator therapy due to not having an *F508del* copy are more likely to Black, Asian and Minority ethnic groups. Of particular note is the proportion of people of Asian ethnicity was higher in people with no *F508del* copy (19.2% of people) than those with at least one *F508del* copy (1.2% of people).[6]

2.2 Overall aims and objectives of the assessment

The purpose of this MTA is to assess the clinical and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within their marketing authorisations for treating CF, compared with each other and established clinical management in England and Wales.

3 Assessment of clinical effectiveness

3.1 Method for reviewing effectiveness

The external assessment group (EAG) performed a systematic literature review (SLR) of the clinical effectiveness evidence of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA for treating cystic fibrosis (CF), and reports it in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[107]

3.1.1 Identification of studies

The EAG performed systematic searches of MEDLINE, Embase and CENTRAL, and grey literature sources, to identify all randomised controlled trials (RCTs, excluding Phase I RCTs) and all non-randomised Phase III or Phase IV clinical trials that report on the clinical effectiveness or safety of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA in people with CF with at least one *F508del* mutation.

De novo searches of MEDLINE and Embase were conducted using search terms for cystic fibrosis and LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, which are presented in Table 90 (MEDLINE: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations) and Table 91 (Embase) of Appendix 9.1.1. For CENTRAL, the EAG identified the Cystic Fibrosis Trials Register as an up-to-date systematic search repository for CF RCTs.[108] The Cystic Fibrosis Trials Register is a continually-updated register of RCTs relating to CF, compiled from database searches of MEDLINE (weekly searches from 1966 to present), Embase (searched 1974 to August 1995) and CENTRAL (searched on each new issue of the Cochrane library), and also includes records hand-searched from the Journal of Cystic Fibrosis, Pediatric Pulmonology and conference abstracts. As such, the EAG's search strategy for CENTRAL used the Cystic Fibrosis Trial Register filter and used search terms for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within this. The EAG's search strategy for CENTRAL is presented in Table 94 of Appendix 9.1.2, and further details of the Cystic Fibrosis Trials Register are presented in Appendix 9.1.2 (including Table 92 and Table 93). The Cystic Fibrosis Trials Register was the primary search of a large-scale Cochrane review relevant to the MTA, "*Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del)*" (Southern *et al.* 2020).[108]

The EAG's database searches of MEDLINE and Embase were performed separately via Ovid, and then deduplicated against each other. The remaining records were deduplicated against the trials indexed

on the Cystic Fibrosis Trial Register. Deduplication was performed using a custom script in R 4.2.0.[109] The resulting records entered screening for inclusion in the SLR.

The EAG conducted grey literature searches to identify any records not indexed in MEDLINE, Embase or the Cystic Fibrosis Trials Register via CENTRAL, and any ongoing studies. The following grey literature searches were performed by a single reviewer:

3.1.1.1 Conference proceedings

- European Cystic Fibrosis Conference abstracts 2020, 2021 and 2022;
- Annual North American Cystic Fibrosis Conference abstracts 2020, 2021 and 2022.

3.1.1.2 Trial Registries and Registers

- US National Institutes of Health Database (ClinicalTrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP);
- European Medicines Agency (EMA) (www.clinicaltrialsregister.eu/ctrsearch/search).

The EAG's search strategy for WHO ICTRP and EMA matched that used by the Southern *et al.*:[108] "Cystic fibrosis AND (VX OR corrector)". For the US National Institutes of Health database search, the EAG's search strategy was: Condition or disease: cystic fibrosis AND Other terms: VX OR corrector OR "Vertex Pharmaceuticals" OR CFTR AND Study type: Interventional Studies (Clinical Trials).

3.1.1.3 CDSR/DARE/HTA database

- The Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database was searched via the Centre for Reviews and Dissemination (CRD) database, using the key word "cystic fibrosis".
- The Cochrane Database of Systematic Reviews was searched using the key words "cystic fibrosis" and the intervention terms from Table 94 of Appendix 9.1.2 to identify any Cochrane reviews relevant to the current appraisal. During scoping, the EAG identified Southern *et al.* as a Cochrane review highly relevant to the MTA. Following discussion with the Cochrane Cystic Fibrosis and Genetic Disorders Group, the EAG was notified that the Southern *et al.* review is currently undergoing a large update, and that the review authors provided materials from the updated unpublished Cochrane review to facilitate the conduct of the EAG's systematic review, including but not limited to:

- A full list of included and excluded trials in the Cochrane review update, including reasons for exclusion;
- A confidential copy of the updated Cochrane review;
- Details on how the Cystic Fibrosis Trials Register is compiled, and details of the latest search dates;
- Discussion and clarification as required throughout the project.

3.1.1.4 HTA bodies

As the CRD Databases were last updated in March 2018, the following English-language HTA body websites were searched to identify HTA appraisals relevant to the current MTA, with references of any eligible studies contained within the HTA documents extracted:

- NICE;
- Pharmaceutical Benefits Advisory Committee (PBAC);
- Scottish Medicines Consortium (SMC);
- Canadian Agency for Drugs and Technologies in Health (CADTH).

Each HTA body was searched on its website of records for "cystic fibrosis".

3.1.1.5 Company submissions

- The Company submission was searched for relevant unpublished data, and data were also retrieved from clinical study reports and data on file provided by the Company.

No language restrictions were applied in any search strategy, but only records with a full-text published in English were included in the SLR. Abstracts published in English were included if they contained relevant data.

3.1.1.6 Types of studies included and prioritised

RCTs (excluding Phase I RCTs) and non-randomised Phase III or Phase IV clinical trials were included in the SLR. Following scoping searches, the EAG anticipated the evidence base would be of different sizes between age ranges and genotypes, with some interventions having multiple Phase III or Phase IV RCTs available within a certain genotype and age range, and others with no Phase III or Phase IV RCT data. Hence, the EAG prioritised studies for extraction based on the study designs available for each intervention, specifically:

- Data were extracted for all included Phase III or Phase IV RCTs;
- Should no Phase III or Phase IV RCT data be available for an intervention within a group of interest, relevant Phase II RCT data were extracted;
- Should no Phase II, Phase III or Phase IV RCT data be available for an intervention within a group of interest, then data from relevant non-randomised Phase III or Phase IV clinical trials were be extracted for this group.

3.1.2 *Inclusion and exclusion criteria*

Table 11 details the inclusion and exclusion criteria of the SLR. Based on these criteria, two reviewers independently reviewed all titles and abstracts. Full texts of any titles/abstracts that may be relevant were obtained where possible and the full text of each study was assessed by two independent reviewers for inclusion in the SLR. Discrepancies were resolved by discussion, with a third reviewer resolving any outstanding conflicts.

Table 11. Inclusion and exclusion criteria of the SLR

Factor	Inclusion criteria	Exclusion criteria
Design	RCTs (excluding Phase I RCTs), and non-randomised Phase III or Phase IV trials	• Phase I RCTs • Non-randomised studies, except for Phase III or Phase IV clinical trials • Observational studies • Case reports • *In vitro* studies • SLRs/MAs[a]
Population	People with CF with at least one copy of the *F508del* mutation. Studies will be included if they contain an arm of patients of the following ages for the following interventions: • LUM/IVA, ≥1 year • TEZ/IVA, ≥6 years • ELX/TEZ/IVA, ≥2 years • Ivacaftor monotherapy, ≥2 years	• People with CF who do not have at least one copy of the *F508del* mutation • People with CF where CF genotype is not reported • The study does not report an arm of patients of the following ages for one of: LUM/IVA, ≥1 year; TEZ/IVA, ≥6 years; ELX/TEZ/IVA, ≥2 years; ivacaftor monotherapy, ≥2 years. • People without CF • Animal studies

Interventions	• LUM/IVA • TEZ/IVA • ELX/TEZ/IVA • Ivacaftor monotherapy	Any other intervention
Comparators	The interventions will be compared to each other or established clinical management	Any other comparator
Outcomes	Outcomes listed in Table 12	No outcomes listed in Table 12

[a]SLRs and MAs were included past the abstract screening stage to enable bibliography searching, but were excluded at full-text stage.

Abbreviations: CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane regulator; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; MA: meta-analysis; RCT: randomised controlled trial; SLR: systematic literature review; TEZ: tezacaftor.

3.1.3 Data abstraction strategy

Data were extracted by a single reviewer using a standardised data extraction form, and validated by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Study design, clinical effectiveness data were extracted into Microsoft Excel®, and dose and adverse event data were extracted directly into Microsoft Word®. Outcome data were prioritised for extraction at the following timepoints: Week 4; Week 24; Week 48 and the timepoint of the primary outcome or end of study. Where key relevant data for the economic model were not reported, Vertex were contacted to gain further details. If Vertex were unable to provide the data, it was assumed the data were not available.

For clinical efficacy outcomes, data were preferentially extracted for the intention-to-treat (ITT) populations, where available. For safety outcomes, data were preferentially extracted from the safety analysis set. For missing data, estimates obtained using imputation methods were preferentially extracted, and if multiple methods of imputation are reported, estimates based on multiple imputation or mixed-effects models were preferred over last observation carried forward, or variants of this method.

Table 12 lists the outcomes included in the NICE final scope and the variables that were extracted for these outcomes as part of the SLR.[100] The EAG prioritised variables likely to be included in the economic model for extraction.

Table 12. Outcomes and corresponding data extracted as part of the SLR.

Outcomes included in NICE final scope[100]	Data extracted, if reported
Mortality	All-cause mortality
Lung function	Absolute and change from baseline: • $ppFEV_1$ • Lung clearance index 2.5 Number of people with, or time until: • Lung transplant • Need for lung transplant
Respiratory symptoms	Absolute and change from baseline: • CFQ-R respiratory domain score
Body mass index	Absolute and change from baseline: • Weight • Weight for age z-score • BMI
Pulmonary exacerbations	• Study reported definition of pulmonary exacerbation • Any measure of absolute or relative frequency or time until: Pulmonary exacerbations • Pulmonary exacerbations requiring IV antibiotics or hospitalisation
Pulmonary bacterial colonisation	Trial defined frequency or relative frequency of: • *Pseudomonas* colonisation

Need for hospitalisation and other treatments	Trial reported:
	• Hospitalisation
	  ○ Number of days
	  ○ Number of episodes
	  ○ Planned hospitalisation vs unplanned hospitalisation

	○ Intensive care unit use • Other CF treatment use • Other non-CF treatment use
Adverse effects of treatment	Number of people with: • Any serious adverse event (Grade 3 and above) • Any serious treatment-emergent adverse event (Grade 3 and above) • Any trial-defined adverse event of special interest • Adverse events of particular importance as identified by the EAG's clinical experts, including: • Adverse events relating to the liver • Cataracts or lens opacities • Hypertension
Health-related quality of life	Absolute and change from baseline: • EQ-5D-5L and EQ-5D-3L • Cystic Fibrosis Questionnaire-Revised (CFQ-R), total score or respiratory domain • CFQ Child, total score or respiratory domain • CFQ-Parent (for child) , total score or respiratory domain If no EQ-5D measure was reported, the EAG extracted SF-36 data when available.
Sweat chloride	Absolute and change from baseline: • Sweat chloride
Not included in NICE scope	• Development of CF-related diabetes

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane regulator; EAG: external assessment group; EQ-5D: EuroQol five-dimensions: HR: hazard ratio; IV: intravenous; MA: meta-analysis; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SLR: systematic literature review.

3.1.4 *Critical appraisal strategy*

Study quality was assessed by a single reviewer, and independently checked for agreement by a second reviewer. Any disagreements were resolved by discussion and, when necessary, a third reviewer. Risk of bias was assessed at both the study and key outcome level. At the study level, risk of bias was assessed using the risk of bias tables presented in Table 99 in Appendix 9.2. At the

outcome level, risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2).[110] The RoB 2 template was completed for the following outcomes that informed the economic model: change from baseline in $ppFEV_1$, rate of pulmonary exacerbations, and adverse events. A quality assessment was not performed for single-arm non-randomised studies, which were assumed to be at high risk-of-bias when they were used to inform relative treatment effects.

3.1.5 Methods of data synthesis

Extracted data and a quality assessment for each study of clinical effectiveness are presented in tables and described as a narrative summary in Section 3.2.2.1 and Appendix 9.2 and Appendix 9.3.

The EAG conducted a feasibility assessment for network meta-analyses (NMA) of each of the clinical efficacy outcomes that are used in the economic model, namely: change from baseline in $ppFEV_1$, change from baseline in weight-for-age z-score and pulmonary exacerbations requiring IV antibiotics. The feasibility assessment was based around the quantity of evidence available within each genotype (F/F, F/Gating, F/MF and F/RF) and age-group (6 to 11 years, 12+ years). The similarity of studies available for each group was assessed by comparing the following study and sample characteristics: disease severity; treatment history; eligibility criteria; comparator dosing; placebo response; end-point definition and timing; definition of pulmonary exacerbation; withdrawal frequency; clinical trial setting and study design.[111]

NMAs were deemed feasible for the absolute change from baseline in $ppFEV_1$ and weight-for-age z-score for the F/F, F/MF and F/Gating 12+ years populations (Section 3.2.2.4), and were performed following the techniques outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[112] Contrast-based NMAs were performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation, implemented in JAGS using the '*gemtc*' package (version 1.0-1) in R 4.2.0.[113] NMAs were conducted using four chains with results based on 100,000 iterations after a "burn in" of 10,000 iterations. Convergence was assessed by visually assessing the convergence of the shrink factor towards one in Brooks-Gelman-Rubin diagnostic plots, and through verifying that the point estimate of the multivariate potential scale reduction factor was less than 1.05.[114] The '*gemtc*' default uninformative prior distributions were used for all treatment effects.[113]

Fixed effect NMAs were performed when the maximum number of studies informing a single contrast was two or less across a network. For networks where at least three studies informed a

single contrast, both fixed effect and random effects NMAs were explored. This was conducted for the F/F 12+ years ppFEV$_1$ NMA and the F/Gating 12+ years ppFEV$_1$ and weight-for-age z-score NMAs. The relative fit of each model was compared using the deviance information criterion (DIC), and the posterior distribution of the estimated between-study standard deviation was inspected to assess whether sufficient posterior updating had occurred. For the F/F 12+ years ppFEV$_1$ NMA, the DIC was lower in the fixed effect NMA (DIC = 6.2) than the random effects NMA (DIC = 8.0), and the mode of posterior distribution of the estimated between-study standard deviation was 0. Hence, only the results of the fixed effect NMA are presented. For the F/Gating 12+ years ppFEV$_1$ and weight-for-age z-score NMAs, the DICs were lower in the random effect NMA (DIC = 8.1 ppFEV$_1$, 8.5 weight-for-age z-score) than the corresponding fixed effect NMAs (DIC = 9.0 ppFEV$_1$, 13.5 weight-for-age z-score), and the posterior distribution of the estimated between-study standard deviation was not dominated by the prior. Hence, for the F/Gating analyses, both the results of the fixed effect and random effects NMAs are presented.

Treatment effects are presented in league tables as weighted mean differences for continuous data. When not reported, missing standard errors were estimated from the width of confidence intervals for use in the NMA models. Where the Company also submitted indirect treatment comparisons, the consistency of the Company estimates with the EAG estimates is commented on. Due to the limited number of studies informing the NMAs, the EAG and Company estimates are often aligned, but the EAG notes that small differences in the results often occur due to the EAG using trial-reported outcomes, where available. In contrast, the Company aligned the covariate structures of each model, using individual participant data, before conducting their analyses.

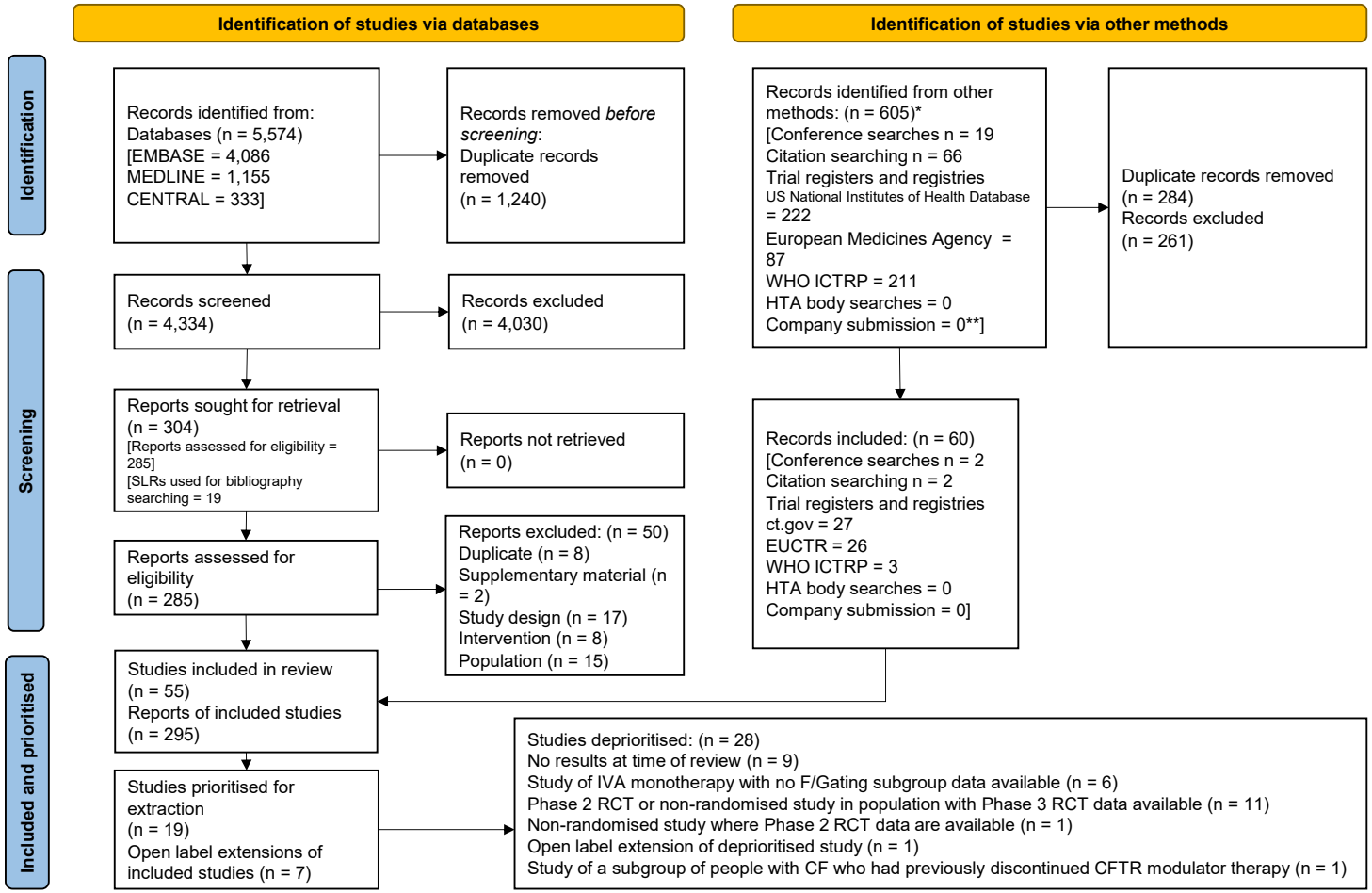
3.2 Results

3.2.1 Quantity and quality of research available

Figure 1 is a PRISMA flow diagram of the identification of records and studies included in the EAG's SLR. The EAG's database searches were conducted on 16 February 2023 and retrieved a total of 5,574 records. After deduplication, 4,334 records were appraised in the title and abstract review. Of these, 304 records were included from the title and abstract review: 19 records (including 2 duplicates) were relevant SLRs used for later bibliographic searching,[43, 115-129] and 285 records proceeded to full text review. Two-hundred and thirty records were included at full text review, and 49 records were excluded at full text review. Excluded records are presented in Table 117 of Appendix 9.5, along with the reasons for exclusion. Grey literature searching identified a further 60

records, including two relevant conference abstracts, two records identified from the Cochrane review and 56 records from clinical trial registries. Overall, 295 records were included in the SLR, from 55 unique studies. The results of the EAG's clinical SLR were consistent with the results of the Company's SLR for clinical trials, and the EAG is satisfied that the Company's SLR identified all evidence relevant to the decision problem. A critique of the Company's SLR is provided in Appendix 9.1.4.

Figure 1. PRISMA flow diagram of records included in the clinical systematic literature review



*All records from Southern et al. were screened but not included in this

Following the Assessment Protocol,[130] studies were prioritised for clinical analyses based on data availability according to the following hierarchy for each intervention in each prespecified age group (1 to 2 years, 2 to 5 years, 6 to 11 years and 12+ years):

- All included Phase III or Phase IV RCTs were prioritised;
- Should no Phase III or Phase IV RCT data be available for an intervention within a group of interest, relevant Phase II RCTs were prioritised;
- Should no Phase II, Phase III or Phase IV RCT data be available for an intervention within a group of interest, then data from non-randomised Phase III or Phase IV clinical trials were prioritised for this group.

Of the 54 studies included in the SLR, 19 were prioritised for extraction and seven further studies were open-label extension studies associated with the prioritised studies. The 29 studies that were deprioritised are presented in Table 116 of Appendix 9.5, along with the following reasons for their deprioritisation:

- No results at time of review (n = 9);
- Study of IVA monotherapy with no F/Gating subgroup data available (n = 6);
- Phase 2 RCT or non-randomised study in population with Phase 3 RCT data available (n = 11);
- Non-randomised study where Phase 2 RCT data are available (n = 1);
- Open label extension of deprioritised study (n = 1);
- Study of a subgroup of people with CF who had previously discontinued CFTR modulator therapy (n = 1).

Table 13 provides a brief overview of the studies prioritised in the SLR, and Table 14 lists the open-label extension studies. Linked references to the studies prioritised in the SLR can be found in Appendix 9.4.

Table 13. Summary of studies prioritised from the systematic review of clinical effectiveness

Study	Vertex Protocol	Genotype/Mutation	Age, years	Interventions, comparators and doses	Phase and Randomisation	Follow-up duration
Studies including ELX/TEZ/IVA						
Sutharsan 2022[131]	VX18-445-109	F/F	12+	• ELX/TEZ/IVA (200 mg qd/ 100 mg qd/ 150 mg q12h) • TEZ/IVA (100 mg qd/ 150 mg q12h)	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Barry 2021[132]	VX18-445-104	F/RF F/Gating	12+	• ELX/TEZ/IVA (200 mg qd/100 mg qd/150 mg q12h) • TEZ/IVA (100 mg qd/ 150 mg q12h) • IVA (150 mg q12h)	Phase 3, randomised	Efficacy: 8 Weeks Safety: 12 Weeks
Middleton 2019[61]	VX17-445-102	F/MF	12+	• ELX/TEZ/IVA (200 mg qd/100 mg qd/ 150 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Heijerman 2019[133]	VX17-445-103	F/F	12+	• ELX/TEZ/IVA (200 mg qd/100 mg qd/150 mg q12h) • TEZ/IVA (100 mg qd/ 150 mg q12h)	Phase 3, randomised	Efficacy: 4 Weeks Safety: 8 Weeks
Mall 2022[134]	VX19-445-116	F/MF	6 to 11	• ELX/TEZ/IVA (if <30 kg: 100 mg qd/50 mg qd/75 mg q12h) • ELX/TEZ/IVA (if ≥30 kg: 200 mg qd/ 100 mg qd/ 150 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks

Zemanick 2021[135]	VX18-445-106	F/F F/MF	6 to 11	• ELX/TEZ/IVA (if <30 kg: 100 mg qd/ 50 mg qd/ 75 mg q12h) • ELX/TEZ/IVA (if ≥30 kg: 200 mg qd/ 100 mg qd/ 150 mg q12h)	Phase 3, non-randomised	Efficacy: 24 Weeks Safety: 28 Weeks
NCT04537793[136]	VX20-445-111	F/F F/MF	2 to 5	• Part B • ELX/TEZ/IVA (if ≥10 kg to < 14 kg: 80 mg qd/40 mg qd/60 mg am daily and 59.5 mg daily pm for IVA) • ELX/TEZ/IVA (if ≥14 kg 80 mg qd/40 mg qd/ 75 mg q12h)	Phase 3, non-randomised	Safety: 28 Weeks
Studies including TEZ/IVA, excluding those including ELX/TEZ/IVA						
Taylor-Cousar 2017[137]	VX14-661-106	F/F	12+	• TEZ/IVA (100 mg qd/ 150 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Rowe 2017[138]	VX14-661-108	F/RF F/Gating (not a relevant population for this MTA)	12+	• TEZ/IVA (100 mg qd/ 150 mg q12h) • Placebo • IVA (150 mg qd)	Phase 3, randomised	Crossover trial consisting of two 8-week treatment periods with an 8-week washout period between
Davies 2021[139]	VX16-661-115	F/F F/RF	6 to 11	• TEZ/IVA (if <40 kg: 50 mg qd/75 mg g12h) • TEZ/IVA (if ≥40 kg: 100 mg qd/ 150 mg q12h)	Phase 3, randomised	Efficacy: 8 Weeks Safety: 12 Weeks

				• IVA (150 mg qd) • Placebo		
Studies including LUM/IVA						
TRAFFIC Wainwright 2015[42]	VX12-809-103	F/F	12+	• LUM/IVA (400 mg q12h/ 250 mg q12h) • LUM/IVA (600 mg qd/ 250 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
TRANSPORT Wainwright 2015[42]	VX12-809-104	F/F	12+	• LUM/IVA (400 mg q12h/250 mg q12h) • LUM/IVA (600 mg qd/250 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Wilson 2021[140]	VX15-809-112	F/F	12+	• LUM/IVA (400 mg q12h/250 mg q12h) • Placebo	Phase 4, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Ratjen 2017[141]	VX14-809-109	F/F	6 to 11	• LUM/IVA (200 mg q12h/250 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Stahl 2021[142]	VX16-809-121	F/F	2 to 5	• LUM/IVA (if <14 kg: 100 mg qd/125 mg g12h) • LUM/IVA (if ≥14 kg: 150 mg qd/188mg q12h) • Placebo	Phase 2, randomised	Efficacy: 48 Weeks Safety: 48 Weeks
Rayment 2022[143]	VX16-809-122	F/F	1 to 2	• Part B • LUM/IVA (if 7 to <9 kg: 75 mg qd/94mg g12h)	Phase 3, non-randomised	Efficacy: 24 Weeks Safety: 26 Weeks

				• LUM/IVA (if 9 to <14 kg: 100 mg qd/125 mg q12h • LUM/IVA (if ≥14 kg: 150 mg qd/188mg q12h		
Placebo controlled studies of IVA monotherapy						
Ramsey 2011[144]	VX08-770-102	F/Gating, *G551D* mutation	12+	• IVA 150 mg q12h • Placebo	Phase 3, randomised	Efficacy: 48 Weeks Safety: 48 Weeks
De Boeck 2014[145]	VX12-770-111	F/Gating, non-*G551D* mutation	6+ (12+ subgroup data provided by Company)	• IVA 150 mg q12h • Placebo	Phase 3, randomised	Crossover trial consisting of two 8-week treatment periods with a 4 to 8 week washout period between
Moss 2015[146]	VX11-770-110	F/*R117H* mutation	6+ (12+ subgroup data provided by Company)	• IVA 150 mg q12h • Placebo	Phase 3, randomised	Efficacy: 24 Weeks Safety: 28 Weeks
Abbreviations: ELX: elexacaftor; IVA: ivacaftor; kg: kilograms; LUM: lumacaftor; mg: milligrams; q12h: once every 12 hours; qd: once daily: TEZ: tezacaftor.						

Table 14. Open-label extension studies of studies included in the systematic review of clinical effectiveness

OLE study	Vertex Protocol Number	Genotype	Intervention	Age group	Parent studies
Griese 2022[147]	VX17-445-105	F/F F/MF	ELX/TEZ/IVA	12+	Heijerman 2019, Middleton 2019
Ratjen 2021[148]	VX19-445-107	F/F F/MF	ELX/TEZ/IVA	6+	Zemanick 2021
Study 445-110[149]	VX18-445-110	F/RF F/Gating	ELX/TEZ/IVA	12+	Barry 2021
Flume 2021[150]	VX14-661-110	F/F F/RF	TEZ/IVA	12+	Taylor-Cousar 2017
Sawicki 2022[151]	VX17-661-116	F/F F/RF	TEZ/IVA	6+	Davies 2021, Walker 2019
Konstan 2017[152]	VX12-809-105	F/F	LUM/IVA	12+	TRAFFIC, TRANSPORT
Chilvers 2021[153]	VX15-809-110	F/F	LUM/IVA	6+	Ratjen 2017, Milla 2017

Abbreviations: ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; OLE: open-label extension; TEZ: tezacaftor.

3.2.1.1 ELX/TEZ/IVA

Seven studies were prioritised in the SLR that reported at least one ELX/TEZ/IVA arm (Table 15). All seven studies were Phase 3 clinical trials sponsored by Vertex. Four were RCTs in people with CF aged 12+ years:

- Sutharsan 2022 and Heijerman 2019 were TEZ/IVA active-controlled Phase 3 RCTs recruiting people with an F/F CF genotype;[131, 133]
- Barry 2021 was an active controlled Phase 3 RCT recruiting people with either F/RF or F/Gating CF genotypes. F/RF participants not in the ELX/TEZ/IVA arm received TEZ/IVA, and F/Gating participants not in the ELX/TEZ/IVA arm received IVA monotherapy;[132]
- Middleton 2019 was a placebo-controlled Phase 3 RCT recruiting people with an F/MF CF genotype.[61]

One trial was an RCT in people with CF aged 6 to 11 years:

- Mall 2022 was a placebo-controlled Phase 3 RCT that recruited people aged 6 to 11 years with an F/MF CF genotype.[134]

The final two studies were single-armed Phase 3 trials in children:

- Zemanick 2021 was a Phase 3 non-randomised trial of people with CF aged 6 to 11 years with either an F/F or F/MF genotype;[135]
- NCT04537793 was a Phase 3 non-randomised trial of people with CF aged 2 to 5 years with either an F/F or F/MF genotype.[136]

Table 15. Data availability for studies including ELX/TEZ/IVA by age and CF genotype

Age	Genotype			
	F/F	F/RF	F/MF	F/Gating
2 to 5 years	NCT04537793[136]	No studies identified	NCT04537793[136]	No studies identified
6 to 11 years	Zemanick 2021[135]	No studies identified	Mall 2022[134] Zemanick 2021[135]	No studies identified
12+ years	Sutharsan 2022[131] Heijerman 2019[133]	Barry 2021[132]	Middleton 2019[61]	Barry 2021[132]

Abbreviations: CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; TEZ: tezacaftor

3.2.1.2 TEZ/IVA

Six studies were prioritised in the SLR that reported at least one TEZ/IVA arm (Table 16). All six studies were Phase 3 clinical trials sponsored by Vertex. Three were RCTs in people with CF aged 12+ that also included an ELX/TEZ/IVA arm and were described in Section 3.2.1.1:

- Sutharsan 2022 and Heijerman 2019 were ELX/TEZ/IVA active-controlled Phase 3 RCTs recruiting people with an F/F CF genotype;[131, 133]
- Barry 2021 was an active controlled Phase 3 RCT recruiting people with either F/RF or F/Gating CF genotypes. F/RF participants not assigned to ELX/TEZ/IVA received TEZ/IVA.[132]

Two studies were placebo controlled RCTs in people with CF aged 12+ years:

- Taylor-Cousar 2017 was a Phase 3 placebo-controlled RCT in participants aged 12+ years with an F/F genotype;[137]

- Rowe 2017 was a cross-over placebo-controlled RCT in participants aged 12+ years with an F/RF genotype.[138] Rowe 2017 also included patients with an F/Gating genotype; however, as F/Gating is outside of the marketing authorisation of TEZ/IVA, this subgroup is not considered further.

One study was a PBO controlled RCT in people with CF aged 6 to 11 years:

- Davies 2021 was a Phase 3 placebo- or IVA-controlled RCT in people with CF aged 6 to 11 with either an F/F or F/RF CF genotype.[139] While Davies 2021 was an RCT, efficacy data were only reported for the TEZ/IVA arm (n =54), as "placebo [n = 10] or IVA [n = 3] groups were used for blinding purposes only".[154] Safety data, was, however, available for all three arms.

Table 16. Data availability for studies including TEZ/IVA by age and CF genotype

Age	Genotype			
	F/F	F/RF	F/MF	F/Gating
6 to 11 years	Davies 2021[139]	Davies 2021[139]	Genotype outside of marketing authorisation	Genotype outside of marketing authorisation
12+ years	Taylor-Cousar 2017[137] Heijerman 2019[133] Sutharsan 2022[131]	Rowe 2017[138] Barry 2021[132]		

Abbreviations: CF: cystic fibrosis; IVA: ivacaftor; TEZ: tezacaftor

3.2.1.3 LUM/IVA

Six studies were prioritised in the SLR that reported at least one LUM/IVA arm (Table 17). Five studies were Phase 3 clinical trials sponsored by Vertex, one study was a randomised Phase 4 clinical trial sponsored by Vertex, and one study was a randomised Phase 2 clinical trial sponsored by Vertex. All studies were in people with an F/F CF genotype. Three studies were RCTs in people with CF aged 12+:

- TRAFFIC was a placebo-controlled Phase 3 RCT in people with CF aged 12+ who have an F/F CF genotype;[42]
- TRANSPORT was a placebo-controlled Phase 3 RCT in people with CF aged 12+ who have an F/F CF genotype;[42]
- Wilson 2021 was a placebo-controlled Phase 4 RCT in people with CF aged 12+ who have an F/F CF genotype.[140]

One study was prioritised in the 6 to 11 years age group:

- Ratjen 2017 was a placebo-controlled Phase 3 RCT in people with CF aged 6 to 11 who have an F/F CF genotype.[141]

One study was prioritised in the 2 to 5 years age group:

- Stahl 2021 was a placebo-controlled Phase 2 RCT in people with CF aged 2 to 5 who have an F/F CF genotype.[142]

One study was prioritised in the 1 to 2 years age group:

- Rayment 2022 was a non-randomised Phase 3 clinical trial in people with CF aged 1 to 2 who have an F/F CF genotype.[143]

Table 17. Data availability for studies including LUM/IVA by age and CF genotype

Age	Genotype			
	F/F	F/RF	F/MF	F/Gating
1 to 2 years	Rayment 2022[143]	Genotype outside of marketing authorisation	Genotype outside of marketing authorisation	Genotype outside of marketing authorisation
2 to 5 years	Stahl 2021[142]			
6 to 11 years	Ratjen 2017[141]			
12+ years	TRAFFIC[42] TRANSPORT[42] Wilson 2021[140]			

Abbreviations: CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor.

3.2.1.4 IVA monotherapy

Although not included as a comparator in the Final Scope issued by NICE, the pivotal trial of ELX/TEZ/IVA in the F/Gating 12+ years population, Barry 2021,[132] was an IVA-controlled RCT. In order to compare ELX/TEZ/IVA to ECM in the F/Gating population, an indirect treatment comparison using data from PBO-controlled IVA trials was required. Three Phase 3 PBO-controlled RCTs of IVA were identified in the EAG's SLR, all sponsored by Vertex:

- Ramsey 2011 was a PBO-controlled RCT of IVA in patients aged 12+ years with a *G551D* gating mutation. The Company provided data on the subset of patients from this study who also had an *F508del* mutation, i.e., who had an F/Gating CF genotype.[144]
- De Boeck 2014 was a PBO-controlled RCT of IVA in patients aged 6+ years with a non-*G551D* gating mutation. The Company provided data on the subset of patients from this study who also had an *F508del* mutation, i.e., who had an F/Gating CF genotype, and who were 12+ years.[145]
- Moss 2014 was a PBO-controlled RCT of IVA in patients aged 6+ years with an *R117H* mutation. *R117H* is a non-gating residual function mutation, however it is within the marketing authorisation of IVA monotherapy alongside gating mutations, but is not within the marketing authorisation of TEZ/IVA. People with an *R117H* mutation were included in the F/Gating group of Barry 2021. The Company provided data on the subset of patients from this study who also had an *F508del* mutation, i.e., who had an F/Gating (*R117H*) CF genotype, and who were 12+ years.[146]

3.2.1.5 Quality Assessment

An overview of the study level quality assessment performed by the EAG is presented in Table 18, with reasons provided for any items rated as some concern. An expanded version of this table with comments for all items is presented in Table 99 in Appendix 9.2. In addition, Version 2 of the Cochrane risk-of-bias tool (RoB2) was completed for the following outcomes within each study:[110] $ppFEV_1$/$LCI_{2.5}$; pulmonary exacerbations; and adverse event reporting. The completed checklists are provided in Table 100, Table 101 and Table 102 of Appendix 9.2.

Table 18. EAG's study-level quality assessment of RCTs included in the clincial effectiveness SLR

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Sutharsan 2022[131]	Low	Low	Low	Low	Low	Low	Low
Barry 2021[132]	Low	Low	Low	Low	Low	Low	Low
Middleton 2019	Low	Low	Low	Some concerns	Low	Low	Low
Heijerman 2019[133]	Low	Low	Low	Low	Low	Low	Low
Mall 2022[134]	Low	Low	Low	Some concerns	Low	Low	Low
Taylor-Cousar 2017	Low	Low	Low	Some concerns	Low	Low	Low
Rowe 2017	Low	Low	Low	Some concerns	Low	Low	Low
Davies 2021	Low	Low	Low	Some concerns	Some concerns 54/55 TEZ/IVA, 3/3 IVA and 8/11 Placebo (for $LCI_{2.5}$, 9/11 for $ppFEV_1$) were included in the analyses, representing a higher percentage of missing data in the placebo group (as per clinicaltrials.gov data tables). Reasons for missing data were not provided to assess whether missingness depended on the outcome's true value.	Low	Some concerns
TRAFFIC	Low.	Low	Low	Some concerns	Low	Low	Low

TRANSPORT	Low	Low	Low	Some concerns	Low	Low	Low
Wilson 2021	Low	Low	Low	Some concerns	Some concerns For $ppFEV_1$, 8 (11%) of participants had missing outcome data.	Low	Low
Ratjen 2017	Low	Low	Low	Some concerns	Low	Low	Low
Stahl 2021	Low	Low	Low	Some concerns	Low	Low	Low
Ramsey 2011 (F/Gating subgroup)	Some concerns The study was not stratified by the subgroup reported. No large differences between the subgroups were observed but limited data on each group was available.	Low	Low	Some concerns	Some concerns It was unclear if there was missing data as it was unclear how many people comprised the subgroup of interest.	Some concerns This was a *post-hoc* analysis. It is unclear how the analysis was developed and if multiple analyses were performed. The alignment between this analysis and the pre-specified analyses from Barry 2021 reduces the risk of bias.	Some concerns
De Boeck 2014 (F/Gating 12+ subgroup)	Some concerns As *per* Ramsey 2011.	Low	Low	Some concerns	Some concerns As *per* Ramsey 2011.	Some concerns As *per* Ramsey 2011.	Some concerns
Moss 2015 (F/Gating 12+ subgroup)	Some concerns As *per* Ramsey 2011	Low	Low	Some concerns	Some concerns As *per* Ramsey 2011.	Some concerns As *per* Ramsey 2011.	Some concerns

Abbreviations: EAG: external assessment group; IVRS: interactive voice response system; IWRS: interactive web response system: $LCI_{2.5}$: lung clearance index 2.5; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SLR: systematic literature review.

Of the 16 RCTs included from the SLR, 12 were rated as low risk of bias. Four RCTs were identified at a higher risk of bias: Davies 2021, Ramsey 2011 (F/Gating *post hoc* subgroup analysis), De Boeck 2014 (F/Gating *post hoc* subgroup analysis) and Moss 2015 (F/Gating *post hoc* subgroup analysis). Davies was assessed as at a high risk of bias due to the placebo (n = 10) and IVA (n = 3) control groups being used for blinding purposes only, and efficacy data only being reported for TEZ/IVA. As such, the outcome data from this trial are uncontrolled and are approximately equivalent to a single-arm trial. For the three RCTs of IVA monotherapy compared to placebo, namely Ramsey 2011, De Boeck 2014 and Moss 2015, the quality assessment was conducted with regards to the F/Gating subgroup of patients for which outcome data were provided by the Company. These were *post-hoc* subgroup analyses performed by the Company to provide a connected evidence network between ELX/TEZ/IVA and placebo, via IVA monotherapy. Randomisation was not stratified on this subgroup and the analyses were not prespecified. As such each of these analyses were rated at risk of bias. Nevertheless, the EAG notes that the analyses performed by the Company were performed in-line with the prespecified analyses performed across the CFTR modulator clinical trials, minimising the likelihood that the reported analyses were selectively reported.

Throughout the RCTs included in the SLR, the EAG's risk of bias assessment consistently noted some concerns about the blinding of outcome assessment. Specifically, the EAG noted that it was plausible that participants or outcome assessors could guess the intervention a participant was receiving in placebo-controlled trials, i.e., being unblinded due to the clinical effects of the treatment on the participant. This is because spontaneous and large improvements in sweat chloride and spirometry measures are implausible for patients on a stable CF treatment regimen who are not receiving CFTR modulator therapy. The Company acknowledged this possibility in several study CSRs, and to mitigate this bias, [redacted]

At the outcome level, the EAG completed RoB2 assessments for ppFEV$_1$/LCI$_{2.5}$; pulmonary exacerbations; and adverse event reporting. These are presented in Table 100, Table 101 and Table 102 of Appendix 9.2. In general, the measurement of ppFEV$_1$, LCI$_{2.5}$, and pulmonary exacerbations when reported as efficacy outcomes were assessed to be at low risk of bias in RCTs, with low rates of missing outcome data across most trials. However, the EAG noted concerns about the consistency of the recording of pulmonary exacerbations when recorded as adverse events between sites within the same study and between different studies. The EAG notes, however, that are general concerns

about non-protocol defined adverse event reporting,[156] rather than being specific to pulmonary exacerbations in CF clinical trials.

The EAG did not complete a formal risk of bias assessment for weight-for-age z-score, as change from baseline in weight-for-age z-scores was only calculated for participants aged 20 and younger in the trials. Change from baseline in weight-for-age z-score was calculated for the full trial populations in *post hoc* analyses that were later provided by the Company. In response to a clarification question, the Company stated that this was because growth statistics are only available up to age 20. In order to calculate a weight-for-age z-score for people aged 21 and older, the Company applied the growth statistics from patients aged 20 and older. Overall, the EAG considers the measurement of change from baseline in weight-for-age z-score to likely be a robust measure across studies. The EAG considers the use of a change from baseline statistic, rather than absolute values, to likely mitigate the effects of using growth statistics of 20-year-olds for older participants, and notes that any consequences will equally affect participants in CFTR modulator and placebo arms in RCTs.

Following the Assessment Protocol, the EAG considered all single-arm trials at a high risk of bias when used to inform relative treatment effects in the economic model. The EAG is particularly concerned about the risk of bias in single-arm studies that collected data during the COVID-19 pandemic, as viral shielding likely led to lower rates of pulmonary exacerbations and preserved, or even improved, lung function, compared to the period prior to the pandemic, across respiratory disorders.[157, 158] Hence, the occurrence of COVID-19 is confounder when interpreting the results of single-arm clinical trials that collected data from 2020 onwards. Table 19 lists the Start Date and Primary Completion Date, as listed on ClinicalTrials.gov, of the single-arm studies identified by the EAG that may be confounded by COVID-19. These studies included both single-arm Phase 3 trials of ELX/TEZ/IVA in people under 12, as well as the Phase 3 single-arm trial of LUM/IVA in infants aged 1 to 2 years. Of note, all three open-label extension studies of ELX/TEZ/IVA with results available at the time of review involved data collection throughout 2020 and 2021, and are therefore at high risk of bias due to COVID-19 related confounding.

Table 19. Study start dates and primary completion dates of studies prioritised in the EAG SLR where data collection overlapped with the COVID-19 pandemic.

Study	Intervention	Genotype	Age	Start Date	Primary Completion Date
Primary single-arm clinical trials					
Zemanick 2021	ELX/TEZ/IVA	F/F, F/MF	6 to 11	2 October 2018	7 August 2020
NCT04537793	ELX/TEZ/IVA	F/F, F/MF	2 to 5	19 November 2020	3 June 2022
Rayment 2022	LUM/IVA	F/F	1 to 2	7 September 2018	29 October 2021
Extension studies					
Griese 2022	ELX/TEZ/IVA	F/F, F/MF	12+	9 October 2018	9 January 2023
Ratjen 2021	ELX/TEZ/IVA	F/F, F/MF	6+	17 February 2020	April 2024 (estimated)
Study 445-110	ELX/TEZ/IVA	F/F, F/MF	12+	5 December 2019	16 December 2022
Sawicki 2022	TEZ/IVA	F/F, F/RF	6+	25 April 2018	28 October 2020

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; SLR: systematic literature review; TEZ: tezacaftor

3.2.2 EAG assessment of clinical effectiveness

3.2.2.1 Critical review and synthesis of information

Detailed data extraction tables of study design, baseline characteristics and clinical outcomes of each study prioritised in the SLR are presented in Table 103 to Table 112 in Appendix 9.4. In the following section, the key clinical outcome data that inform the economic model are presented by intervention and age group.

3.2.2.1.1 ELX/TEZ/IVA

3.2.2.1.1.1 2 to 5 years

NCT04537793 (VX20-445-111) was a Phase 3 non-randomised trial of people with CF aged 2 to 5 with either an F/F or F/MF genotype.[136, 159] Part A recruited 18 participants to evaluate the pharmacokinetics and safety and tolerability of ELX/TEZ/IVA, and Part B recruited 75 participants to evaluate the pharmacokinetics, safety and tolerability and efficacy of ELX/TEZ/IVA. Part B is most relevant to the current research and so is focussed on here. The study period of NCT04537793 overlapped with the COVID-19 pandemic (Start Date: 19 November 2020; Primary Completion Date:

3 June 2022), and as such the EAG assesses the $LCI_{2.5}$, pulmonary exacerbation and weight-for-age z-score data to be at very high risk of bias. Through 24 weeks, participants on ELX/TEZ/IVA experienced a [redacted] decrease (improvement) in $LCI_{2.5}$, and a [redacted] increase in weight-for-age z-score. [redacted] participants experienced a pulmonary exacerbation during the study, although only [redacted] required hospitalisation or IV antibiotics (Table 20).

Table 20. Clinical efficacy outcomes of study NCT04537793 of ELZ/TEZ/IVA in people with CF aged 2 to 5 with either an F/F or F/MF genotype.

NCT04537793: Part B, FAS at Week 24	ELX/TEZ/IVA (n=75) (n F/F = 23; n F/MF = 52)
Absolute change from baseline through Week 24 in sweat chloride, mmol/L, LS mean (95% CI)	[redacted]
Absolute change from baseline through Week 24 in $LCI_{2.5}$, LS mean (95% CI)	[redacted]
Number of participants with PEx, n (%)	[redacted]
Number of participants with PEx requiring hospitalisation or IV antibiotics, n (%)	[redacted]
Absolute change from baseline in weight-for-age z-score at Week 24 (95% CI)	[redacted]
[redacted]	

Abbreviations: CI: confidence interval; ELX: elexacaftor; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; PEx: pulmonary exacerbations; TEZ: tezacaftor.

Given the efficacy outcomes included in the economic model were judged to be at high risk of bias, the EAG considers the absolute change from baseline through Week 24 in sweat chloride to be an important clinical endpoint for this trial that is at low risk of bias due to:

- The lack of a plausible mechanism by which the COVID-19 pandemic could confound this outcome and;
- The low likelihood of spontaneous improvement in sweat chloride without CFTR modulators.

Participants in NCT04537793 experienced a [redacted] change from baseline in sweat chloride through Week 24, from a mean baseline of [redacted]. This change from baseline demonstrates the clinical efficacy of ELX/TEZ/IVA in the 2 to 5 age group, and the

magnitude of the sweat chloride response is in-line with that seen at older age groups Sections (3.2.2.1.1.2 and 3.2.2.1.1.3).

3.2.2.1.1.2 6 to 11 years

Zemanick 2021 (VX18-445-106) was a Phase 3 non-randomised trial of ELX/TEZ/IVA in children aged 6 to 11 with either an F/F or F/MF CF genotype.[135] The study period of Zemanick 2021 overlapped with the COVID-19 pandemic (Start Date: 2 October 2018; Primary Completion Date: 7 August 2020), and as such the EAG assesses the $LCI_{2.5}$, pulmonary exacerbation and weight-for-age z-score data to be at high risk of bias, but notes that much of the data collection may have occurred prior to COVID–19. Through 24 weeks, participants on ELX/TEZ/IVA experienced a –1.71 (95% CI: 2.11 to –1.30) decrease (improvement) in $LCI_{2.5}$, and a 0.25 (95% CI: 0.16 to 0.33) increase in weight–for–age z–score. Four (6%) participants experienced a pulmonary exacerbation during the study, although only [redacted] required hospitalisation or IV antibiotics (Table 21). Participants in Zemanick 2021 experienced a –60.9 mmol/L (95% CI: –63.7 to –58.2) change from baseline in sweat chloride through Week 24, from a mean baseline of 102.2 mmol/L.

Table 21. Clinical efficacy outcomes of Zemanick 2021 of ELZ/TEZ/IVA in people with CF aged 6 to 11 with either an F/F or F/MF genotype.

Zemanick 2021: mITT at Week 24	ELX/TEZ/IVA (n=66)
Absolute change from baseline through Week 24 in sweat chloride, mmol/L, LS mean (95% CI)	–60.9 (–63.7 to –58.2)
Absolute change from baseline through Week 24 in $LCI_{2.5}$, LS mean (95% CI)	–1.71 (–2.11 to –1.30)
Absolute change from baseline through Week 24 in $ppFEV_1$, LS mean (95% CI)	10.2 (7.9 to 12.6)
Number of participants with PEx, n (%)	4 (6%)
Number of participants with PEx requiring hospitalisation or IV antibiotics, n (%)	[redacted]
Absolute change from baseline in weight-for-age z-score at Week 24 (95% CI)	0.25 (0.16 to 0.33)

Abbreviations: CI: confidence interval; ELX: elexacaftor; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; $LCI_{2.5}$: lung clearance index 2.5; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; mITT: modified intention-to-treat; TEZ: tezacaftor

Mall 2022 (VX19-445-116) was a placebo-controlled Phase 3 RCT of ELX/TEZ/IVA in children with CF aged 6 to 11 with an F/MF CF genotype.[134] Through 24 weeks, participants on ELX/TEZ/IVA

experienced a –2.26 (95% CI: –2.71 to –1.81) greater decrease (improvement) in $LCI_{2.5}$ compared to placebo, and 11.0 (95% CI: 6.9 to 15.1) greater increase in $ppFEV_1$ compared to placebo. Participants treated with ELX/TEZ/IVA experienced a [redacted] increase in weight-for-age z-score at Week 24, relative to placebo. Pulmonary exacerbations were reported as adverse events through Week 28 and followed MedDRA 24.0 coding. Fourteen (22.95%) participants experienced a non-serious pulmonary exacerbation in the placebo arm, compared to 1 (1.67%) in the ELX/TEZ/IVA. Three (4.92%) participants experienced a serious pulmonary exacerbation in the placebo arm, compared to 0 in the ELX/TEZ/IVA arm (Table 22).

Table 22. Clinical efficacy outcomes of Mall 2022 of ELZ/TEZ/IVA in people with CF aged 6 to 11 with an F/MF genotype.

Mall 2022: FAS at Week 24	ELX/TEZ/IVA (n=60)	Placebo (n=61)
Absolute change from baseline through Week 24 in sweat chloride, mmol/L, LS mean (95% CI)	–52.1 (–55.0 to –49.2)	–0.9 (–3.8 to 2.0)
Difference from placebo	–51.2 (–55.3 to –47.1)	
Absolute change from baseline through Week 24 in $LCI_{2.5}$, LS mean (95% CI)	–2.29 (–2.60 to –1.97)	–0.02 (–0.34 to 0.29)
Difference from placebo	–2.26 (–2.71 to –1.81)	
Absolute change from baseline through Week 24 in $ppFEV_1$, LS mean (95% CI)	9.5 (6.6 to 12.4)	–1.5 (–4.4 to 1.4)
Difference from placebo (95% CI)	11.0 (6.9 to 15.1)	
Number of participants with PEx adverse event (not including serious), n (%). *Reported as adverse event through Week 28 only.*	1 (1.67)	14 (22.95)
Number of participants with serious PEx adverse event, n (%). *Reported as adverse event through Week 28 only.*	0 (0.00)	3 (4.92)
Number of participants with PEx requiring hospitalisation or IV antibiotics, n (%)	NR	NR
Absolute change from baseline in weight-for-age z-score at Week 24 (95% CI)	[redacted]	[redacted]
Difference from placebo (95% CI)	[redacted]	

Abbreviations: CI: confidence interval; ELX: elexacaftor; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; TEZ: tezacaftor.

3.2.2.1.1.3 12+ years

Sutharsan 2022 (VX18-445-109) was a TEZ/IVA-controlled Phase 3 RCT of ELX/TEZ/IVA in people with CF aged 12+ with an F/F CF genotype.[131] Prior to baseline, participants completed a 4-week TEZ/IVA (100 mg qd/ 150 mg q12h) run-in period. Through 24 weeks, participants randomised to ELX/TEZ/IVA experienced a 10.2 (95% CI: 8.2 to 12.1) greater increase in $ppFEV_1$ compared to participants randomised to TEZ/IVA. Participants treated with ELX/TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score at Week 24 compared to participants randomised to TEZ/IVA. Pulmonary exacerbations were reported as adverse events through Week 28 and followed MedDRA 23.0 coding. Thirty-two (36.36%) participants experienced a non-serious pulmonary exacerbation in the TEZ/IVA arm, compared to 10 (11.49%) in the ELX/TEZ/IVA arm. Nine (10.23%) participants experienced a serious pulmonary exacerbation in the TEZ/IVA arm, compared to 1 (1.15%) in the ELX/TEZ/IVA arm (Table 23).

Heijerman 2019 (VX17-445-103) was a TEZ/IVA-controlled Phase 3 RCT of ELX/TEZ/IVA in people with CF aged 12+ with an F/F CF genotype.[133] Prior to baseline, participants completed a 4-week TEZ/IVA (100 mg qd/ 150 mg q12h) run-in period. Through 4 weeks, participants randomised to ELX/TEZ/IVA experienced a 10.0 (95% CI: 7.4 to 12.6) greater increase in $ppFEV_1$ compared to participants randomised to TEZ/IVA. Pulmonary exacerbations were reported as adverse events through Week 8 and followed MedDRA 21.1 coding. Five (9.62%) participants experienced a non-serious pulmonary exacerbation in the TEZ/IVA arm, compared to 0 in the ELX/TEZ/IVA arm. One (1.92%) participant experienced a serious pulmonary exacerbation in the TEZ/IVA arm, and 1 (1.15%) participant experienced a serious pulmonary exacerbation in the ELX/TEZ/IVA arm (Table 23).

Barry 2021 was an active controlled Phase 3 RCT recruiting people with CF aged 12+ with either F/RF or F/Gating CF genotypes.[132] F/RF participants were randomised to either ELX/TEZ/IVA or TEZ/IVA, and received a 4-week TEZ/IVA (100 mg qd/ 150 mg q12h) run-in period. F/Gating participants, including F/*R117H* participants, were randomised to either ELX/TEZ/IVA or IVA monotherapy, and received a 4-week IVA monotherapy (150 mg q12h) run-in period. Through 8 weeks, F/RF participants randomised to ELX/TEZ/IVA experienced a 2.0 (95% CI: 0.5 to 3.4) greater increase in $ppFEV_1$ compared to participants randomised to TEZ/IVA. Participants treated with ELX/TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score at Week 8

compared to participants randomised to TEZ/IVA. Through 8 weeks, F/Gating participants randomised to ELX/TEZ/IVA experienced a 5.8 (95% CI: 3.5 to 8.0) greater increase in $ppFEV_1$ compared to participants randomised to IVA monotherapy. Participants treated with ELX/TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score at Week 8 compared to participants randomised to IVA monotherapy. Pulmonary exacerbations were reported for the overall Barry 2021 cohort, rather than by CF genotype, as adverse events through Week 12 and followed MedDRA 23.0 coding. Ten (7.94%) participants experienced a non-serious pulmonary exacerbation in the TEZ/IVA or IVA monotherapy arms, compared to 2 (1.52%) in the ELX/TEZ/IVA arms. Seven (5.56%) participants experienced a serious pulmonary exacerbation in the TEZ/IVA or IVA monotherapy arms, compared to two (1.52%) in the ELX/TEZ/IVA arm (Table 23).

Middleton 2019 (VX17-445-102) was a placebo-controlled Phase 3 RCT of ELX/TEZ/IVA in people with CF aged 12+ with an F/MF CF genotype.[133] Prior to baseline, there was no active run-in period. Through 24 weeks, participants randomised to ELX/TEZ/IVA experienced a 14.3 (95% CI: 12.7 to 15.8) greater increase in $ppFEV_1$ compared to participants randomised to placebo. Participants treated with ELX/TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score at Week 24 compared to participants randomised to placebo, and fewer participants experienced protocol-defined pulmonary exacerbations in the ELX/TEZ/IVA arm (20.3%) than the placebo arm (56.5%, Table 23).

Table 23. Clinical efficacy outcomes of RCTs of ELZ/TEZ/IVA in people with CF aged 12+

	Sutharsan 2022 mITT through 24 weeks F/F		Heijerman 2019 FAS through 4 weeks F/F		Barry 2021 FAS through 8 weeks F/RF		Barry 2021 FAS through 8 weeks F/Gating		Middleton 2019 FAS through 24 weeks F/MF	
	ELX/TEZ/IVA (n=87)	**TEZ/IVA (n=88)**	**ELX/TEZ/IVA (n=55)**	**TEZ/IVA (n=52)**	**ELX/TEZ/IVA (n=82)**	**TEZ/IVA (n=81)**	**ELX/TEZ/IVA (n=50)**	**IVA (n=45)**	**ELX/TEZ/IVA (n=200)**	**Placebo (n=203)**
Absolute change from baseline in sweat chloride, mmol/L, LS mean (95% CI)	–46.2 (–48.7 to –43.7)	–3.4 (–5.8 to –1.0)	–43.4 (–46.9 to –40.0)	1.7 (–1.9 to 5.3)	–23.1 (–25.6 to –20.6)	–1.7 (–0.9 to 4.3)	–21.8 (–25.7 to -17.8)	–1.8 (–5.7 to 2.2)	–42.2 (–40.4 to –41.8)	–0.4 (–2.2 to 1.4)
Difference from TEZ/IVA or placebo (95% CI)	–42.8 (–46.2 to –39.3)		–45.1 (–50.1 to –40.1)		–20.0 (–25.4 to –14.6)		–24.8 (–28.4 to –21.2)		–41.8 (–44.4 to –39.3)	
Absolute change from baseline in ppFEV$_1$, LS mean (95% CI)	11.2 (9..8 to 12.6)	1.0 (-0.4 to 2.4)	10.4 (8.6 to 12.1)	0.4 (-1.4 to 2.3)	2.5 (1.4 to 3.5)	0.5 (–0.5 to 1.5)	5.8 (4.2 to 7.5)	0.1 (–1.6 to 1.7)	13.9 (12.8 to 15.0)	–0.4 (–1.5 to 0.7)
Difference from TEZ/IVA or placebo (95% CI)	10.2 (8.2 to 12.1)		10.0 (7.4 to 12.6)		2.0 (0.5 to 3.4)		5.8 (3.5 to 8.0)		14.3 (12.7 to 15.8)	
Number of participants with PEx adverse event (not including serious), n (% of SAS)	10 (11.49)*	32 (36.36)*	0 **	5 (9.62)**	Combined across genotypes:*** ELZ/TEZ/IVA = 2 (1.52%) Active control = 10 (7.94%)				41 (20.30)	83 (41.29)

Number of participants with serious PEx adverse event, n (% of SAS)	1 (1.15)*	9 (10.23)*	1 (1.82)**	1 (1.92)**	Combined across genotypes: ELZ/TEZ/IVA = 2 (1.52%) Active control = 7 (5.56%)				11 (5.45)	33 (16.42)
Number of participants with protocol defined PEx, (%)	NR	NR	NR	NR	NR	NR	NR	NR	41 (20.5)	113 (56.5)
Annual event rate PEx requiring IV antibiotics	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
Difference from TEZ/IVA or placebo (rate ratio, 95% CI)	NR		NR		NR		NR		[redacted]	
Absolute change from baseline in weight-for-age z-score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from TEZ/IVA or placebo (95% CI)	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: CI: confidence interval; ELX: elexacaftor; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; mITT: modified intention-to-treat; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; SAS; safety analysis set; TEZ: tezacaftor.

* Reported as adverse event through Week 28.

** Reported as adverse event through Week 8.

*** Reported as adverse event through Week 12.

3.2.2.1.2 TEZ/IVA

3.2.2.1.2.1 6 to 11 years

Davies 2021 (VX16-661-115) was a Phase 3 RCT of TEZ/IVA in children aged 6 to 11 with either an F/F or F/RF CF genotype. Participants were randomised 4:1 either to TEZ/IVA or to a "blinding arm" (placebo for F/F, IVA monotherapy for F/RF), and the study was only powered to detect a treatment effect within the TEZ/IVA arm, approximating a non-randomised trial with blinding. Through 8 weeks, participants on TEZ/IVA experienced a –0.51 (95% CI: –0.74 to –0.29) decrease (improvement) in $LCI_{2.5}$, a 2.8 (95% CI: 1.0 to 4.6) increase in $ppFEV_1$ and a –0.04 (SD: 0.17) decrease in weight-for-age z-score. Three (5.56%) participants experienced a pulmonary exacerbation adverse event during the study, although none were rated as severe. Table 24 presents these data, alongside the efficacy and pulmonary exacerbation data from the two blinding arms. The EAG notes that outcome data were not available for the F/F and F/RF subgroups of participants treated with TEZ/IVA in this trial.

Table 24. Clinical efficacy outcomes of Davies 2021 of TEZ/IVA in people with CF aged 6 to 11 with either an F/F or F/RF genotype.

Davies 2021: mITT at Week 8	TEZ/IVA (n=54) (F/F n=42, F/RF n=12)	IVA F/RF (n=3)	Placebo F/F (n=10)
Absolute change from baseline through Week 8 in sweat chloride, mmol/L, LS mean (95% CI)	–12.3 (–15.3 to –9.3)	–1 (SD: 9)	–1 (SD: 12.3)
Absolute change from baseline through Week 8 in $LCI_{2.5}$, LS mean (95% CI)	–0.51 (–0.74 to –0.29)	–0.61 (SD: 0.88)	0.10 (SD: 1.16)
Absolute change from baseline through Week 8 in $ppFEV_1$, LS mean (95% CI)	2.8 (1.0 to 4.6)	–0.4 (SD: 6.0)	–3.7 (SD: 6.1)
Number of participants with PEx adverse event (not including serious), n (% of SAS). *Reported as adverse event through Week 12 only*	3 (5.56)	0	2 (20.0)
Number of participants with serious PEx adverse event, n (% of SAS). *Reported as*	0	0	0

adverse event through Week 12 only			
Absolute change from baseline in weight-for-age z-score at Week 8	–0.04 (SD: 0.17)	0.03 (SD: 0.23)	–0.02 (SD: 0.15)

Abbreviations: Abbreviations: CI: confidence interval; IV: intravenous; IVA: ivacaftor; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; mITT: modified intention-to-treat; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; SAS; safety analysis set; TEZ: tezacaftor.

In the Company submission, Walker 2019 (VX15-661-113) was also presented as a source of clinical efficacy data for the acute effects of TEZ/IVA in people with CF aged 6 to 11 years.[160] Walker 2019 was a Phase 3 non-randomised trial, but was deprioritised in the EAG SLR due to RCT evidence being available in the same population from Davies 2021. However, the EAG notes that due to the small sample size of the control "blinding" arms in Davies 2021, Walker 2019 and Davies 2021 may provide a similar quality of evidence. The EAG compares the efficacy data from the Davies 2021 TEZ/IVA arm and Walker 2019 in Table 25. The EAG considers these outcome data to be consistent, but notes that: i) despite overlapping with each other, the confidence intervals for the change from baseline in $ppFEV_1$ for Davies 2021 excluded 0, but did not for Walker 2019, ii) a higher rate of pulmonary exacerbations were reported in Walker 2019.

Table 25. Clinical efficacy outcomes of Davies 2021 and Walker 2019 of TEZ/IVA in people with CF aged 6 to 11 with either an F/F or F/RF genotype.

	Davies 2021: Week 8 **TEZ/IVA** **(n=54)** **(F/F n=42, F/RF n=12)**	**Walker 2019 Part B: Week 24** **TEZ/IVA** **(n=70)*** **(F/F n=61, F/RF n=9)**
Absolute change from baseline through Week 8 (Davies 2021) or Week 24 (Walker 2019) in sweat chloride, mmol/L, LS mean (95% CI)	–12.3 (–15.3 to –9.3)	–14.5 (–17.4 to –11.6)
Absolute change from baseline through Week 8 (Davies 2021) or Week 24 (Walker 2019) in $LCI_{2.5}$, LS mean (95% CI)	–0.51 (–0.74 to –0.29)	NR
Absolute change from baseline through Week 8 (Davies 2021) or Week 24	2.8 (1.0 to 4.6)	0.9 (–0.6 to 2.3)

(Walker 2019) in ppFEV$_1$, LS mean (95% CI)		
Number of participants with PEx adverse event (not including serious), n (% of SAS). *Reported as adverse event through Week 12 (Davies 2021) or Week 28 (Walker 2019) only*	3 (5.56)	16 (22.9)
Number of participants with serious PEx adverse event, n (% of SAS). *Reported as adverse event through Week 12 (Davies 2021) or Week 28 (Walker 2019) only*	0	2 (2.9)
Absolute change from baseline in weight-for-age z-score at Week 8 (Davies 2021) or Week 24 (Walker 2019)	–0.04 (SD: 0.17)	0.0 (–0.05 to 0.05)

*N = 64 participants had baseline measurements

Abbreviations: Abbreviations: CI: confidence interval; IV: intravenous; IVA: ivacaftor; LCI$_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; mITT: modified intention-to-treat; PEx: pulmonary exacerbations; ppFEV$_1$: percent predicted forced expiratory volume in one second; SAS; safety analysis set; TEZ: tezacaftor.

3.2.2.1.2.2 12+ years

Three studies including TEZ/IVA in the 12+ years age group were presented in Section 3.2.2.1.1.3, with TEZ/IVA being an active control arm in RCTs of ELX/TEZ/IVA in Sutharsan 2022, Heijerman 2019 and Barry 2021. Due to the 4-week TEZ/IVA run-in period used in these trials, the change from baseline at Week 24 for participants on TEZ/IVA is close to 0, for most variables. This is because most of the acute clinical effects of TEZ/IVA would have manifested in the 4-week TEZ/IVA run-in period for participants naïve to TEZ/IVA, rather than in the post-baseline efficacy period.

Taylor-Cousar 2017 (VX14-661-106) was a Phase 3 placebo-controlled RCT in people with CF aged 12+ with an F/F CF genotype.[137] Through 24 weeks, participants randomised to TEZ/IVA experienced a 4.0 (95% CI: 3.1 to 4.8) greater increase in ppFEV$_1$ compared to participants randomised to placebo. Participants treated with TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score at Week 24 compared to participants randomised to placebo. Pulmonary exacerbations were reported as a protocol-defined efficacy outcome through Week 24 and as adverse events through Week 28 following MedDRA 19.1 coding. There were 78 protocol-defined pulmonary exacerbations in the TEZ/IVA arm, compared to 122 in the placebo arm (Table 26).

Rowe 2017 (VX14-661-108) was a Phase 3 placebo-controlled crossover RCT in people with CF aged 12+ with an F/RF CF genotype.[138] Participants were randomised to one of six treatment sequences, receiving either TEZ/IVA, IVA monotherapy or placebo for 8 weeks, followed by an 8-week washout period, and then either TEZ/IVA, IVA monotherapy or placebo for a further 8 weeks. Primary and secondary endpoints were reported as averages across treatment periods for the following contrasts: IVA monotherapy vs placebo, TEZ/IVA vs placebo and, TEZ/IVA vs IVA monotherapy. As IVA monotherapy is not within the scope of this MTA and there are head-to-head trial data for TEZ/IVA vs placebo, the IVA monotherapy data are not considered further here. Across both 8-week treatment periods, participants receiving to TEZ/IVA experienced a 6.8 (95% CI: 5.7 to 7.8) greater increase in ppFEV$_1$ compared to participants receiving placebo. Participants receiving TEZ/IVA experienced a [redacted] greater increase in weight-for-age z-score across treatment periods compared to participants receiving placebo. Pulmonary exacerbations were reported as a protocol-defined efficacy outcome and as adverse events through Week 28 following MedDRA 19.1 coding. There were 11 protocol-defined pulmonary exacerbations in the TEZ/IVA arm, compared to 20 in the placebo arm (Table 26).

Table 26. Clinical efficacy outcomes of placebo-controlled RCTs of TEZ/IVA in people with CF aged 12+

	Taylor-Cousar 2017 mITT through 24 weeks F/F		Rowe 2017 FAS across both 8-week treatment periods F/RF	
	TEZ/IVA (n=248)	**Placebo (n=256)**	**TEZ/IVA (n=161)**	**Placebo (n=161)**
Absolute change from baseline in sweat chloride, mmol/L, LS mean (95% CI)	–9.9* (–10.9 to –8.9)	0.2** (–0.8 to 1.2)	–9.9 (–11.8 to –8.0)	–0.4 (–2.3 to 1.5)
Difference from placebo (95% CI)	–10.1 (–11.4 to –8.8)		–9.5 (–11.7 to –7.3)	
Absolute change from baseline in $ppFEV_1$, LS mean (95% CI)	3.4 (2.7 to 4.0)	–0.6 (–1.3 to 0.0)	6.5 (5.6 to 7.3)	–0.3 (–1.2 to 0.6)
Difference from placebo (95% CI)	4.0 (3.1 to 4.8)		6.8 (5.7 to 7.8)	
Number of participants with PEx adverse event (not including serious), n (% of SAS)	57 (22.7)***	75 (29.1)***	19 (11.73)†	25 (15.43)†
Number of participants with serious PEx adverse event, n (% of SAS)	23 (9.16)***	32 (12.4)***	4 (2.47)†	8 (4.94)†
Number protocol defined PEx events, (annualised event rate)	78 (0.64)	122 (0.99)	11 (0.34)	20 (0.63)
Rate ratio of PEx events requiring IV antibiotics vs placebo (95% CI)	0.53 (0.34 to 0.80)		0.54 (0.26 to 1.13)	

Absolute change from baseline in weight-for-age z-score	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo (95% CI)	[redacted]		[redacted]	

*n=240 for this outcome

**n=242 for this outcome

*** Reported as adverse event in SAS through Week 28, SAS n = 251 TEZ/IVA, SAS n = 256 placebo.

†Reported as adverse event in SAS through Week 28, SAS n = 162 for both TEZ/IVA and placebo

Abbreviations: CI: confidence interval; IVA: ivacaftor; LUM: lumacaftor; LS: least squares; mITT: modified intention-to-treat; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; SAS; safety analysis set; TEZ: tezacaftor.:

3.2.2.1.3 LUM/IVA

3.2.2.1.3.1 1 to 2 years

Rayment 2022 (VX16-809-122) was a Phase 3 non-randomised trial of people with CF aged 1 to 2 years with an F/F CF genotype.[143] Part A recruited 14 participants for a treatment duration of 15 days and Part B recruited 47 participants for a treatment duration of 24 weeks. The results of Part B are presented here. The study period of Rayment 2022 overlapped with the COVID-19 pandemic (Start Date: 7 September 2018; Primary Completion Date: 29 October 2021), and as such the EAG assesses the pulmonary exacerbation and weight-for-age z-score data to be at high risk of bias, but notes that much of the data collection was likely completed prior to COVID-19. Through 24 weeks, participants on LUM/IVA experienced a 0.06 (95% CI: –0.05 to 0.17) increase in weight-for-age z-score. In the 26-week safety assessment period, 10 (21.1%) participants experienced a non-serious adverse event of pulmonary exacerbation, and three (6.5%) participants experienced a serious adverse event of pulmonary exacerbation (Table 20). A spirometry outcome, $LCI_{2.5}$ was due to be collected as part of a substudy, but this recruited only one participant. The EAG's clinical experts highlighted the difficulty in measuring spirometry outcomes in infants. In lieu of spirometry outcomes, the EAG considers the absolute change from baseline through Week 24 in sweat chloride to be an informative clinical outcome that is likely prognostic of future spirometry results.

Participants treated with LUM/IVA had a mean reduction of –29.1 mmol/L (95% CI: –34.8 to –23.4) in sweat chloride through Week 24. However, the EAG considers there to be a high risk of bias in both the sweat chloride and change in weight-for-age z-score data due to a high rate of data missingness. Only 24 of the 46 participants in the FAS provided a sweat chloride measurement at Week 24, and only 38 participants had a weight-for-age z-score measurement at Week 24. The EAG considers it plausible that such data were not missing at random. [redacted]

Table 27. Clinical efficacy outcomes of Rayment 2022 of LUM/IVA in people with CF aged 1 to 2 years with an F/F CF genotype.

Rayment 2022: Part B, FAS at Week 24	LUM/IVA (n=46)
Absolute change from baseline through Week 24 in sweat chloride, mmol/L, LS mean (95% CI)	–29.1 (–34.8 to –23.4), n = 24
Absolute change from baseline through Week 24 in $LCI_{2.5}$, LS mean (95% CI)	NR
Number of participants with non-serious PEx adverse event through Week 26, n (%)	10 (21.2%)
Number of participants with serious PEx adverse event through Week 26, n (%)	3 (6.5%)
Absolute change from baseline in weight-for-age z-score at Week 24 (95% CI)	0.06 (–0.05 to 0.17), n = 38

Abbreviations: CI: confidence interval; ELX: elexacaftor; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; LS: least squares; PEx: pulmonary exacerbations; NR: not reported.

3.2.2.1.3.2 2 to 5 years

Stahl 2021 (VX16-809-121) was a placebo-controlled Phase 2 RCT of LUM/IVA in children with CF aged 2 to 5 years with an F/F CF genotype.[142] Stahl 2021 was defined as an exploratory study to explore the impact of LUM/IVA on disease progression in CF in people aged 2 to 5, and had a primary endpoint of the absolute change from baseline in MRI global chest score at Week 48. However, all key variables relevant to the economic model of this MTA were reported as secondary outcomes for both LUM/IVA and placebo, and as such, the EAG considers Stahl 2021 to be a stronger source of data on the relative treatment effect of LUM/IVA compared to ECM than the Phase 3 non-randomised trials in this population.

Through 48 weeks, participants randomised to LUM/IVA experienced a –0.37 [redacted] decrease in $LCI_{2.5}$, compared to a 0.32 [redacted] increase for participants randomised to placebo. Participants randomised to LUM/IVA experienced a 0.13 (95% CI: –0.01 to 0.27) increase in weight–for–age z–score at Week 28, compared to a –0.07 (–0.24 to 0.11) decrease for participants randomised to placebo. There were 26 (annual event rate: 0.75) protocol-defined pulmonary exacerbations in the LUM/IVA arm, and 19 (annual event rate: 1.17) in the placebo arm (Table 28).

Table 28. Clinical efficacy outcomes of Stahl 2021 of LUM/IVA in people with CF aged 2 to 5 with an F/F CF genotype.

Stahl 2021: FAS at Week 48	LUM/IVA (n=35)	Placebo (n=16)
Absolute change from baseline through Week 48 in sweat chloride, mmol/L, LS mean (95% CI)	–25.4 [redacted]	1.0 [redacted]
Difference from placebo	NR	
Absolute change from baseline through Week 48 in $LCI_{2.5}$, LS mean (95% CI)	–0.37 (–0.85 to 0.10)	0.32 (–0.20 to 0.84)
Difference from placebo	NR	
Number of protocol defined PEx events (event rate per year)	26 (0.75)	19 (1.17)
Number of participants with PEx adverse event (not including serious), n (%). *Reported as adverse event through Week 48.*	15 (42.86)	9 (56.25)
Number of participants with serious PEx adverse event, n (%). *Reported as adverse event through Week 48*	3 (8.57)	1 (6.25)
Absolute change from baseline in weight-for-age z-score at Week 48 (95% CI)	0.13 (–0.01 to 0.27)	–0.07 (–0.24 to 0.11)
Difference from placebo	NR	

Abbreviations: CI: confidence interval; ELX: elexacaftor; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; LS: least squares; PEx: pulmonary exacerbations; NR: not reported.

In the Company submission, McNamara 2019 (VX15-809-115) was used as the source of clinical efficacy data for the acute effects of LUM/IVA in people with CF aged 2 to 5.[160] McNamara 2019 was a Phase 3 non-randomised trial. Due to the model structure and assumptions, the only data applied from this study was absolute change in weight-for-age z-score, compliance, and discontinuation. Table 29 compares these data from Stahl 2021 and McNamara 2019. The EAG notes that the change from baseline weight-for-age z-score data are more consistent between Stahl 2021 and, i) data from participants aged 1 to 2 years and 6 to 11 years treated with LUM/IVA (Sections 3.2.2.1.3.1 and 3.2.2.1.3.2), and ii) data from participants aged 2 to 5 years treated with ELX/TEZ/IVA (3.2.2.1.1.1).

Table 29. A comparison of weight-for-age z-score, treatment compliance and discontinuation data from Stahl 2021 and McNamara 2019.

	Stahl 2021 at Week 48 (n=35)	McNamara 2019 at Week 24 (n=60)
Change from baseline weight-for-age z-score (95% CI)	0.13 (–0.01 to 0.27)	[redacted]
Treatment compliance	[redacted]	[redacted]
Annual rate of discontinuation	[redacted]	0.149
Abbreviations: CI: confidence interval		

3.2.2.1.3.3 6 to 11 years

Ratjen 2017 (VX14-809-109) was a placebo-controlled Phase 3 RCT of LUM/IVA in children with CF aged 6 to 11 with an F/F CF genotype.[141] Through 24 weeks, participants on LUM/IVA experienced a –1.09 (95% CI: –1.43 to –0.75) greater decrease in $LCI_{2.5}$ compared to placebo, and 2.4 (95% CI: 0.4 to 4.4) greater increase in $ppFEV_1$ compared to placebo. Participants treated with LUM/IVA experienced a [redacted] increase in weight–for–age z–score at Week 24. Through Week 24, 20 participants experienced a protocol defined pulmonary exacerbation in the LUM/IVA arm (annualised event rate: [redacted]), compared to 15 participants in the placebo arm (annualised event rate: [redacted], Table 30).

Table 30. Clinical efficacy outcomes of Ratjen 2017 of LUM/IVA in people with CF aged 6 to 11 with an F/F genotype.

Ratjen 2017: FAS at Week 24	LUM/IVA (n=103)	Placebo (n=101)
Absolute change from baseline through Week 24 in sweat chloride, mmol/L, LS mean (95% CI)	–21.6 (SE: 1.3)	3.2 (SE: 1.3)
Difference from placebo	NR	
Absolute change from baseline through Week 24 in $LCI_{2.5}$, LS mean (95% CI)	–1.01 (–1.3 to –0.8)	0.08 (–0.2 to 0.3)
Difference from placebo (95% CI)	–1.09 (–1.43 to –0.75)	

Absolute change from baseline through Week 24 in ppFEV$_1$, LS mean (95% CI)	1.1 (–0.4 to 2.6)	–1.3 (–2.8 to 0.2)
Difference from placebo (95% CI)	2.4 (0.4 to 4.4)	
Number of protocol defined PEx events (event rate per year)	[redacted]	[redacted]
Annualised estimated event rate of PEx requiring hospitalisation	[redacted]	[redacted]
Number of participants with PEx requiring IV antibiotics, n (%)	[redacted]	[redacted]
Number of participants with PEx adverse event (not including serious), n (%). *Reported as adverse event through Week 28 only*	16 (15.84)	13 (12.62)
Number of participants with serious PEx adverse event, n (%). *Reported as adverse event through Week 28 only*	5 (4.95)	8 (7.77)
Absolute change from baseline in weight-for-age z-score at Week 24	[redacted]	[redacted]
Difference from placebo (95% CI)	[redacted]	

Abbreviations: CI: confidence interval; ELX: elexacaftor; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; LCI$_{2.5}$: lung clearance index 2.5; IV: intravenous; FAS: full analysis set; PEx: pulmonary exacerbations; ppFEV$_1$: percent predicted forced expiratory volume in one second.

3.2.2.1.3.4 12+ years

Wainwright 2015 reported the results of TRAFFIC (VX12-809-103) and TRANSPORT (VX12-809-104), which were both Phase 3 placebo-controlled RCTs of LUM/IVA in participants aged 12+ years with an F/F CF genotype. In both TRAFFIC and TRANSPORT, participants were randomised to one of three arms: LUM/IVA (400 mg q12h/250 mg q12h); LUM/IVA (600 mg qd/250 mg q12h); or placebo. As in TA398,[161] the LUM/IVA (600 mg qd/250 mg q12h) arm is not considered further as this dose is not included in the marketing authorisation, and there is evidence that the treatment effects differ across doses.[42]

Through 24 weeks in TRAFFIC, participants randomised to LUM/IVA experienced a 2.6 (95% CI: 1.18 to 4.01) greater increase in ppFEV$_1$ compared to participants randomised to placebo. There were 73 (annualised event rate: 0.71) protocol-defined pulmonary exacerbations in the LUM /IVA arm, compared to 112 (annualised event rate: 1.08) in the placebo arm (Table 26). In TRANSPORT, participants randomised to LUM/IVA experienced a 3.0 (1.56 to 4.44) greater increase in ppFEV$_1$ compared to participants randomised to placebo. There were 79 (annualised event rate: 0.67) protocol-defined pulmonary exacerbations in the LUM/IVA arm, compared to 139 (annualised event

rate: 1.18) in the placebo arm (Table 26). The relative difference in change from baseline weight-for-age z-score was available for TRAFFIC and TRANSPORT pooled, and was [redacted] higher in the TRAFFIC/TRANSPORT LUM/IVA arms compared to placebo. TRAFFIC and TRANSPORT were the only trials of CFTR modulator combination therapies to report EQ-5D data. For both trials, the mean difference in change from baseline in EQ-5D-3L between LUM/IVA and placebo was lower than 0.01 (TRAFFIC: 0.0095; TRANSPORT –0.0009, Table 31).

Wilson 2021 was a Phase 4 placebo-controlled RCT of LUM/IVA in participants aged 12+ years with an F/F CF genotype.[140] Through 24 weeks, participants randomised to receive LUM/IVA experienced a 3.4 (–1.2 to 8.1) greater change from baseline in ppFEV$_1$ than participants randomised to placebo, although absolute pPFEV1 decline through Week 24 in both arms. The number of participants with serious PEx adverse events through Week 28 was 8 (23.53%) in the LUM/IVA arm, and 6 (16.67%) in the placebo arm (Table 31).

Table 31. Clinical efficacy outcomes of placebo-controlled RCTs of LUM/IVA in people with CF aged 12+

	TRAFFIC (Wainwright 2015) FAS through 24 weeks F/F		TRANSPORT (Wainwright 2015) FAS through 24 weeks F/F		Wilson 2021 FAS through 24 weeks	
	LUM/IVA (n=182)	**Placebo (n=184)**	**LUM/IVA (n=187)**	**Placebo (n=187)**	**LUM/IVA (n=34)**	**Placebo (n=36)**
Absolute change from baseline in sweat chloride, mmol/L, LS mean (95% CI)	NR	NR	NR	NR	NR	NR
Difference from placebo	NR		NR		NR	
Absolute change from baseline in ppFEV$_1$, LS mean (95% CI)	2.16 (SE: 0.53)	–0.44 (SE: 0.524)	2.85 (SE: 0.54)	–0.15 (SE: 0.539)	–0.6 (–4 to 2.9)	–4.0 (–7.3 to –0.7)
Difference from placebo (95% CI)	2.6 (1.18 to 4.01)		3.0 (1.56 to 4.44)		3.4 (–1.2 to 8.1)	
Number of participants with PEx adverse events (not including serious), n (% of SAS), reported at Week 28	54 (29.67)	58 (31.52)	50 (26.74)	74 (39.78)*	8 (23.53)	6 (16.67)
Number of participants with serious PEx adverse events, n (% of SAS), reported at Week 28	17 (9.34)	41 (22.28)	24 (12.83)	48 (25.81)*	8 (23.53)	6 (16.67)
Number protocol defined PEx events, (annualised event rate)	73 (0.71)	112 (1.08)	79 (0.67)	139 (1.18)	NR	NR

Number protocol defined PEx events requiring hospitalisation, (annualised event rate)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Number protocol defined PEx events requiring IV antibiotics, (annualised event rate)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Rate ratio of PEx events requiring IV antibiotics vs placebo	Data only available for TRAFFIC/TRANSPORT pooled: 0.44				NR	NR
Absolute change from baseline in weight-for-age z-score	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Difference from placebo (95% CI)	[redacted]				NR	NR
Absolute change from baseline in EQ-5D-3L	0.01 (SE: 0.008)	0.0006 (SE: 0.007)	0.011 (SE: 0.007)	0.012 (SE: 0.007)	NR	NR
Difference from placebo (95% CI)	0.0095 (–0.011 to 0.030)		–0.0009 (–0.019 to 0.017)		NR	NR

*n=186 for this outcome

Abbreviations: CI: confidence interval; FAS: full analysis set; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; mITT: modified intention-to-treat; PEx: pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in one second; SAS; safety analysis set.

3.2.2.2 *Relationship between clinical efficacy and baseline lung function*

To consider the relationship between baseline lung function and clinical effectiveness, the EAG extracted subgroup data for the relative treatment effect of absolute change from baseline in $ppFEV_1$ from the clinical trials included in the SLR, by baseline $ppFEV_1$ groups. These were reported as pre-specified subgroups in the eight pivotal Phase 3 RCTs of people with CF aged 12+: Middleton 2019; Barry 2021; Sutharsan 2022; Heijerman 2019; Taylor-Cousar 2017; Rowe 2017; TRAFFIC; and TRANSPORT.[42, 61, 131-133, 137, 138] Data were presented for each subgroup, although no interaction modelling was performed. The definition of subgroups differed between trials, with some trials reporting only subgroup data for only the <70 $ppFEV_1$ and ≥70 $ppFEV_1$ groups at baseline, but others also including categories of <40 $ppFEV_1$ and ≥40 $ppFEV_1$ at baseline. These subgroup data are presented in Table 32. The EAG notes that the relative treatment effect of the CFTR modulator interventions was consistently larger for the $ppFEV_1$ <70 at baseline group than the $ppFEV_1$ ≥70 at baseline group, but notes that the magnitude of this difference was inconsistent between studies.

From these subgroup analyses, the EAG considers it likely that there is a relationship between baseline $ppFEV_1$ and the acute increase in $ppFEV_1$ following CFTR modulator therapy, however notes that:

- The subgroups reported lack clinical justification, and the relationship between baseline $ppFEV_1$ and acute change in $ppFEV_1$ would be more adequately modelled using baseline $ppFEV_1$ as a continuous predictor in a model allowing for a non-linear interaction between baseline $ppFEV_1$ and acute increase in $ppFEV_1$, e.g., a restricted cubic spline;
- It is plausible that the same acute increase in individuals with different baseline $ppFEV_1$ can have different clinical interpretations and prognostic ability, especially due to ceiling effects at high $ppFEV_1$ levels.
    - For people with CF and preserved lung function (e.g., high baseline $ppFEV_1$), the EAG's clinical experts suggested the benefit of CFTR modulators for these individuals may be more visible in the prevention or delaying of lung function decline, rather than through an acute increase in $ppFEV_1$.

Table 32. Between treatment difference in absolute change from $ppFEV_1$, by $ppFEV_1$ subgroup, for people with CF aged 12+ years

Study	Intervention	Genotype	Timepoint	Between treatment difference in absolute change from $ppFEV_1$, by $ppFEV_1$ subgroup				
				$ppFEV_1$ <40	$ppFEV_1$ ≥40	≥40 $ppFEV_1$ <70	$ppFEV_1$ <70	$ppFEV_1$ ≥70
Middleton 2019	ELX/TEZ/IVA vs placebo	F/MF	Week 24	NR	NR	NR	14.2 (95% CI: 12.0 to 16.3)	13.0 (95% CI: 10.6 to 15.5)
Barry 2021	ELX/TEZ/IVA vs TEZ/IVA or IVA	F/RF or F/Gating	Week 8	NR	NR	NR	4.5 (95% CI: 2.7 to 6.4)	2.5 (95% CI: 0.8 to 4.2)
Sutharsan 2022	ELX/TEZ/IVA vs TEZ/IVA	F/F	Week 24	NR	NR	NR	20.8 (95% CI: 14.5 to 27.1)	12.1 (95% CI: 6.5 to 17.7)
Heijerman 2019	ELX/TEZ/IVA vs TEZ/IVA	F/F	Week 4	NR	NR	NR	11.2 (95% CI: 8.0 to 14.4)	6.3 (95% CI: 2.3 to 10.4)
Taylor-Cousar 2017	TEZ/IVA vs placebo	F/F	Week 24	3.5 (95% CI: 1.0 to 6.1)	NR	4.2 (95% CI: 3.1 to 5.2)	NR	3.7 (95% CI: 2.2 to 5.2)
Rowe 2017	TEZ/IVA vs placebo	F/RF	Week 8	4.4 (95% CI: 0.9 to 7.9)	NR	4.3 (95% CI: 2.9 to 5.7)	NR	5.7 (95% CI: 3.8 to 7.6)
TRAFFIC	LUM/IVA vs placebo	F/F	Week 24	1.60 (95% CI: –4.52 to 7.73)	2.73 (95% CI: 1.26 to 4.20)	NR	2.95 (95% CI: 1.33 to 4.57)	2.19 (95% CI: –0.81 to 5.19)
TRANSPORT	LUM/IVA vs placebo	F/F	Week 24	4.37 (95% CI: 0.91 to 7.82)	2.79 (95% CI: 1.24 to 4.34)	NR	3.57 (95% CI: 1.89 to 5.24)	1.62 (95% CI: –1.26 to 4.50)

Abbreviations: CI: confidence interval; CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; $ppFEV_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

3.2.2.3 *Generalisability of clinical trial data to clinical practice in England and Wales*

The clinical trials informing the cost-effectiveness analysis were international, multicentre, trials, primarily consisting of sites across Northern American, Europe and Australia (Appendix Table 103), which may raise concerns about the generalisability of the clinical trial data to clinical practice in England and Wales. However, the EAG's clinical experts considered clinical practice across these regions to be largely generalisable to clinical practice in England and Wales, and did not consider variables that may differ across countries to likely modify the treatment effect of CFTR modulators. The EAG notes that the doses used across the trials included in the EAG's SLR matched the doses outlined in the product SmPCs, with the exception of:

- NCT04537793: There is no current marketing authorisation of ELX/TEZ/IVA in people aged 2 to 5;[159]
- Davies 2021: In the SmPC for TEZ/IVA for people with CF aged 6 to 11, the weight threshold for receiving the higher TEZ/IVA dose (100 mg qd/ 150 mg q12h) rather than the lower TEZ/IVA dose (50 mg qd/ 75 mg q12h) is 30kg. In Davies 2021 this threshold was 40kg.[139] The EAG did not consider this to likely affect the generalisability of the trial results to clinical practice in England and Wales to a large degree.

The EAG's clinical experts noted that clinical outcomes for people with CF have continually improved in the decade before CFTR modulators were routinely available, and as such data from recent clinical trials are more likely generalisable to clinical practice in England and Wales than data from early trials of CFTR modulators.[1] The EAG notes that the median predicted survival of individuals with CF has consistently increased in the 2000s,[15] and that the use of dornase alfa and hypertonic saline solution – key mucolytic therapies used in ECM – has consistently increased from 2008 to 2018.[162] However, the EAG considers that in randomised controlled trials, changes to ECM and baseline survival of CF patients are likely to have similar impact across the intervention and control arms, and as such the relative treatment effects from earlier CFTR modulator RCTs are likely still generalisable to clinical practice in England and Wales today.

The EAG notes that the inclusion criteria of the clinical trials for people with CF aged 12+ years included a criterion of 40% to 90% ppFEV$_1$ at screening. This was noted in TA398 as a possible limitation of the generalisability of the trial results to patients with severe lung disease, likely

awaiting transplant (<40% $ppFEV_1$) or those with very mild CF (≥90%).[161] Following discussion with its clinical experts, the EAG considers that:

- People with a $ppFEV_1$ outside of 40% to 90% are still likely to benefit from CFTR modulator therapy;
- For people with a $ppFEV_1$ <40%, the magnitude of the CFTR modulator treatment effect may be limited by pre-existing irreversible lung damage. However, in the TEZ/IVA and LUM/IVA trials where subgroup data were reported for the small number of participants with baseline $ppFEV_1$ <40% despite screening $ppFEV_1$ ≥40%, the magnitude of the treatment response was similar to the overall cohorts (Table 32). The EAG also notes that:
    - In a Vertex-sponsored single-arm trial of LUM/IVA in people with CF aged 12+ years and advanced lung-disease (mean $ppFEV_1$at baseline = 29.1), $ppFEV_1$ did not increase by Week 24;[163]
    - In the Final Analysis of the UK Data Collection Agreement, participants who initiated ELX/TEZ/IVA with a baseline $ppFEV_1$ <40% experienced an increase in $ppFEV_1$ after one year ([redacted], 95% CI: [redacted] that was similar in magnitude to the increase observed in clinical trials for participants with a higher baseline $ppFEV_1$.[164]
- For people with $ppFEV_1$ >90%, a lower acute increase in $ppFEV_1$ is likely than people with $ppFEV_1$ <90%, due to ceiling effects. However, the EAG's clinical experts considered that such individuals may be the people who can achieve the best clinical outcomes on CFTR modulator therapies, due to the potential of the therapies to limit lung-function decline before any irreversible damage has occurred, and to reduce the likelihood of pulmonary bacterial colonisation.

As such, the EAG considers that while the acute effects of CFTR modulator therapies for people with $ppFEV_1$ outside of 40% to 90% are uncertain, people with $ppFEV_1$ greater than 90% will likely gain a similar, if not greater, long-term clinical benefit of CFTR modulator to those with $ppFEV_1$ within 40% to 90%. The long-term clinical outcomes of CFTR modulator treatment for people with $ppFEV_1$ <40% is more uncertain for LUM/IVA and TEZ/IVA. In 2014, 18.3% of people aged 16+ years attending UK specialist adult centres had a $ppFEV_1$ <40%,[103] and as such this group comprises a significant proportion of the incident CF population. However, should CFTR modulators be approved for routine commissioning, nearly all patients eligible for CFTR modulators in the incident population would take up treatment prior to their $ppFEV_1$ declining to <40%.

The EAG notes that the clinical trial data presented in Section 3.2 may have limited generalisability to the incident population of children who initiate ELX/TEZ/IVA aged 2. The EAG notes the lack of data available for such children: the mean age of children in the clinical trial of ELX/TEZ/IVA for children aged 2 to 5 years was [redacted] years,[159] and the results of the long-term extension trial of this group are not yet available. The EAG's clinical experts noted that if ELX/TEZ/IVA was initiated very early, i.e., before substantial lung or pancreatic damage had occurred, it is plausible that ELX/TEZ/IVA may prevent most lung-function and other clinical decline for these individuals. While plausible, the EAG notes substantial uncertainty regarding the long-term clinical outcomes of people aged 2 initiating ELX/TEZ/IVA due to:

- The lack of any data on the long-term clinical outcomes of people aged 2 initiating ELX/TEZ/IVA;
- The likelihood of irreversible severe pancreatic and other organ damage prior to the age of 2,[165] with substantial damage likely occurring *in utero*;[166]
- The effects of CFTR modulator therapy on restoring CFTR-mediated bicarbonate transport throughout the body are more unclear than the effects of CFTR modulator therapy on restoring chloride ion transport.[167]

Hence, while the EAG notes that children initiating ELX/TEZ/IVA at age 2 may have more positive clinical outcomes than people initiating ELX/TEZ/IVA at an older age, the magnitude and consistency of the treatment response in the long-term is uncertain.

3.2.2.4 Adverse effects of treatment

Data on the adverse effects of CFTR modulator treatments from trials identified in the SLR are presented in Appendix 9.3.5. For ELX/TEZ/IVA, the number of participants experiencing adverse events and serious adverse events was lower in the ELX/TEZ/IVA arms than the placebo or TEZ/IVA control arms of RCTs. For LUM/IVA and TEZ/IVA, the number of participants experiencing adverse events and serious adverse events was similar in the CFTR modulator arms and the control arms of RCTs. However, as pulmonary exacerbations were recorded as adverse events in CFTR modulator clinical trials, and CFTR modulator therapies reduce the rate of pulmonary exacerbations, the incidence of specific adverse events that are not pulmonary exacerbations is important to consider. The EAG therefore extracted data on adverse events highlighted as important by the EAG's clinical experts – liver adverse events, cataracts and lens opacities, and hypertension – and adverse events

of special interest reported throughout the CFTR modulator clinical trial programme – liver adverse events and rash events.

The number of participants experiencing increased alanine aminotransferase, increased aspartate aminotransferase and increased gamma-glutamyltransferase was numerically greater for ELX/TEZ/IVA and TEZ/IVA compared to placebo, and similar between LUM/IVA and placebo. The EAG notes that:

- The magnitude of the increased number of liver AEs was larger for ELX/TEZ/IVA than TEZ/IVA;
- The main cost of these non-serious liver adverse events is likely realised in the likelihood of discontinuation due to the adverse events, rather than the cost of treating or investigating the adverse event itself.

Rash events were more frequent in the ELX/TEZ/IVA and LUM/IVA arms compared to placebo arms in RCTs, but were not elevated in TEZ/IVA arms compared to placebo arms.

When reported in the clinical trials included in the SLR, the incidence of cataracts, lens opacities and hypertension was low across all arms of the trials (Appendix Table 113 and Table 114), but the safety analysis period for most trials was only 28 weeks. The EAG's clinical experts highlighted that the 28-week safety periods may have been insufficient to detect meaningful elevations in the rate of cataracts, lens opacities and hypertension related to the long-term use of CFTR modulators. The reporting of cataracts, lens opacities and hypertension was inconsistent across extension study CSRs, and no controlled data are available. The EAG considers the magnitude of any increase in cataracts, lens opacities and hypertension following CFTR modulator to be uncertain in existing data, and notes that currently there is no evidence that such AEs are frequent enough to incur large costs (Table 33). Nevertheless, the EAG notes that follow-up data over a person's lifetime are not available, and as such there is outstanding uncertainty concerning the effects of CFTR modulator therapy on cataracts, lens opacities and hypertensions, as well as AEs more broadly.

Table 33. The frequency of cataract and hypertension AEs in CFTR modulator trial open label extension studies.

	Griese 2022	Ratjen 2022	VX18-445-110	Flume 2021	Sawicki 2022	Konstan 2017	Chilvers 2021
Week	144 (Interim Analysis)	96	96 (Interim analysis)	96	96	96	264

Intervention	ELX/TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	TEZ/IVA	TEZ/IVA	LUM/IVA	LUM/IVA
Genotype	F/F or F/MF	F/F or F/MF	F/Gating or F/RF	F/F or F/RF	F/F or F/RF	F/F	F/F
N SAS	506	64	251	1042	130	1029	239
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N cataracts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

3.2.2.4.1 Mental health

Serious adverse events relating to mental health were not common in clinical trials of CFTR modulators. However, stakeholder submissions highlighted a complex relationship between treatment with CFTR modulators and a person's mental health. The UK Psychosocial Professionals in Cystic Fibrosis submission stated that the improved long-term prognosis associated with CFTR modulators can have "considerable positive implications" for their mental health of patients who, following effective treatment may be able to "consider a fulfilling future".[168] However, the submission also highlighted anecdotal evidence of mental health difficulties developing, or increasing in severity, following CFTR modulator therapy use. Such concerns were also highlighted in the CF Trust submission,[29] and the EAG's clinical experts commented that some patients have discontinued ELX/TEZ/IVA because of the individual's concern about the mental health impacts of ELX/TEZ/IVA treatment.

The EAG considers the relationship between CFTR modulator therapy and mental health adverse effects to be uncertain, likely to have complex and differing effects on a person's mental health, and an area to prioritise for future research. The EAG notes that the frequency of psychiatric disorder adverse events reported in RCTs with 28-week safety follow-up included in the EAG's SLR were low, and there was little evidence to suggest any were elevated over placebo (Table 34).[42, 61, 131, 137] The

EAG therefore considers that mental health adverse events are unlikely to be captured adequately in the short-term clinical trial data currently available. The EAG notes uncertainty around the rates of mental health AEs that are related to CFTR modulator therapies, although they are likely to be low, and considers that the development of mental health AEs is likely to be specific to certain individual circumstances. The EAG considers the costs for such individuals may be captured in the rate of discontinuation of therapy, and further notes that mental health AEs are likely to be quite rare, costs beyond those associated with discontinuation are unlikely to make a meaningful impact on the average cost-effectiveness of treatment with CFTR modulator therapy.

Table 34. Psychiatric disorders reported across RCTs of CFTR combination modulator therapies in people with CF aged 12+ years over 28 weeks safety follow-up.

	TRAFFIC		TRANSPORT		Taylor-Cousar 2017		Sutharsan 2022		Middleton 2019	
Week 28	PBO	LUM/IVA	PBO	LUM/IVA	PBO	TEZ/IVA	TEZ/IVA	ELX/TEZ/IVA	PBO	ELX/TEZ/IVA
	N = 184	N = 172	N = 186	N = 187	N = 258	N = 251	N = 88	N = 87	N = 201	N = 202
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders (overall)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mood swings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed mood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; ELX: elexacaftor; IVA: ivacaftor; PBO: placebo; RCT: randomised controlled trial; TEZ: tezacaftor.

3.2.2.5 *Indirect treatment comparisons*

Where no direct head-to-head trial data existed for interventions and comparators included in the NICE final scope for a specific age group and genotype combination, the EAG assessed the feasibility of indirect treatment comparisons for the variables entering the economic model, namely change from baseline in $ppFEV_1$, weight-for-age z-score and the frequency of pulmonary exacerbations. The EAG performed indirect treatment comparisons for the following groups:

- F/F genotype aged 12+ years;
- F/RF genotype aged 12+ years;
- F/Gating genotype aged 12+ years.

In addition, there was no head-to-head trial data of key comparators, but also no connected evidence network to perform anchored ITCs in the following groups:

- F/F genotype aged 6 to 11 years: For this population, the Company submitted an unanchored individual participant data-based indirect treatment comparison, whereas the EAG preferred an assumption based-approach.

All NMA models converged, and Brooks-Gelman-Rubin diagnostic plots for each model are presented in Appendix 9.7.

3.2.2.5.1 F/F 6 to 11 years

For the F/F 6 to 11 years population, only single-arm data were available for ELX/TEZ/IVA from Zemanick 2021.[135] To generate a relative treatment effect of ELX/TEZ/IVA vs placebo, the Company conducted an unanchored IPD ITC using a mixed model repeated measures (MMRM) analysis, using treatment group, visit and treatment-by-visit intervention as fixed effects, and adjusting for sex and baseline values of the dependent variable. While the EAG agrees that an IPD MMRM may be the most suitable method to perform an unanchored indirect treatment comparison in this population, the EAG was concerned that the placebo arm used in this indirect treatment comparison, from Ratjen 2017,[141] may have overestimated the rate of $ppFEV_1$ decline for participants receiving ECM. In Ratjen 2017, the absolute change from baseline in $ppFEV_1$ through 24 weeks of treatment in the placebo arm was –2.1%, approximately –4.2% per year. This point-estimate is inconsistent with the assumed rate of annual long-term rate of decline in the F/F population sourced from real-world data in either the Company submission (–1.32% per year, Sawicki 2022[3]), or the EAG base case (–0.65%

per year, average of ages 6 to 11 digitised from Szczesniak 2023 stochastic model[17]). Hence, the EAG does not consider the Company's unanchored IPD MMRM analyses to provide reasonable estimates for relative treatment effects of TEZ/IVA or ELX/TEZ IVA in the 6 to 11 F/F population. The EAG considered the following alternative assumptions:

- Assuming no rate of decline for participants receiving ECM;
- A naïve correction of the single arm trial data using the estimated rate of decline from Szczesniak 2023, 0.3% over 24 weeks;
- Assuming equivalent efficacy of ELX/TEZ/IVA between F/MF and F/F genotypes (note, this approach was not available for TEZ/IVA as F/MF is outside of the marketing authorisation).

A comparison of the assumptions considered by the EAG, and the EAG's preferred assumptions, are presented in Table 35.

Table 35. Different sources of estimates for the relative acute increase from baseline in $ppFEV_1$ and weight-for-age z-score in the F/F 6 to 11 years populations.

Change from baseline: F/F 6 to 11 years	Source	Value	EAG Notes
$ppFEV_1$			
LUM/IVA vs Placebo	Ratjen 2017	[redacted] or 2.4 (95% CI: 0.4 to 4.4)	Upper estimate from Company MMRM analysis aligned with Zemanick 2021[135] and adjusted for sex. Lower estimate taken directly from Ratjen 2017.
TEZ/IVA vs Placebo	Company IPD model: base case	[redacted]	EAG considered the assumed rate of decline for ECM to be clinically implausible
	Company IPD model: supporting analysis	[redacted]	
	Davies 2021, no correction	2.8 (95% CI: 1.0 to 4.6)	**EAG preference** Conservative to assume no rate of decline on ECM
	Davies 2021, adjusted using Szczesniak 2023	3.1	The EAG considers this a reasonable alternative assumption, but notes additional uncertainty is introduced by applying the correction
ELX/TEZ/IVA vs Placebo	Company IPD model	[redacted]	EAG considered the assumed rate of decline for ECM to be clinically implausible
	Zemanick 2022, F/F subgroup, adjusted using Sawicki 2022	[redacted]	EAG prefers alternative source of real-world evidence for ppFEV1 decline
	Zemanick 2022, F/F subgroup, no correction	11.2 (95% CI: 7.2 to 15.2)	**EAG preference** Conservative to assume no rate of decline on ECM

	Zemanick 2022, F/F subgroup, adjusted using Szczesniak 2023	11.5	The EAG considers this a reasonable alternative assumption, but notes additional uncertainty is introduced by applying the correction
	Mall 2022: relative treatment effect of ELX/TEZ/IVA in placebo-controlled RCT in F/MF genotype	11.0 (95% CI: 6.9 to 15.1)	The EAG considers this a reasonable alternative assumption
Weight-for-age z-score			
LUM/IVA vs Placebo	Company IPD model	[redacted]	EAG considers the inclusion of unanchored placebo data from Ratjen 2017 to be inappropriate due to the unexpected rate of ppFEV$_1$ decline
	Ratjen 2017	0.04 (95% CI: –0.03 to 0.10)	**EAG preference**
TEZ/IVA vs Placebo	Company IPD model	[redacted]	EAG considers the inclusion of unanchored placebo data from Ratjen 2017 to be inappropriate due to the unexpected rate of ppFEV$_1$ decline
	Davies 2021	–0.04 (SD: 0.17)	EAG considers it implausible treatment with CFTR modulators will lead to a decrease in weight-for-age z-score relative to ECM
	Assumption	0	**EAG preference**
ELX/TEZ/IVA vs Placebo	Company IPD model	[redacted]	EAG considers the inclusion of unanchored placebo data from Ratjen 2017 to be inappropriate due to the unexpected rate of ppFEV$_1$ decline
	Zemanick 2022	[redacted]	**EAG preference**

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; ECM: established clinical management; ELX: elexacaftor; IPD: individual participant data; IVA: ivacaftor; MMRM: mixed model repeated measures; NMA: network meta-analysis; ppFEV$_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

In lieu of robust indirect-treatment comparison data, the EAG's preferred assumptions for the F/F 6 to 11 age group are:

Acute increase in $ppFEV_1$

- LUM/IVA vs placebo: 2.4 (95% CI: 0.4 to 4.4), direct trial evidence from Ratjen 2017;[141]
- TEZ/IVA vs placebo: 2.8 (95% CI: 1.0 to 4.6), taken from the single-arm estimate of Davies 2021;
- ELX/TEZ/IVA vs placebo: 11.2 (95% CI: 7.2 to 15.2), taken from the single-arm estimate of Zemanick 2022.

Weight-for-age z-score

- LUM/IVA vs placebo: 0.04 (95% CI: –0.03 to 0.10), direct trial evidence from Ratjen 2017;[141]
- TEZ/IVA vs placebo: 0, EAG assumption that weight-for-age z-score would not decrease on TEZ/IVA relative to ECM;
- ELX/TEZ/IVA vs placebo: 0.28 (0.18 to 0.39), single-arm trial data from Zemanick 2022.

For pulmonary exacerbations requiring IV antibiotics, the Company did not conduct an indirect treatment comparison as only two studies reported pulmonary exacerbations as a protocol defined outcome, Ratjen 2017 (LUM/IVA vs placebo) and Zemanick 2022 (ELX/TEZ/IVA). In Ratjen 2017, [redacted] participants in the LUM/IVA arm experienced a pulmonary exacerbation requiring IV antibiotics through Week 24, compared to [redacted] participants in the placebo arm. In Zemanick 2022, [redacted] participant experienced a pulmonary exacerbation requiring IV antibiotics through Week 24.

While Davies 2021 (TEZ/IVA) did not report the number of pulmonary exacerbations requiring IV antibiotics, the EAG considers the number of pulmonary exacerbations recorded as serious adverse events (SAE) to be a related, albeit less reliably measured, outcome. In Davies 2021, 3 (5.6%) participants in the TEZ/IVA arm had a recorded pulmonary exacerbation SAE through Week 12, compared to 3 (15.4%) participants in the PBO or IVA monotherapy blinding arms.

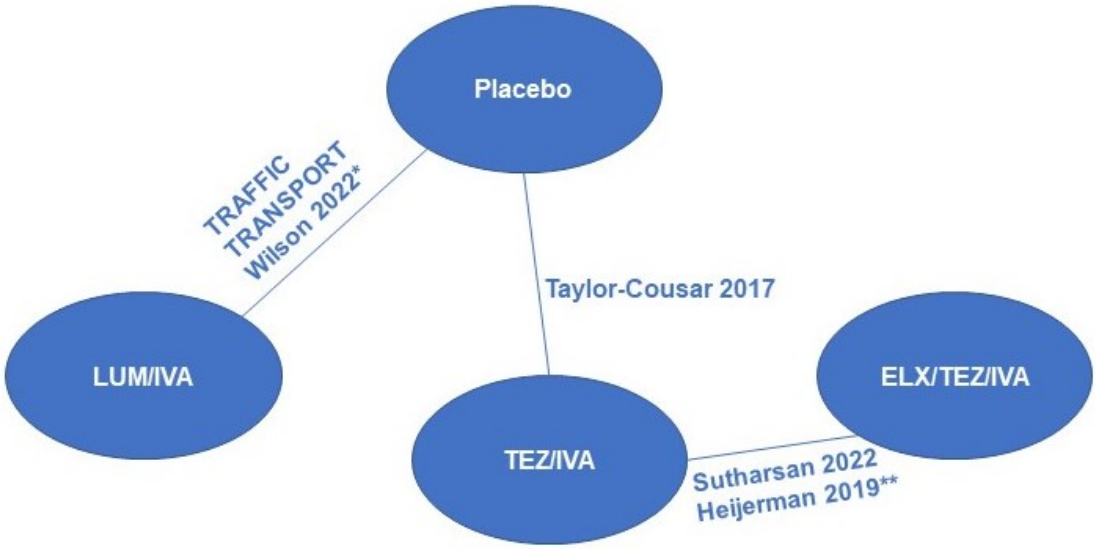
In the economic model, the Company does not apply a direct treatment effect on pulmonary exacerbations requiring IV antibiotics for people aged <12 years, although an indirect effect through $ppFEV_1$ is observed (section 4.2.1.5.3). The EAG considers this a reasonable, although potentially

conservative, approach that is unlikely to have a large impact on the model results due to the overall low rate of pulmonary exacerbations requiring IV antibiotics in people <12 years.

3.2.2.5.2 F/F 12+ years

For the F/F 12+ years population, the EAG assessed indirect treatment comparisons to be feasible for the absolute change from baseline in ppFEV$_1$ through Week 24, and the absolute change from baseline at Week 24 for weight-for-age z-score. Six studies reported a change from baseline in ppFEV$_1$, three placebo-controlled RCTs of LUM/IVA, one placebo-controlled RCT of TEZ/IVA, and two TEZ/IVA controlled RCTs of ELX/TEZ/IVA. For the change from baseline in ppFEV$_1$ analysis, the EAG's base case included the five studies reporting this outcome through Week 24. In a sensitivity analysis, the EAG also included Heijerman 2019, which reported change from baseline in ppFEV1 at Week 4. Heijerman 2019 was only included in the sensitivity analysis as it was considered plausible that the absolute change from baseline in ppFEV$_1$ may not be a similar outcome between Week 4 and Week 24 as not all participants may have achieved the full magnitude of treatment response by Week 4, and some decline in ppFEV$_1$ may also have occurred by Week 24. Across the studies included in the NMA, patients had similar non-CFTR modulator prior medications (Appendix Table 108) and a similar disease severity indicated by a similar baseline ppFEV$_1$ and CFQ-R RD score (Appendix Table 104 and Table 105). They key ppFEV$_1$ eligibility criteria was the same, 40% to 90%, across all studies, study discontinuation was infrequent, and in placebo-controlled trials the placebo response was similar. Each included study was assessed to be of low risk-of-bias at both the study-level and the ppFEV$_1$ outcome level, with the exception of Wilson 2021 which was rated as "some concerns" due to 11% of participants missing outcome data for ppFEV$_1$. Overall, the EAG did not consider there to be evidence of any large violation of the transitivity assumption of NMA. The EAG notes that one of the trials was a Phase IV trial of LUM/IVA, Wilson 2021, conducted at sites only in Australia and UK, and where ppFEV$_1$ was a secondary outcome only. However, the EAG did not consider the trial to be too dissimilar to the Phase 3 trials to be dropped from the base case. Four of the Phase 3 trials, TRAFFIC, TRANSPORT, Taylor-Cousar 2017 and Sutharsan 2022, reported change in weight-for-age z-score. A network diagram is presented in Figure 2.

Figure 2. Network diagram for the EAG 12+ years F/F network meta-analyses.



*Included in the ppFEV$_1$ NMAs only

**Included in the ppFEV$_1$ sensitivity analysis only

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; TEZ: tezacaftor

The results of the EAG's base case NMA for the absolute change in ppFEV$_1$ through Week 24 are presented in a league-table in Table 36. For each CFTR modulator, the treatment effect was positive, and the 95% credible intervals excluded 0. For the two contrasts informed by indirect evidence only, the mean estimated increase in ppFEV$_1$ through Week 24 between ELX/TEZ/IVA and placebo was 14.20 (95% CrI: 12.07 to 16.31), and between ELX/TEZ/IVA and LUM/IVA it was 11.37 (95% CrI: 9.03 to 13.70). The only contrast for which the 95% credible intervals crossed 0 was the mean estimated increase in ppFEV$_1$ at Week 24 between TEZ/IVA and LUM/IVA 1.17 (95% CrI: –0.13 to 2.46).

Table 36. Results of the EAG base-case NMA for absolute change from baseline in ppFEV$_1$ through Week 24 in the F/F 12+ years population.

ppFEV$_1$: F/F 12+ years: EAG base-case	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA
ELX/TEZ/IVA	ELX/TEZ/IVA	—	—	—
LUM/IVA	11.37 (9.03 to 13.70)	LUM/IVA	—	—
Placebo	14.20 (12.07 to 16.31)	2.83 (1.84 to 3.81)	Placebo	—
TEZ/IVA	10.20 (8.25 to 12.16)	–1.17 (–2.46 to 0.13)	–4.00 (–3.15 to –4.85)	TEZ/IVA

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; NMA: network meta-analysis; ppFEV$_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

The results of the EAG sensitivity analysis, including the Week 4 data from Heijerman 2019,[133] were directly in-line with the base case analysis, and are presented in Table 37 (lower diagonal) and compared with Company NMA results (upper diagonal). The EAG sensitivity analysis is compared to the Company ITC analysis for ELZ/TEZ/IVA against placebo, as the same studies were included in these analyses, whereas the EAG base case also included Wilson 2022.

Table 37. Results of the EAG sensitivity NMA (lower diagonal) and Company ITC and estimates (upper diagonal) for absolute change from baseline in ppFEV$_1$ through Week 24 in the F/F 12+ years population.

ppFEV$_1$: F/F 12+ years: EAG sensitivity analysis	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA
ELX/TEZ/IVA	ELX/TEZ/IVA	NR	[redacted]	[redacted]
LUM/IVA	11.29 (9.26 to 13.32)	LUM/IVA	[redacted]	NR
Placebo	14.11 (12.35 to 15.90)	2.83 (1.84 to 3.82)	Placebo	[redacted]
TEZ/IVA	10.11 (8.57 to 11.68)	–1.17 (–2.48 to 0.14)	–4.00 (–4.85 to –3.15)	TEZ/IVA

Abbreviations: EAG: external assessment group; ELX: elexacaftor; ITC: indirect treatment comparison; IVA: ivacaftor; NMA: network meta-analysis; ppFEV$_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

Note. The Company performed an ITC for ELX/TEZ/IVA against placebo, and other reported Company contrasts come directly from clinical trial estimates. Company estimates were reported to one decimal place only.

The results of the EAG's NMA for the absolute change weight-for-age z-score at Week 24 are presented in a league-table in Table 38. For all ELX/TEZ/IVA contrasts, the treatment effect was positive, and the 95% credible intervals excluded 0. The LUM/IVA vs placebo contrast was the only other contrast to have 95% credible intervals excluding 0, and the magnitude of the effect was small, [redacted] For the two contrasts informed by indirect evidence only, the mean estimated increase in weight-for-age z-score at Week 24 between ELX/TEZ/IVA and placebo was [redacted], and between ELX/TEZ/IVA and LUM/IVA it was 0.35 [redacted]

Table 38. Results of the EAG NMA for absolute change from baseline in weight-for-age z-score at Week 24 in the F/F 12+ years population.

WFAZ: F/F 12+ years	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA
ELX/TEZ/IVA	ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	LUM/IVA	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	Placebo	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	TEZ/IVA

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; NMA: network meta-analysis; TEZ: tezacaftor; WFAZ: weight-for-age z-score

The Company performed Bucher indirect comparisons between ELX/TEZ/IVA and placebo in the F/F 12+ years group. The estimated Bucher mean difference from the Company analyses were in-line with the EAG's results: absolute change in ppFEV$_1$ from baseline through 24 weeks: [redacted] absolute change in weight-for-age z-score from baseline at 24 weeks: [redacted]. The EAG notes that for the weight-for-age z-score outcome, the EAG estimate is the same as the Company estimate. As only two studies inform this contrast, the EAG's NMA posterior distribution centred on the Bucher mean estimate.

Neither the EAG nor the Company considered indirect comparisons for pulmonary exacerbations requiring IV antibiotics to be feasible. Of the 7 studies included in the EAG SLR for the F/F 12+ years age group, pulmonary exacerbations requiring IV antibiotics were reported as a protocol-defined outcome for three: TRAFFIC, TRANSPORT and Taylor-Cousar 2017. While all studies did report the number of pulmonary exacerbation serious adverse events, the EAG considers the Company's method of applying the rate of pulmonary exacerbations requiring IV antibiotics from the F/MF genotype for the F/F genotype in the economic model to be the most appropriate assumption. The number of pulmonary exacerbations requiring IV antibiotics, and the number of participants experiencing serious pulmonary exacerbation adverse events for the F/F 12+ years group, along with the F/MF 12+ ELX/TEZ/IVA data, are presented in Table 39.

Table 39. Rate ratio of pulmonary exacerbations of CFTR modulators compared to placebo, and percentage of participants with serious pulmonary exacerbations in the F/F genotype, 12+ years.

Study	Intervention	Comparator	Rate ratio of participants with pulmonary exacerbations requiring IV antibiotics (intervention vs placebo)	Percentage of participants with serious pulmonary exacerbation adverse events, % of SAS at week 28	
				Intervention	Comparator
TRAFFIC	LUM/IVA	Placebo	[redacted]	9.34	22.28
TRANSPORT	LUM/IVA	Placebo		12.83	25.81
Wilson	LUM/IVA	Placebo	NR	23.53	16.67
Taylor-Cousar 2017	TEZ/IVA	Placebo	0.53 (95% CI: 0.34 to 0.82)	9.16	12.4
Sutharsan 2022	ELX/TEZ/IVA	TEZ/IVA	NR	1.15	10.23
Heijerman 2019	ELX/TEZ/IVA	TEZ/IVA	NR	1.82*	1.92*

Middleton 2019	ELX/TEZ/IVA F/MF genotype	Placebo	0.22 (95% CI: 0.11 to 0.43)	5.45	16.42

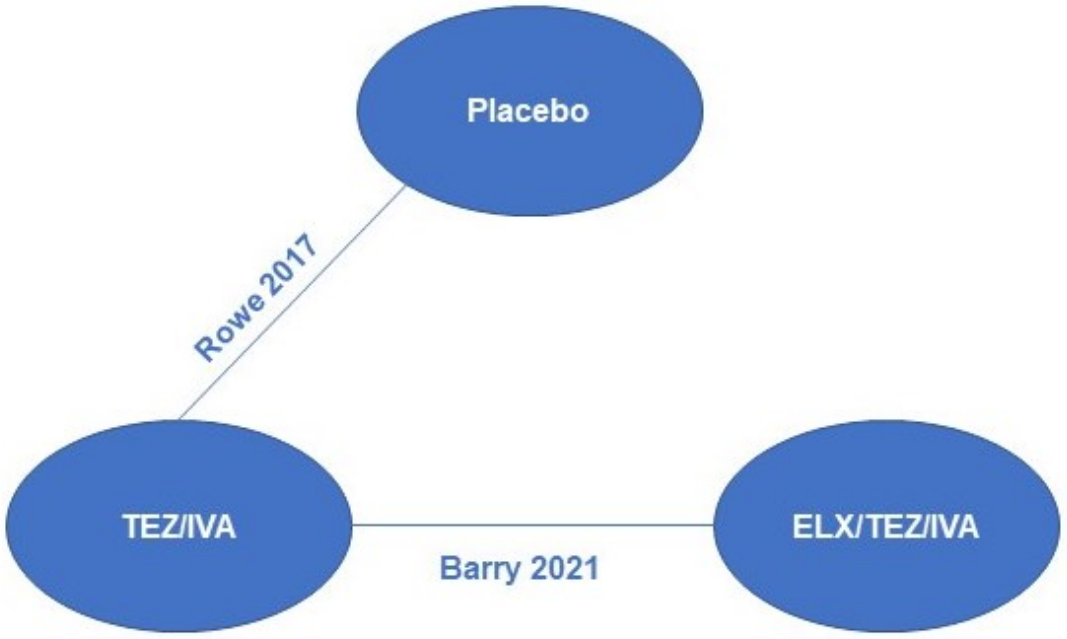
*Reported at Week 4

Abbreviations: CI: confidence interval; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; NR: not reported; SAS: safety analysis set; TEZ: tezacaftor

3.2.2.5.3 F/RF 12+ years

In the F/RF 12+ years population, only two studies were included in the EAG's SLR and the Company's analysis: Rowe 2017 (F/RF subgroup: TEZ/IVA vs PBO) and Barry 2021 (F/RF subgroup: ELZ/TEZ/IVA vs PBO). In both studies included in the NMA, patients had similar non-CFTR modulator prior medications (Appendix Table 108). Participants in Barry 2021 had a slightly higher baseline $ppFEV_1$ (mean TEZ/IVA 68.10, mean placebo 67.80) than participants in Rowe 2017 (mean TEZ/IVA 61.80, mean placebo 62.10), however this is likely in part due to the TEZ/IVA run-in period for Barry 2021 elevating $ppFEV_1$ levels, which is accounted for in the indirect comparison. The EAG therefore considers the participants to be similar between Barry 2021 and Rowe 2017. They key $ppFEV_1$ eligibility criterion was the same, 40% to 90%, across all studies and study discontinuation was infrequent (Appendix Table 107). Both studies were assessed to be of low risk-of-bias at both the study-level and the $ppFEV_1$ outcome level. While Rowe was a cross-over trial, with participants contributing data to both the TEZ/IVA and placebo arms, the EAG considers the wash-out period of 8-weeks between treatments to be adequate to remove any biasing effects of pre-treatment. A network diagram for the F/RF 12+ years population is presented in Figure 3.

Figure 3. Network diagram for the EAG 12+ years F/RF network meta-analyses.



Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

The EAG notes that because only two studies inform the contrast between ELX/TEZ/IVA and placebo, the EAG's NMA model will centre on the same estimates as an equivalent Bucher analysis, such as that conducted by the Company. The EAG's NMA estimate of the absolute change from baseline in ppFEV1 through 8 weeks between ELX/TEZ/IVA and placebo was 8.80 (95% CrI: 7.01 to 10.61). The Company's Bucher estimate for this contrast was [redacted] The slight difference between the EAG's estimate and the Company estimate could be due to:

- Differences in the MMRM model structure reported by Barry 2021 (used by EAG) and the MMRM performed for this analysis by the Company, or;
- Differences stemming from the rounding of results in Barry 2021, where outcome data were presented to one decimal place.

For the change in weight-for-age z-score at Week 8, the EAG's estimate is directly in line [redacted] with the Company estimate [redacted]

Similar to the F/F population, pulmonary exacerbations requiring IV antibiotics were not reported in the ELX/TEZ/IVA trial for the F/RF population. In the economic model, the Company again applied

the relative rate of pulmonary exacerbations requiring IV antibiotics from the F/MF. The EAG considers this approach to be reasonable, and notes the consistency of the rate ratio estimated in the F/RF population for TEZ/IVA vs placebo (Rowe 2017: 0.54) with the rate ratio estimated in the F/F population for TEZ/IVA vs placebo (Taylor-Cousar 2017: 0.53).

3.2.2.5.4 F/Gating 12+ years

In the F/Gating 12+ years population, four studies were included in the EAG's SLR and the Company's analysis: Barry 2021 (F/Gating subgroup: ELZ/TEZ/IVA vs PBO); Ramsey 2011 (*post-hoc* F/*G551D* subgroup IVA vs PBO); De Boeck 2014 (*post-hoc* F/*non-G551D* 12+ years subgroup IVA vs PBO) and; Moss 2015 (*post-hoc* F/*R117H* 12+ years subgroup IVA vs PBO). Compared to the NMAs for the F/F 12+ years population and the F/RF 12+ years population, the EAG considers the transitivity assumption to likely be violated in the F/Gating NMA. This is because the prevalence of specific gating or *R117H* mutations, and concomitant best supportive care medications, may be treatment effect modifiers which differed across studies. Specifically:

- The *R117H* mutation is associated a milder CF phenotype than gating mutations, which may limit the acute increase in $ppFEV_1$ possible for a participant with preserved lung function.[169] This can be seen in the higher average baseline $ppFEV_1$ of Moss 2015 (*post-hoc* F/*R117H* 12+ years subgroup) than the other IVA trials (Appendix Table 106). The distribution of non-F508del CF mutations in Barry 2021 (F/Gating subgroup), Ramsey 2011 (*post-hoc* F/*G551D*), De Boeck 2014 (*post-hoc* F/*non-G551D* 12+ years subgroup) and Moss 2015 (*post-hoc* F/*R117H* 12+ years subgroup) are presented in Table 40.
- Inhaled hypertonic saline was not an approved therapy during Ramsey 2011 and De Boeck 2014, and is known to reduce the rate of pulmonary exacerbations in CF.[144, 145] The exclusion of inhaled hypertonic saline in Ramsey 2011 and De Boeck 2014 may be offset by a higher use of dornase alfa (73.1% in the placebo arm and 65.1% of the ivacaftor arm across Ramsey 2011, compared to 52% across both arms in Barry 2021), but it is likely that ECM was less optimised in these early ivacaftor trials, which could have overestimated the treatment effect of the ivacaftor, relative to ECM today.

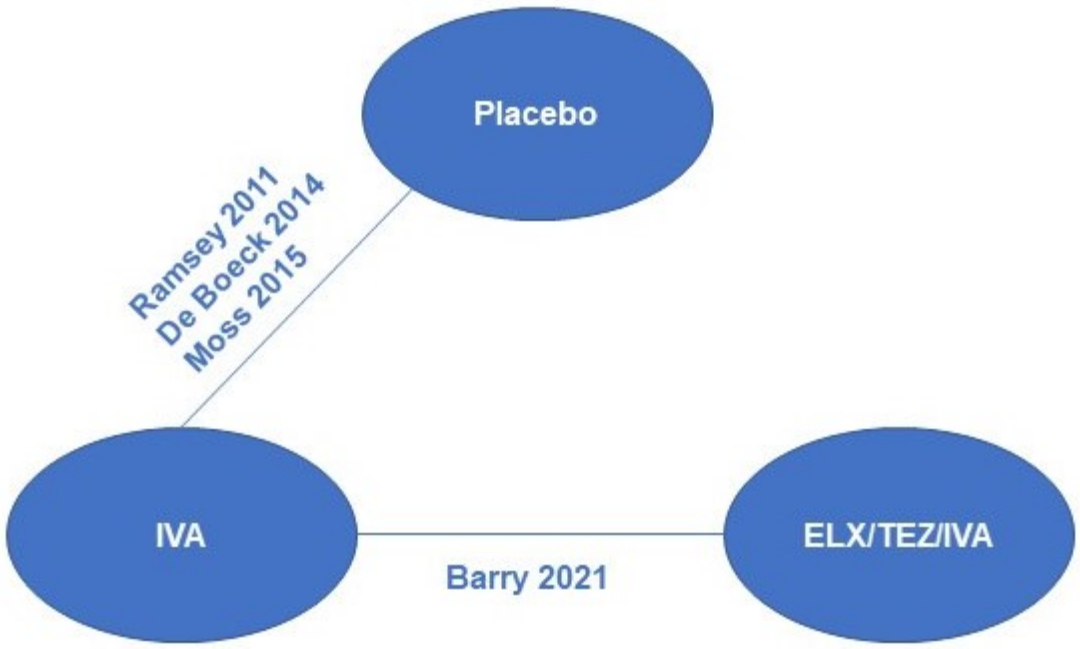
Table 40. The distribution of non-*F508del* mutations in study subgroups included in the F/Gating NMA.

Study	Arm	N	*G551D*, n	*G551D* %	*R117H*, n	*R117H* %	Other, n	Other %
Barry 2021	ELX/TEZ/IVA	50	35	70	8	16	7	14
	IVA	45	26	58	8	18	11	24
Ramsey 2011	IVA	64	64	100	0	0	0	0
	Placebo	58	58	100	0	0	0	0
De Boeck 2014	IVA	17	0	0	0	0	17	100
	Placebo	17	0	0	0	0	17	100
Moss 2015	IVA	20	0	0	20	100	0	0
	Placebo	19	0	0	19	100	0	0
Total IVA vs PBO	IVA	101	64	63	20	20	17	17
	Placebo	94	58	62	19	20	17	18

Abbreviations: ELX: elexacaftor; IVA: ivacaftor; NMA: network meta-analysis; TEZ: tezacaftor

The EAG notes the meaningful clinical heterogeneity across studies that could enter the F/Gating NMA, and also notes that the Company provided analyses of the ivacaftor trial *post-hoc* F/Gating subgroups were deemed at risk of bias due to the analyses breaking randomisation, and having limited reporting of participant characteristics. The EAG did not consider it feasible to conduct analyses separately within different F/Gating subgroups, as these data were not available from Barry 2021. The EAG also notes that while the distribution of F/Gating mutations differs across Ramsey 2011, De Boeck 2014 and Moss 2015, the pooled distribution of mutations is similar to the distribution of mutations in Barry 2021. Nevertheless, the F/*R117H* genotype comprises only 19% of participants across the studies considered for inclusion in the NMA, whereas the F/*R117H* genotype comprised [redacted] of genotyped individuals in England and Wales over 6 years in 2021. As such, the results of any indirect comparisons may overestimate the efficacy of ELX/TEZ/IVA relative to ECM for the F/Gating (including F/*R117H*) population in clinical practice. A network diagram for the F/Gating 12+ years population is presented in Figure 4.

Figure 4. Network diagram for the EAG 12+ years F/Gating (including F/*R117H*) network meta-analyses.



Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

The EAG presents the results of both fixed effect and random effects NMAs for the F/Gating population. The EAG considers the point estimates of the fixed effect and random effect estimates to be consistent with each other, and notes no meaningful difference in DIC; DIC was similar between the random effect NMA (DIC = 8.1) and the fixed effect NMAs (DIC = 9.0). The EAG considers the 95% CrI intervals of the ppFEV$_1$ model to be implausibly wide (e.g., the upper 95% CrI for ELX/TEZ/IVA vs placebo contrast 27.21), and hence the EAG's preference is for the fixed-effect NMA for the absolute change in ppFEV$_1$. The EAG notes that because of the network structure, the EAG's fixed effect NMA model will centre on the same estimates as an equivalent Bucher analysis that first pooled the IVA monotherapy trial data through meta-analysis, such as that conducted by the Company. For the weight-for-age z-score analysis, the EAG does not consider the 95% CrIs to be implausibly wide, and so prefers the results of the random effects NMA model, which had a lower DIC (8.5) than the fixed effect NMAs (13.5).The EAG's fixed effect NMA estimate of the absolute change from baseline in ppFEV$_1$ through 8 weeks between ELX/TEZ/IVA and placebo was [redacted]. The Company's Bucher estimate for this contrast was [redacted] The EAG's estimate differs slightly from the Company estimate, due to the reported difference in

ppFEV1 through 8 weeks between ELX/TEZ/IVA in the Barry 2021 publication being 5.8, whereas the difference used by the Company following alignment of the MMRM structures with the IVA trials was [redacted] The results of both the EAG's fixed effect and random effects ppFEV$_1$ NMAs are presented in Table 41.

Table 41. Results of the EAG NMA for absolute change from baseline in ppFEV$_1$ through Week 8 in the F/Gating 12+ years population.

ppFEV$_1$: F/Gating 12+ years	ELX/TEZ/IVA	IVA	Placebo
ELX/TEZ/IVA	ELX/TEZ/IVA	RE: –5.82 (–16.85 to 5.55)	[redacted]
IVA	FE: 5.80 (3.53 to 8.06) RE: 5.82 (–5.55 to 16.85)	IVA	[redacted]
Placebo	[redacted]	[redacted]	Placebo

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; NMA: network meta-analysis; ppFEV$_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

For the change in weight–for–age z–score at Week 8, the EAG's random effects estimate of the difference between ELX/TEZ/IVA and placebo, [redacted] was in line with the Company estimate [redacted] albeit with a wider uncertainty interval due to using the random effects model. The results of both the EAG's fixed effect and random effects weight–for–age z–score NMA are presented in Table 42. Pulmonary exacerbations requiring IV antibiotics were not reported in Barry 2021, and, in the economic model, the Company applied the rate ratio of Pulmonary exacerbations requiring IV antibiotics from the F/MF 12+ population to the F/Gating 12+ population. The EAG considers this assumption to be appropriate.

Table 42. Results of the EAG NMA for absolute change from baseline in weight–for–age z–score at Week 8 in the F/Gating 12+ years population.

WFAZ F/F 12+ years	ELX/TEZ/IVA	IVA	Placebo
ELX/TEZ/IVA	ELX/TEZ/IVA	RE: –0.01 (–0.26 to 0.24)	[redacted]
IVA	FE: 0.01 (–0.06 to 0.08) RE: 0.01 (–0.24 to 0.26)	IVA	[redacted]
Placebo	[redacted]	[redacted]	Placebo

Abbreviations: EAG: external assessment group; ELX: elexacaftor; FE: fixed effect; IVA: ivacaftor; NMA: network meta-analysis; RE: random effects; TEZ: tezacaftor; WFAZ: weight-for-age z-score

3.2.2.5.5 Confidence in Network Meta-Analysis (CINeMA)

Confidence in Network Meta-Analysis (CINeMA) is a framework used to evaluate confidence in the results from NMAs.[170] Following the Assessment Protocol, the EAG comments on each of the CINeMA domains across the NMAs performed by the EAG in Table 43.

Table 43. An assessment of the EAG's NMAs following the Confidence in Network Meta-Analysis framework.

CINeMA Domain	EAG Comment
Within-study bias	The EAG notes that most studies were rated as at low risk of at the study level, (Table 18) for ppFEV$_1$ (Table 100) and for weight-for-age-z-score (Section 3.2.1.5). No studies were rated at high-risk of bias. The EAG considers there to be some concerns about within-study bias in the F/Gating NMAs, for which only *post-hoc* subgroup analyses inform the IVA vs placebo comparison, and therefore the indirect comparison between ELX/TEZ/IVA and placebo.
Reporting bias	The EAG considers the likelihood of reporting bias to be low for all NMAs, given the availability of ppFEV$_1$ data from the published literature, and unpublished weight-for-age z-score data provided by the Company. While no statistical assessment of publication bias was performed, the EAG considers these analyses to be at low risk from publication bias because of the likelihood that all relevant trials will have been registered and identified in the SLR, and the Company's transparent reporting of the Vertex CFTR modulator trial programme.
Indirectness (to decision problem)	The EAG considered the trials to be largely generalisable to UK clinical practice (Section 3.2.2.3), but notes the genotype prevalence in the F/Gating RCTs are inconsistent with UK clinical practice (Section 3.2.2.5.4).
Imprecision	The EAG notes that minimum clinically important differences for ppFEV$_1$ and weigh-for-age z-score have not been defined, and as such the precision of estimates from the NMAs cannot be compared to them.
Heterogeneity	Due to the small number of studies informing each NMA, heterogeneity was not explored within each NMA. Nevertheless, the EAG considered the patient characterises of trials within each NMA to largely similar between studies. The EAG noted likely meaningful heterogeneity in F/Gating NMAs because:

	• The severity of F/Gating genotypes may differ, especially when including the *R117H* genotype that may lead to milder disease.[146, 169] The frequency of the R117H genotype within studies informing the F/Gating NMAs varied from 0% to 100%. • Inhaled hypertonic saline was not a permitted medication in two of the IVA placebo-controlled RCTs.[144, 145]
Incoherence	It was not possible to assess incoherence in the EAG's NMAs due to contrasts only being informed by direct or indirect evidence.

Abbreviations: CINeMA Confidence in Network Meta-Analysis; EAG: External Assessment Group; NMA: Network meta-analysis; IVA: ivacaftor; RCT: randomised controlled trial; UK: United Kingdom.

Overall, the EAG considers the NMAs to be at low risk of bias due to within-study biases, reporting bias and indirectness. However, the EAG considers the results of the NMAs to be limited by:

- The lack of defined minimum clinically important differences for $ppFEV_1$ and weight-for-age z-score, although the EAG notes that these outcomes directly inform the survival and cost-effectiveness modelling, and;
- The small number of studies within each network, which precluded a robust assessment of heterogeneity.

3.2.2.5.6 Efficacy data for evidence gaps

There was no trial evidence for ELX/TEZ/IVA in the F/Gating or F/RF 6 to 11 years groups. For these groups, the Company use assumptions to generate efficacy data for the F/Gating and F/RF 6 to 11 years groups from observed trial data in the 12+ years groups, and the 6 to 11 years F/F and F/MF groups. For $ppFEV_1$, the Company noted that the, "magnitude of the [relative acute treatment effect compared to ECM of] IVA/TEZ/ELX on $ppFEV_1$ in patients with F/MF and F/F genotypes aged 6-11 years was approximately [redacted] and [redacted] of the[relative acute treatment effect compared to ECM] in patients aged ≥12 years of the same genotype." For the F/Gating and F/RF subgroups, the Company multiplied the treatment effect observed in the 12+ years subgroup by [redacted] and [redacted], and then took the average of these values, producing:

- F/Gating acute increase in $ppFEV_1$: [redacted]
- F/RF acute increase in $ppFEV_1$: [redacted]

As outlined in Section 3.2.2.5.1, the EAG considers the Company's ITC to likely overestimate the ELX/TEZ/IVA treatment effect in the 6 to 11 years F/F population, and as such does not consider the acute increase in ppFEV$_1$ treatment effect to likely be [redacted] of the treatment effect in 12+ years. The EAG considered the following assumptions to calculate a treatment effect in the F/Gating 6 to 11 years group:

- Multiplying the treatment effect calculated via the EAG's in the 12+ years NMA, [redacted] by [redacted] the relative reduction observed in the F/MF trial data between 6 to 11 years and 12+ years. This gives an estimate of the F/Gating treatment effect in 6 to 11 years of [redacted]
- Applying the treatment effect observed in Zemanick 2021 (single-arm ELX/TEZ/IVA, 6 to 11 years, F/F and F/MF genotypes), assuming no rate of decline for ECM: 10.2 (95% CI: 7.9 to 12.6);
- Applying the treatment effect observed in Mall 2022 (ELX/TEZ/IVA vs placebo, 6 to 11 years, F/MF genotype): 11.0 (95% CI: 6.9 to 15.1).

The EAG notes that each of these estimates are similar, and prefers to apply the treatment effect observed in Mall 2022, as it is a relative treatment effect directly observed in an RCT of people aged 6 to 11. The EAG's clinical experts considered it reasonable to assume the treatment effects of CFTR modulators would be similar between F/F, F/MF and F/Gating genotypes.

For the F/RF 6 to 11 years population, the EAG does not consider applying the treatment effect observed in other mutation groups to be appropriate, as the F/RF genotype leads to milder CF, and potentially ceiling effects in ppFEV$_1$. As such, the EAG's preferred assumption is to multiply the treatment effect observed in the F/RF 12+ population by [redacted] the relative reduction observed in the F/MF trial data between 6 to 11 years and 12+ years. This gives an estimate of the F/Gating ppFEV$_1$ treatment effect in 6 to 11 years of 6.776.

For the acute change in weight-for-age z-score, the Company noted that the, "magnitude of the [relative acute treatment effect compared to ECM of] IVA/TEZ/ELX on weight-for-age z-score in patients with F/MF and F/F genotypes aged 6-11 years was approximately [redacted] and [redacted] of the efficacy [relative acute treatment effect compared to ECM of] in the populations with F/F and F/MF genotypes aged ≥12, respectively." For the F/Gating and F/RF 6 to 11 years groups, the Company multiplied the treatment effect observed in the 12+ years subgroup by [redacted] and [redacted] and then took the average of these values, producing:

- F/Gating acute increase in weight-for-age z-score: [redacted]
- F/RF acute increase in weight-for-age z-score: [redacted]

The EAG considers the approach for the F/RF population to produce a plausible estimate; however the EAG considers the assumed increase in weight-for-age z-score for the F/Gating population to likely be conservative. Based on discussion with its clinical experts, and from the underlying mechanism of ELX/TEZ/IVA, the EAG considers it likely that the magnitude of ELX/TEZ/IVA treatment effect on weight-for-age z-score will be similar in the F/Gating to F/MF and F/F genotypes. As such, the EAG's preferred assumptions for the acute increase in weight-for-age z-score for the F/Gating and F/RF aged 6 to 11 years groups are:

- F/Gating acute increase in weight-for-age z-score: [redacted] applying the efficacy data from the F/MF 6 to 11 years Phase III RCT;
- F/RF acute increase in weight-for-age z-score: [redacted], based on the Company approach of applying the observed reduction in weight-for-age z-score treatment effect between the 12+ years and 6 to 11 years groups in the F/MF and F/F genotypes.

3.2.2.6 Annual rate of $ppFEV_1$ decline

In addition to causing an acute increase in $ppFEV_1$, CFTR modulators may also affect the long-term rate of $ppFEV_1$ decline in CF. Long-term $ppFEV_1$ decline is a key predictor of survival for people with CF,[171, 172] and therefore an important feature of models of CF survival. However, few long term or head-to-head data are available comparing the long-term impact of LUM/IVA, TEZ/IVA, ELX/TEZ/IVA and ECM on the annual rate of $ppFEV_1$ decline compared to ECM because:

- The open-label extension studies of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA are single-armed;
- The open-label extension studies of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA have a maximum follow-up duration of 144 Weeks available at the time of analysis;
- In real-world settings, uptake of CFTR modulators has been rapid for eligible patients once available. This means that synthetic control cohorts are limited to historical controls or a select group of contemporaneous controls who are ineligible for CFTR modulator therapy, or chose not to initiate CFTR modulator therapy;
- In real-world settings, only limited follow-up is available for LUM/IVA and TEZ/IVA because most people with CF receiving LUM/IVA and TEZ/IVA switched to ELX/TEZ/IVA once it became available.

3.2.2.6.1 COVID-19 pandemic-related confounding

Where uncontrolled data are available concerning the long-term clinical outcomes of people with CF treated by CFTR modulator combination therapy, the COVID-19 pandemic introduced a host of confounding factors that make interpreting data collected from March 2020 onwards difficult. The COVID-19 pandemic likely affected health outcomes for people with CF. For example, lockdowns, social distancing and viral shielding were associated with reduced viral transmission and respiratory infections, and this may reduce the rate of lung function decline of people with CF.[157] In addition to direct impacts on respiratory infections, the COVID-19 pandemic was associated with changes to CF healthcare and resource use, for example a shift to virtual medical appointments and home-based spirometry.[173,174]

Early data suggest that the rate of respiratory infections and lung-function decline in people with CF may have slowed in 2020 and 2021. In a USA single-centre study of children between 2 and 11 years who were ineligible for ELX/TEZ/IVA at the time, Patel *et al.* 2021 reported a markedly lower rate of pulmonary exacerbations in 16 March to 15 May in 2020 (18% of patients having exacerbations) compared to the same period in 2019 (44% of patients having exacerbations).[175] In the UK, similar data have been reported for people with chronic obstructive pulmonary disease (COPD); compared to a matched-period prior to the pandemic, the COVID-19 pandemic was associated with fewer acute exacerbations of COPD, with a rate ratio of 0.57.[176]

Direct evidence of lung function-preservation in people with CF during the COVID-19 pandemic was observed in an Australian registry-based study (n=3112).[157] Doumit *et al.* reported an annual rate of ppFEV$_1$ decline of –0.13 (95% CI: –0.36 to 0.11) in people with CF in the 24 months prior to a COVID-19 index date (16 March 2020). In the 12 months following index, the annual slope was +1.76 (95% CI: 1.46 to 2.05), i.e., an average increase in ppFEV$_1$ during COVID-19. The majority of the Doumit cohort were CFTR modulator-naïve, and restricting the cohort to only people who had no modulator use in the study period provided consistent results: an annual slope of ppFEV$_1$ of –0.14 (95% CI: –0.38 to 0.12) in people with CF in the 24 months prior to COVID-19 index date, and an annual slope of ppFEV$_1$ of +1.71 (95% CI: 1.30 to 2.15) in the 12 months following index date. Collectively, these data highlight how uncontrolled studies of the effects of CFTR modulator therapy that collected data during the COVID-19 pandemic are at high risk of bias, if COVID-19 related confounding is not adequately accounted for.

The EAG notes that COVID-19-related confounding is a particular concern for studies of the long-term effects of ELX/TEZ/IVA, for which all Phase 3 open-label extension studies collected data in 2020 and 2021, and for which real-world data collected in the UK (as part of the Data Collection Agreement) since August 2020 are also affected. Given the lack of long-term head-to-head data comparing CFTR modulators and ECM, the EAG now critiques the Company's sources of $ppFEV_1$ decline data and outlines the EAG's preferred assumptions for the rate of $ppFEV_1$ decline for people treated with CFTR modulators. The EAG considers these data to be a key uncertainty in the economic modelling of CFTR modulator combination therapy for CF.

3.2.2.6.2 ELX/TEZ/IVA

For people with CF receiving ELX/TEZ/IVA, the EAG identified three sources of data that could inform the long-term rate of $ppFEV_1$ decline in the economic models for ELX/TEZ/IVA:

- Griese 2022 and Study 445-110: the two Phase III open-label extension studies of ELX/TEZ/IVA with data available at the time of analysis;[147, 177]
- The Vertex Final Analysis for ELX/TEZ/IVA of UK CF Registry Data, performed as part of the Data Collection Agreement;[164]
- Newsome 2022, an independent estimation of the rate of $ppFEV_1$ decline for people with CF and gating mutations treated with IVA monotherapy using UK CF Registry Data.[178]

Griese 2022 (VX17-445-105) is a 192 week Phase 3 open-label extension study of Heijerman 2019 and Middleton 2019, with interim Week 144 results available at the time of this appraisal. F/F or F/MF participants received ELX/TEZ/IVA for 144 weeks, with an annual rate of change in $ppFEV_1$ reported as +0.07 (95% CI: –0.12 to 0.26) across all participants. In a historical matched-controls from the US CF Registry, Lee 2023 estimated that people with CF treated with ELX/TEZ/IVA had a mean annual rate of change in $ppFEV_1$ of +0.39 (95% CI: −0.06 to 0.85), whereas the mean annual rate of change in $ppFEV_1$ of matched controls was −1.92 (95% CI: −2.16 to −1.69).[179] A similar absence of lung-function decline for people treated with ELX/TEZ/IVA, but with data collection across the COVID-19 pandemic, was reported in in the Week 96 interim analysis of Study 445-110 (open label extension of Barry 2021, F/Gating and F/RF genotypes). In Study 445-110, an overall change-from baseline in $ppFEV_1$ at Week 96 of [redacted] was reported, consistent with no large decline from the change from baseline reported at Week 8: +3.7 (95% CI: 2.8 to 4.6).

The EAG does not consider the data from Griese 2022 and Study 445-110 to provide robust evidence of the long-term effects of ELX/TEZ/IVA on $ppFEV_1$ progression, because these analyses do not account for COVID-19-related confounding. These analyses are therefore at high risk of underestimating the rate of lung-function decline of people treated with ELX/TEZ/IVA outside of periods of viral shielding, and the magnitude of this overestimation is uncertain. In response to clarification questions, the Company later cited Week 192 data from Griese 2022, stating that: "The 192-week data in study 445-105, also reported a flat ppFEV1 change over the entire follow-up period (>3 years). At 192- weeks the mean annualised rate of change in ppFEV1 for ELX/TEZ/IVA was 0.02 (95% CI: -1.04, 0.19)."180 The EAG received the Week 192 CSR and the associated Polineni 2023 46th European Cystic Fibrosis Conference presentation for Study 445-105 on 21 July 2023.180, 18[1] Study initiation was 09 October 2018 for the first eligible patient signing the informed consent form, and the last patient completed the study on 09 January 2023. Therefore, all patients who completed the Study would have had their Week 192 visit between 14 June 2022 and 09 January 2023 – providing around 12 to 18 months of data after most social distancing measures were removed in the UK (although note Study 445-105 was an international study n=304 enrolled patients form North America and n=202 patients from Europe and Australia). From these data, the EAG notes that:

- Details of the methods of Polineni 2023 192-week annualised rate of change analysis were not reported, including the length of the acute-period exclusion window, and there was no ECM control group;
- The annualised change from baseline data analysis still likely underestimates the rate of change analysis due to overlapping substantially with the COVID-19 pandemic;
- The point at which most COVID-19 restrictions were lifted in the UK does not necessarily mean that all COVID-19 related confounding was "removed" at this point, as patients may still have engaged in greater viral shielding after this date. Currently, the Company has not provided evidence in support of CF patients returning to pre-COVID levels of activity at the same point as COVID restrictions were lifted across countries, which would provide reassurance that some form of enhanced shielding was not continuing after this data;
- The absolute change from baseline in $ppFEV_1$ reported at Week 192 in Griese 2022 was [redacted] (95% CI: [redacted], F/MF PBO to ELX/TEZ/IVA), [redacted] (95% CI: [redacted], F/MF PBO ELX/TEZ/IVA to ELX/TEZ/IVA), [redacted] (95% CI: [redacted], F/F PBO to ELX/TEZ/IVA), and [redacted] (95% CI: [redacted], F/F PBO to ELX/TEZ/IVA).[181] This is consistent with no large decrease in $ppFEV_1$ across the 192 Week follow-up, including the COVID-19 pandemic, however;

- N=[redacted] of participants prematurely discontinued Study 445-105, and the absolute change from parent study baseline in ppFEV$_1$ at OL Week 192 was only reported for [redacted] of patients.

The EAG is concerned that the high rate of missing data at Week 192 may bias estimates of the annualised rate of change in ppFEV$_1$ from these data, and considers it plausible that missing data are not missing at random. To investigate this, the EAG requested that Vertex provide the by-visit estimates of absolute change from baseline in ppFEV$_1$, including sample sizes at each visit. These data were not provided, and the EAG considers the Week 144 interim analysis and Week 192 final analysis of Griese 2022 to be at high risk of bias. An alternative estimate of the annual rate of ppFEV$_1$ decline for people treated with ELX/TEZ/IVA comes from the Vertex Final Analysis of the Data Collection Agreement of UK CF Registry Data.[164] This analysis calculated the rate of ppFEV$_1$ for people treated with ELX/TEZ/IVA from 21 August 2020 to 31 December 2022, compared to matched historical controls. A smaller group of patients with severe lung disease (ppFEV$_1$ < 40) were also included in the analysis, who had a longer follow-up duration following earlier compassionate access to ELX/TEZ/IVA. In this analysis, the estimated annual rate of ppFEV$_1$ decline of people treated with ELZ/TEZ/IVA was [redacted] whereas in matched controls the rate of ppFEV$_1$ decline was [redacted] The EAG considers these data to demonstrate that ppFEV$_1$ does decline in the long-term for people treated with ELX/TEZ/IVA. However, the EAG notes that the time window of the Final Analysis, August 2020 to 31 December 2022, still overlaps considerably with the COVID-19 pandemic. As such, the EAG considers this analysis is likely to underestimate the rate of ppFEV$_1$ decline of people treated with ELX/TEZ/IVA.

Currently, the EAG considers all available sources of rate-of-decline ppFEV$_1$ decline data directly measured from people treated with ELX/TEZ/IVA to be at high-risk of bias, as the confounding effects of the COVID-19 pandemic have not been adequately corrected for. The EAG notes that such an analysis may have been possible in the Vertex Final Analysis if a sufficiently large contemporaneous control cohort had been generated; however, the Vertex analysis included only [redacted] patients with a severe MF/severe MF genotype, and a statistical analysis comparing the rate of decline with ELX/TEZ/IVA was not performed. The EAG considers it likely that a sufficient number of people in the UK CF Registry who were not receiving ELX/TEZ/IVA, LUM/IVA or TEZ/IVA, or who were on a stable IVA monotherapy regimen, may have been available to measure the impacts of the COVID-19 pandemic on lung-function decline in people with CF, but notes that such an analysis was not undertaken. In a data request made by the EAG to the UK CF Registry (Request 469),[102] the UK CF

Registry provided the number of people with at least one annual review between 2019 and 2021 who:

- Were aged 12+ years and had no recorded ELX/TEZ/IVA use between 2019 and 2021: [redacted]
- Were aged 6+ years and had no recorded ELX/TEZ/IVA use between 2019 and 2021: [redacted]
- Were aged 12+ years and had no recorded LUM/IVA, TEZ/IVA or ELX/TEZ/IVA use between 2019 and 2021: [redacted]
- Were aged 6+ years and had no recorded LUM/IVA, TEZ/IVA or ELX/TEZ/IVA use between 2019 and 2021: [redacted]
- Were aged 12+ years and had no recorded CFTR modulator use between 2019 and 2021: [redacted]
- Were aged 6+ years and had no recorded CFTR modulator use between 2019 and 2021: [redacted]

While the EAG recognises that such individuals may have distinct CF phenotypes from those who have at least one *F508del* mutation, and often may have less severe CF, the EAG considers that an analysis investigating the rate of change or changes in $ppFEV_1$ of patients not receiving CFTR modulators, or who were on a stable non-ELX/TEZ/IVA CFTR modulator therapy throughout the pandemic may have been able to resolve some uncertainty around the effects of the COVID-19 pandemic on lung function for people with CF. In the absence of an unbiased estimate for the rate of decline of $ppFEV_1$ for people treated with ELX/TEZ/IVA, the EAG considers an estimate of the annual rate of decline of $ppFEV_1$ for people with gating mutations treated with IVA monotherapy to be a reasonable, albeit slightly conservative, estimate of the relative long-term rate of $ppFEV_1$ decline for patients on ELX/TEZ/IVA compared to ECM. This is because:

- Since late 2012, IVA monotherapy has been available for people with certain gating mutations in the UK.[162] As such, long-term follow up on the rate of decline of $ppFEV_1$ for these patients is available prior to the COVID-19 pandemic;[178]
- The EAG's clinical experts suggested the response to IVA in people with a gating mutation would be lower, but close to, to the response to ELX/TEZ/IVA in people with at least one *F508del* mutation;

- In clinical trials, the sweat chloride response to IVA in people with a gating mutation is a similar magnitude to the response to ELX/TEZ/IVA in people with at least one *F508del* mutation, suggesting a similar effect CFTR activity.[61, 133, 144]

The EAG considers Newsome 2022 to provide an independent and unbiased estimate of the long-term treatment effect of IVA on ppFEV$_1$ decline. Newsome 2022 used UK CF Registry data from 2008 to 2016 to perform differences-in-differences analysis to estimate the causal treatment effect of IVA on the long-term rate of ppFEV$_1$ decline, using two negative control cohorts: a historical control cohort of people with a genotype eligible for IVA but in the pre-IVA period (2008 to 2012), and a contemporaneous control cohort of people ineligible for IVA but in the post-IVA period (2013 to 2016). The estimated negative-control corrected treatment effect for IVA treated people in the historical control cohort was a change in ppFEV$_1$ slope of +0.49 (95% CI: −0.15, 1.13), and the estimated negative-control corrected treatment effect for IVA treated people in the contemporaneous control cohort was a change in ppFEV$_1$ slope of +0.49 (95% CI: −0.14, 1.13). The EAG notes that this estimate is a plausible, but conservative, estimate for the likely ELX/TEZ/IVA treatment effect. Following input from the Company and patient and professional bodies, highlighting the likely long-term efficacy of ELX/TEZ/IVA will exceed that of IVA, the EAG considered it reasonable to adjust the Newsome *et al.* estimate of the long-term rate of ppFEV$_1$ decline upwards – based on the ratio of the ELX/TEZ/IVA to IVA acute treatment effect – to provide an estimate for the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA. To do this, the EAG scaled the 37.7% estimate of the IVA treatment effect by the ratio of the IVA to the ELX/TEZ/IVA acute treatment effect from the EAG's preferred NMA. Using this approach, the estimate for the relative reduction in the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA is +0.79% per year (0.49*[15.18/9.38]). The EAG comments further on this adjustment in Section 4.2.1.6.2. The EAG considers this adjusted estimate to also be plausible, but a more optimistic, estimate for the likely ELX/TEZ/IVA treatment effect compared to directly applying the IVA estimate (+0.49)%.

The EAG summarises its critique of different estimate estimates for the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA in Table 44.

Table 44. EAG critique of estimates of the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA.

Source	Difference in annual ppFEV$_1$ slope compared to ECM	EAG comments
Lee 2023[179]	+2.32 (95% CI: NR)	• Measured directly from ELX/TEZ/IVA treated individuals • Not corrected for COVID-19-related confounding • Comparison of clinical trial data to historical registry controls • Very high risk of overestimating ELX/TEZ/IVA treatment effect
Study 445-105 Week 192 OLE data	No decline for ELX/TEZ/IVA	• Measured directly from ELX/TEZ/IVA treated individuals • Not corrected for COVID-19-related confounding • Had some data collection prior to COVID-19 in which no large decline in ppFEV$_1$ was observed • High rate of study discontinuation and missing data • High risk of overestimating ELX/TEZ/IVA treatment effect
Vertex Final Analysis of UK CF Registry Data[164]	[redacted]	• Measured directly from ELX/TEZ/IVA treated individuals • Analysis of UK CF Registry data • Not corrected for COVID-19-related confounding • Comparison with historical matched-controls • High risk of overestimating ELX/TEZ/IVA treatment effect
Adjusted value from Newsome 2022[178]	+0.79 (95% CI: 0.15 to 1.43)	• Initial estimate is measured from IVA treated individuals with gating or other IVA-eligible mutations • Analysis of UK CF Registry data • Unaffected by COVID-19-related confounding • Initial ivacaftor estimate is corrected for both historical and contemporaneous negative control outcomes

		• Estimate is adjusted based on the ratio of the acute treatment effect of ELX/TEZ/IVA to IVA in the F/Gating population • **EAG preference**

Abbreviations: CF: cystic fibrosis; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; UK: United Kingdom

3.2.2.6.3 LUM/IVA and TEZ/IVA

For LUM/IVA and TEZ/IVA, the Phase 3 single-arm open-label extension studies of pivotal clinical trials were completed prior to the COVID-19 pandemic. In the publications of these open-label extension studies, the Company performed *post hoc* comparisons with ECM using propensity score matched-control analyses with historical US CF Registry data. From these, Vertex estimated:

- The annual rate of ppFEV$_1$ decline for LUM/IVA to be −1.33 (95% CI: −1.80 to −0.85), and in matched controls −2.29 (95% CI: −2.56 to −2.03). The mean difference between LUM/IVA and matched controls was [redacted] per year (95% CI: [redacted] a 42% relative reduction;[152]
- The annual rate of ppFEV$_1$ decline for TEZ/IVA to be −0.80 (95% CI: −1.31 to −0.30), and in matched controls −2.08 (95% CI: −2.34 to −1.82). The mean difference between TEZ/IVA and matched controls was +1.27 per year (95% CI +0.71 to +1.84), a 61.5% relative reduction (95% CI: 35.8 to 86.1).[150]

While unaffected by COVID-19 related confounding, the EAG considers each analysis to be at very high risk of underestimating the annual rate of ppFEV$_1$ decline for LUM/IVA and TEZ/IVA compared to ECM, because:

- The Company excluded data from the first 21 days (LUM/IVA) or 22 days (TEZ/IVA) of active treatment, to exclude the acute treatment effect from the analysis. However, in the pivotal trials, the acute increase in ppFEV$_1$ continued to increase up to the Week 4 (28 day) measurement, and potentially up to the Week 8 (56 day) measurement. Hence, the analyses are at risk of underestimating the rate of ppFEV$_1$ decline on LUM/IVA or TEZ/IVA by not fully excluding the acute treatment effects;
- Each analysis matched clinical trial data with historical registry-based data. Although patients were matched using propensity scores, residual confounding is likely. On average,

patients in clinical trials are likely to have fewer comorbidities and a better standard of care due to following the trial protocol than patients contributing data to a registry, and as such an analysis comparing the clinical trial and registry data is likely to underestimate the relative rate of decline for the intervention in the clinical trials compared to ECM.

The EAG therefore considers the Company matched-control analyses to be at very high risk of underestimating the annual rate of $ppFEV_1$, and instead prefers the use of an assumption-based approach.

For LUM/IVA, the EAG does not consider there to be robust evidence of a reduction in rate of decline of $ppFEV_1$ for people treated with LUM/IVA compared to ECM, because:

- In the placebo-controlled TRAFFIC and TRANSPORT,[42] the rate of decline of $ppFEV_1$ between Week 8 and the end of study at Week 24 was steeper for people on LUM/IVA than on placebo, and;
- Throughout the open label extension study, the calculated rate of annual decline was −1.33 (95% CI: −1.80 to −0.85), which is not substantially different from the assumed rate of decline in ECM,[17] and the EAG considered the −1.33 (95% CI: −1.80 to −0.85) estimate to likely underestimate the true annual rate of $ppFEV_1$ decline.

As such, the EAG prefers to implement no reduction in the rate of $ppFEV_1$ decline for patients treated with LUM/IVA. In contrast, the EAG considers there to be some evidence of a reduction in decline in $ppFEV_1$ for TEZ/IVA, but considers the Vertex estimate of a 61.5% relative reduction to be an overestimate. The EAG notes that:

- In the 24-Week treatment period of Taylor-Cousar 2017, $ppFEV_1$ remained stable from Week 4 to Week 24 for TEZ/IVA, whereas $ppFEV_1$ decreased in this period for people in the placebo arm;
- A decline in $ppFEV_1$ was observed for people treated with TEZ/IVA in the long-term extension study. While the EAG considers the Company estimate of this rate of decline, −0.80 (95% CI: −1.31 to −0.30), to be an underestimate, the EAG considers these data to be consistent with a reduction in the rate of decline compared to ECM.

In the absence of an unbiased direct estimate of a long-term treatment effect of TEZ/IVA on $ppFEV_1$, the EAG's preferred approach is to scale the EAG's effect estimate for ELX/TEZ/IVA by the ratio of

the TEZ/IVA to ELX/TEZ/IVA acute treatment effect in the F/F population (4/14.2 = 0.282). The acute treatment effect of TEZ/IVA was 28.2% of the acute treatment effect estimated for EXL/TEZ/IVA, leading to the EAG's preferred assumption of the rate of $ppFEV_1$ decline for TEZ/IVA to be an annual change in the slope of $ppFEV_1$ of +0.22 (calculated as 0.282*0.79), compared to ECM. The Company and EAG assumptions for the long-term rate of $ppFEV_1$ decline for LUM/IVA and TEZ/IVA compared to ECM are presented in Table 45.

Table 45. EAG critique of estimates of the long-term rate of $ppFEV_1$ decline for LUM/IVA and TEZ/IVA.

Source	Difference in annual $ppFEV_1$ slope compared to ECM	EAG comments
LUM/IVA		
Konstan 2017[152]	+0.96 (95% CI: NR)	• Comparison between clinical trial participants and historical matched-registry controls • Does not fully exclude acute treatment effects • Very high risk of overestimating LUM/IVA treatment effect
EAG assumption	0	• Consistent with observed decline in placebo controlled RCTs • Consistent with observed decline in long-term extension studies
TEZ/IVA		
Flume 2021[150]	+1.27 (95% CI: +0.71 to +1.84)	• Comparison between clinical trial participants and historical matched-registry controls • Does not fully exclude acute treatment effects • Larger point estimate than Vertex Final Analysis of ELX/TEZ/IVA – clinically implausible. • Very high risk of overestimating TEZ/IVA treatment effect
EAG calculation	+0.22 (95% CI: −0.42 to 0.86)	• Calculated as 28.2% of the EAG's preferred assumption for the slope for ELX/TEZ/IVA

Abbreviations: CF: cystic fibrosis; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; UK: United Kingdom

3.2.2.6.4 Company response to clarification questions regarding the annual rate of ppFEV$_1$ decline

The EAG asked the Company a range of clarification questions concerning the Company's long-term estimates of the long-term rate of decline of ppFEV$_1$ for people on CFTR modulator therapies, which the EAG considers high risk of bias at underestimating the long-term rate of ppFEV$_1$ decline for people treated with CFTR modulators. The Company stated that: "Overall Vertex disagrees with the EAG conclusion that our estimates underestimate the rate of decline for people on CFTR modulators relative to ECM and believe the values provided in our submission are accurate". The EAG critiques the Company replies to the clarification questions below:

LUM/IVA and TEZ/IVA

The EAG had two major concerns regarding the historical matched control analyses conducted by the Company for LUM/IVA and TEZ/IVA, and does not consider the Company's response to clarification questions to adequately address either:

- Not accounting for the better prognosis of clinical trial participants vs matched registry-based historical control patients.

The Company analyses compared patients enrolled in CFTR modulator clinical trials with propensity-score matched-historical control trials. These analyses are at high risk of bias, even after matching on available baseline characteristics because: i) the standard of care received through following a clinical trial protocol, including likely co-adherence to ECM medications, is likely to be higher in clinical trials than in real world data,[182-184] leading to a slower rate of decline for clinical trial participants, and ii) over time, the care and clinical outcomes for people with CF has improved.[185] The Company analyses do not account for the increase in survival that would have been expected had real-world data been collected in a counterfactual contemporaneous control cohort.[178]

In their response to clarification questions, the Company did not directly address this concern of the EAG's, but did note for the ELX/TEZ/IVA registry-based analysis that [redacted]

- Not adequately excluding the acute effect of LUM/IVA or TEZ/IVA treatment from the long-term rate of change analyses;

In the Company analyses, data were excluded from the first 21 days (LUM/IVA) or 22 days (TEZ/IVA) of active treatment, to exclude the acute treatment effect from the analysis. However, the EAG suggested that in the pivotal trials the acute increase in $ppFEV_1$ continued to increase up to the Week 4 (28 day) measurement, and potentially up to the Week 8 (56 day) measurement. The Company's response to this critique was inconsistent, suggesting that the acute phase lasts 30 days, 28 days or 2 weeks at various stages in the CQ response:

> *"Preclinical data and prior experience with CFTR modulators additionally support that acute improvement in $ppFEV_1$ is observed between week 2 to Day 30."*
>
> *"Vertex agrees… that data from the pivotal TEZ/IVA and LUM/IVA trials, show a further increase in $ppFEV_1$ up to Week 4 (Day 28), however is much less prominent."*
>
> *"The TEZ/IVA and LUM/IVA rate of change analysis are based on clinical trial data (with specific timings of data capture for all patients) which has shown that after 2 weeks of treatment all patients have reached the maximum improvement on $ppFEV_1$."*

The Company further suggested that patients may experience a secondary acute improvement that occurs more gradually than the initial acute phase, reflecting improvements in structural changes other than mucus accumulation in the airways:

> *"The rapid change observed within the week 2 or 30-day period likely represents improvement in mucociliary clearance and removal of mucus plugs. Once the patient passes the acute phase, generally after one month, the change seems to stabilize over time. Any further improvement after the acute phase may indicate improvements in structural changes other than mucus accumulation in the airways."*

The EAG considers that:

- Most of the acute increase in $ppFEV_1$ a patient experiences when treated by CFTR modulator therapy is seen within the first 15 days of treatment, however;
- There is consistent evidence that acute improvements in $ppFEV_1$ continue until the Week 4 (Day 28) measurement in clinical trials, and likely up to Week 8 (Day 56).

Table 46 displays the results of the MMRM analysis of change from baseline in $ppFEV_1$ by visit for the placebo controlled RCTS of CFTR modulators in people with CF aged 12+ years. In all five of the trials,

the absolute and difference-from-placebo LS mean change from baseline was greater at Week 4 than Day 15, and in four of the five placebo-controlled trials, the absolute and difference-from-placebo LS mean change from baseline was greater at Week 8 than Week 4, i.e., suggesting acute increases following CFTR combination modulator therapies can be seen up to Day 56.

Table 46. MMRM analysis of absolute change from baseline in $ppFEV_1$ and difference from placebo for CFTR modulator clinical trials of people with CF aged 12+ years.

Study	Comparison	Day 15	Week 4	Week 8	Week 16	Week 24
TRAFFIC	LS mean difference (95% CI) vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute LS mean change from baseline LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TRANSPORT	LS mean difference (95% CI) vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute LS mean change from baseline LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taylor-Cousar 2017	LS mean difference (95% CI) vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute LS mean change from baseline TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rowe 2017	LS mean difference (95% CI) vs PBO	[redacted]	[redacted]	[redacted]		
	Absolute LS mean change from baseline TEZ/IVA	[redacted]	[redacted]	[redacted]		
Middleton 2019	LS mean difference (95% CI) vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute LS mean change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	from baseline ELX/TEZ/IVA					

Abbreviations: CF: cystic fibrosis; CI: confidence interval; ELX: elexacaftor: IVA: ivacaftor; LS: least squares: PBO: placebo; ppFEV1: percent predicted forced expiratory volume in one second; TEZ: tezacaftor

Based on these data, the EAG considers that only excluding data up to Day 21 (LUM/IVA) or Day 22 (TEZ/IVA) is unlikely to adequately remove the acute treatment effects of LUM/IVA or TEZ/IVA from the Company matched-control analysis. The 30-day exclusion window used for the ELX/TEZ/IVA analysis is more appropriate, but the EAG notes that even this window may be too short to exclude all acute treatment effects. As such, the EAG does not consider the Company estimates of a 42% relative reduction in the rate of $ppFEV_1$ decline for LUM/IVA compared to ECM, or a 61.5% relative reduction in the rate of $ppFEV_1$ decline for TEZ/IVA compared to ECM, to be robust estimates.

ELX/TEZ/IVA

For ELX/TEZ/IVA, the Company provided a historical registry-based matched control analysis of UK CF Registry data collected as part of the Data Collection Agreement. As for the LUM/IVA and TEZ/IVA analyses, the EAG considers that the Company analysis is at risk of not adequately, i) removing the acute treatment effect of CFTR modulator therapy, and ii) accounting for the negative control effect associated with using historical control patients. However, the EAG notes that the magnitude of these concerns are smaller than for the LUM/IVA and TEZ/IVA analyses as a 30-day exclusion window was used for the acute treatment effect, and both the ELX/TEZ/IVA and control patient data was sourced from the UK CF Registry, rather than the CFTR modulator data coming from clinical trial data as for LUM/IVA and TEZ/IVA.

Both the EAG and Company highlighted, however, that the COVID-19 pandemic likely confounds the Company analysis, but the EAG and Company disagreed in the direction of bias resulting from this confounding:

- The EAG considered factors associated with the COVID-19 pandemic likely to reduce the rate of lung-function decline observed for patients on ELX/TEZ/IVA by preserving lung function throughout the COVID-19 pandemic. This could occur directly through a reduction in the rate of pulmonary exacerbations, or more indirectly though other lifestyle changes related to the pandemic. The EAG considers this would lead to data during COVID-19 underestimating the

rate of lung function decline for people treated with ELX/TEZ/IVA. In contrast, the Company provided an argument that the COVID-19 pandemic would lead to an overestimation of the rate of lung function decline for people treated with ELX/TEZ/IVA;

- The Company agreed that factors associated with the COVID-19 pandemic "potentially preserved" lung function in people treated with ELX/TEZ/IVA, but disagreed with the EAG about how to interpret these data: [redacted]

The EAG considers the Company's argument to be clinically implausible. The Company argument appears to be that lockdown measures introduced from March 2020 would lead to a short-term increase in a person's $ppFEV_1$ prior to initiating ELX/TEZ/IVA from August 2020, and this benefit would be lost once lockdown restrictions were lifted – creating the artificial impression of a decline in $ppFEV_1$ for people treated with ELX/TEZ/IVA that would not have occurred outside of measurements affected by the COVID-19 pandemic. In contrast, the EAG considers it more clinically plausible that lung-preservation associated with COVID-19 related factors would occur continually throughout the pandemic – i.e., both before and after ELX/TEZ/IVA initiation – and that this preservation would not be lost once COVID-19 related restrictions were lifted. This is because patients would have avoided lung function damage during lockdowns, social distancing and viral shielding. Hence, the EAG reaffirms that the Company analysis of the long-term rate of change of $ppFEV_1$ for patients treated with ELX/TEZ/IVA relative to ECM – which estimated a relative reduction of 66.8%, is likely an overestimation of the relative reduction of the long-term rate of $ppFEV_1$ decline that patients treated with ELX/TEZ/IVA are likely to experience.

Nevertheless, the EAG considers there to be a large degree of uncertainty around the long-term rate of decline of $ppFEV_1$ for people treated with ELX/TEZ/IVA, and notes that the uncertainty introduced by the COVID-19 pandemic may be unresolvable in existing data. This was echoed by the UK CF Registry Research Committee and clinical members of the UK CF Registry Steering Committee in

response to a CF Registry Data Request submitted by BMJ-TAG,[102] and also by the Company in a response to the Clarification Question (Table 47).

Table 47. Comment on analyses investigating the impact of the COVID-19 pandemic on health outcomes for people with CF from the UK CF Registry Research Committee and clinical members of the UK CF Registry Steering Committee and Vertex.

Body	Comment on analyses investigating the impact of the COVID-19 pandemic on health outcomes for people with CF
Letter on behalf of the UK CF Registry Research Committee and clinical members of the UK CF Registry Steering Committee	*"The committee advise that analysis to understand the impact of the COVID-19 pandemic on health outcomes for people with CF should be undertaken using appropriate methodology and over an appropriate time-frame. The two-year follow up period within the Technology Appraisal protocol is unlikely to be enough time to appropriately determine any long-term impact of the pandemic. The committee however recognise that it would not be feasible to conduct such as analysis before the final review by the Technology Appraisal committee."*
Vertex response to Clarification Questions	"*Adjusting the analysis for the potential confounding effect of shielding/lock-down interventions during the COVID-19 pandemic needs to be further investigated when longer-term real-world data beyond 2022 on patients initiated on ELX/TEZ/IVA are available (outside of the pandemic)."*

Abbreviations: CF: cystic fibrosis; ELX: elexacaftor: IVA: ivacaftor; TEZ: tezacaftor.

3.2.2.6.5 Co-adherence to inhaled therapies

The long-term rate of ppFEV$_1$ decline and other clinical outcomes for people treated with CFTR modulator therapies may be influenced by co-adherence to non-CFTR modulator preventative inhaled therapies, such as inhaled mucolytics and prophylactic antibiotics.[31] In-line with this suggestion, dornase alfa, hypertonic saline and inhaled antibiotic use decreased in people taking IVA monotherapy in years following its introduction for people with CF and eligible gating mutations in the UK, relative to people who were ineligible for IVA.[162] As inhaled mucolytics and prophylactic antibiotics can affect the probability of pulmonary exacerbations and a person's ppFEV$_1$, reduced

adherence to such therapies following CFTR modulator initiation may attenuate the real-world effectiveness of CFTR modulators.

As the EAG uses real-world IVA monotherapy data to inform the rate of long-term ppFEV$_1$ decline for ELX/TEZ/IVA and TEZ/IVA, the effects of a reduction in co-adherence to preventative inhaled therapies similar to that observed for IVA monotherapy are implicitly modelled in the EAG base case. The EAG notes there currently is no robust data on co-adherence to ECM therapies for ELX/TEZ/IVA, but notes that the effect size of ECM medications on ppFEV$_1$ are small in comparison to effective CFTR modulator therapy, and dependent on patient baseline characteristics.[186, 187] The EAG therefore considers the effects of co-adherence to ECM medications for patients taking CFTR modulator therapies to introduce uncertainty into the long-term effectiveness of CFTR modulators therapies, which is currently unresolvable with existing data. However, the EAG notes that measuring adherence to CFTR modulators and preventative inhaled therapies, as well as the consequences of discontinuing some ECM therapies when treated with ELX/TEZ/IVA, are active areas of current research.[188, 189]

3.3 Discussion

3.3.1 Summary of key results

The EAG conducted an SLR and performed NMAs to assess the clinical effectiveness of ELX/TEZ/IVA, TEZ/IVA and LUM/IVA within their marketing authorisations for treating people with CF, with at least one *F508del* mutation. Each CFTR modulator combination therapy was compared with each other and ECM. The EAG prioritised 19 clinical trials from the SLR for clinical analyses, which included 16 RCTs. All included studies were sponsored by the Company. Twelve of the RCTs were assessed to be at low risk of bias and four were assessed as having some concerns. All three non-randomised studies were assessed as high risk of bias.

Overall, the EAG considers there to be strong evidence that treatment with either ELX/TEZ/IVA, TEZ/IVA or LUM/IVA leads to an acute increase in ppFEV$_1$ for people with CF aged 6+ years, relative to ECM. The magnitude of the acute increase was significantly greater for ELX/TEZ/IVA (change from baseline estimate compared to placebo in the 12+ years F/F genotype: 14.20, 95% CI: 12.07 to 16.31) compared to TEZ/IVA (change from baseline estimate compared to placebo in the 12+ years F/F genotype: 4.00, 95% CI: 3.15 to 4.85) and LUM/IVA (change from baseline estimate compared to placebo in the 12+ years F/F genotype: 2.83, 95% CI: 1.84 to 3.81). The magnitude of the acute

increase in ppFEV$_1$ was similar for ELX/TEX/IVA in the F/F, F/MF and F/Gating genotypes, but smaller in the F/RF genotype, which was also the case for TEZ/IVA.

The EAG also considers there to be good evidence that treatment with either ELX/TEZ/IVA, TEZ/IVA or LUM/IVA leads to a reduction in pulmonary exacerbations requiring IV antibiotics for people aged 12+ years, relative to ECM. The magnitude of this reduction was again greater for ELX/TEZ/IVA than LUM/IVA or TEZ/IVA. However, the reporting of pulmonary exacerbations was inconsistent between studies, limiting the evidence base for this outcome. The extent to which CFTR modulator therapy reduces pulmonary exacerbations requiring IV antibiotics in children under 12 years is more uncertain, due to:

- Inconsistent reporting of pulmonary exacerbations as efficacy or safety outcomes between studies;
- The lower rate of pulmonary exacerbations in children under 12 years than people over 12 years creating a floor effect within the study periods and;
- The smaller number of studies and smaller sample sizes within these studies, of combination CFTR modulator therapy for people under 12 years.

The EAG notes that the mechanism by which CFTR modulator therapy reduces pulmonary exacerbations in people aged 12+ years should generalise to the 6 to 11 years age group. However, in the single placebo-controlled study that reported the number pulmonary exacerbations requiring IV antibiotics in participants aged 6 to 11 years, the rate was [redacted] for LUM/IVA ([redacted]) than for placebo [redacted] For ELX/TEZ/IVA, the number of participants with non-serious (ELX/TEZ/IVA, n=1/60, 1.67%; placebo, n=14/61, 22.95%) and serious (ELX/TEZ/IVA, n=0/60, 0.00%; placebo, n=3/61, 4.92%) pulmonary exacerbations reported as adverse events was lower for ELX/TEZ/IVA than placebo. Neither the EAG nor the Company included a direct treatment effect on pulmonary exacerbations requiring IV antibiotics in their economic models for participants under 12 years, although indirect effects via changes in ppFEV$_1$ were included. In light of the limited evidence available, the EAG considers this approach reasonable for LUM/IVA and TEZ/IVA, but conservative for ELX/TEZ/IVA.

Treatment with ELX/TEZ/IVA led to an increased weight-for-age z-score relative to ECM in people with CF aged 6+ years, with the estimated acute increase in weight-for-age z-score ranging from [redacted]) in the 6 to 11 years F/MF genotype group to [redacted] For the

F/RF population, the EAG's ITC estimated a smaller acute increase in weight-for-age z-score for ELX/TEZ.IVA compared to placebo: [redacted] For LUM/IVA the point estimate was closer to 0 in the in 12+ years F/F genotype group, but the 95% CIs still excluded 0 (pooled TRAFFIC/TRANSPORT data: [redacted]). In contrast, there was no significant acute increase compared to placebo for TEZ/IVA in the 12+ years group, or LUM/IVA or TEZ/IVA in the 6 to 11 years populations prioritised in the EAG's SLR.

For people with CF under 6 years, (2 to 5 years for ELX/TEZ/IVA and 1 to 5 years for LUM/IVA), the EAG considers the effects of CFTR modulator therapy on lung function and other efficacy outcomes to be more uncertain because:

- Key studies were performed without a power analysis,[142, 190] or powered to detect a primary safety outcome, only;[159]
- $ppFEV_1$ measurements were not conducted in these trials, as the measurements are not reliable at this age;[60]
- Many people with CF aged less than 6 years may have near-ceiling lung function.

3.3.2 Generalisability

The EAG consider the clinical efficacy data from the CFTR modulator clinical trial programme likely to generalise to clinical practice in England and Wales, and notes that the acute effects of CFTR modulator therapy observed in clinical trials are consistent with those reported in the UK CF Registry. However, the 40% to 90% $ppFEV_1$ inclusion criteria for clinical trials of people aged 12+ years may limit the generalisability of the effects of CFTR modulator therapy to people with $ppFEV_1$ outside of 40% to 90%. The EAG considers that:

- For people with a $ppFEV_1$ greater than 90%, the effects of CFTR modulator therapy in preventing lung decline are likely more important than any acute increases in lung-function, that may be affected by ceiling effects;
- People with CF and $ppFEV_1$ less than 40% have advance lung disease and may be candidates for transplant. There is real-world evidence that such patients experience acute increases in $ppFEV_1$ in-line with the magnitude observed for people with $ppFEV_1$ >40% for ELX/TEZ/IVA, although the response is more uncertain for LUM/IVA and TEZ/IVA;[58, 163, 164]
- While people with CF and $ppFEV_1$ less than 40% comprise around 18% of the prevalent population of adults with CF in the UK,[103] should CFTR modulator therapies be approved for

routine commissioning in England and Wales they would be initiated prior to an individual's ppFEV$_1$ declining to less than 40%.

The EAG's clinical experts noted that if ELX/TEZ/IVA was initiated very early, i.e., before substantial lung or pancreatic damage had occurred, it is plausible that ELX/TEZ/IVA may prevent most lung-function and other clinical decline for these individuals. While plausible, the EAG notes substantial uncertainty regarding the long-term clinical outcomes of people aged 2 initiating ELX/TEZ/IVA due to:

- The current absence of any long-term data for this population;
- The likelihood that some damage may have occurred by aged 2 for this population, especially to the pancreas.

3.3.3 Key issues and uncertainties

The EAG considers the long-term effects of CFTR modulators on the rate of ppFEV$_1$ decline and pulmonary exacerbations to be the major outstanding uncertainty regarding the clinical effectiveness of CFTR modulator therapy. No head-to-head comparative effectiveness data are available for these long-term outcomes for any CFTR combination modulator therapy. Where uncontrolled long-term data are available, follow-up is often limited to 2 to 3 years follow-up, meaning the effects of CFTR combination therapies over the lifetime are highly uncertain. The EAG considers this uncertainty to be heightened for ELX/TEZ/IVA, in which the only long-term data available are from uncontrolled clinical trials and real-world data where data collection windows overlapped substantially with the COVID-19 pandemic. During COVID-19, viral shielding and social distancing are expected to have meaningfully impacted lung-function in people with CF between 2020 and 2022, including a direct reduction in exacerbations due to lower rates of infection, and an associated reduction in lung-function decline due to fewer pulmonary exacerbations and fewer other respiratory infections.[157, 175]

The EAG also notes the following key uncertainties in the clinical effectiveness and safety data from the CFTR modulator clinical trial programme and real-world evidence base:

- EQ-5D data were only collected in two CFTR modulator clinical trials, both of LUM/IVA, meaning the impact of CFTR modulator therapy on EQ-5D, the preferred NICE instrument, is uncertain;

- Data on pulmonary exacerbations were inconsistently reported across clinical trials, with only a minority of clinical trials reporting sufficient data to be included in the economic modelling. Due to this, the effective evidence base for pulmonary exacerbations is much smaller than the evidence base for other clinical variables entering the economic model;
- There are no validated minimally clinically important differences for key clinical outcomes, such as changes in $ppFEV_1$ and weight-for-age z-score, provides uncertainty around the clinical meaningfulness of the response to LUM/IVA and TEZ/IVA, which often had lower bounds of confidence intervals close to, or overlapping, 0 when compared to ECM for the acute changes in $ppFEV_1$ and weight-for-age z-score;
- The adverse event profiles of CFTR combination modulator therapy during the acute phase of clinical trials appear mild; however there is a lack of consistently reported long-term adverse event data on cataracts, lens opacities and hypertension, that may be related to CFTR modulator therapy.

4 Assessment of cost-effectiveness

4.1 Systematic review of existing cost-effectiveness evidence

4.1.1 Methods

A systematic literature review (SLR) was undertaken in February 2023 to identify published economic evaluations of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) for the treatment of cystic fibrosis. A separate search was conducted to identify studies reporting health-related quality of life (HRQoL) data in patients with cystic fibrosis.

Multiple electronic databases were searched including MEDLINE, EMBASE, the International Network of Agencies for Health Technology Assessment (INAHTA) and the Cost-Effectiveness Analysis (CEA) Registry. Further to the database searches, health technology appraisal (HTA) websites including National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC) and Institute for Clinical and Economic Review (ICER) were searched to identify relevant publications. In addition, reference lists of key identified studies were also reviewed for any potentially relevant studies.

The Centre for Reviews and Dissemination (CRD) databases were not searched as the CRD stopped adding records to the Health Technology Assessment (HTA) database in March of 2018 and the Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluations Database (NHS EED) in March of 2015. The EAG considers it unlikely that relevant studies were missed from the CRD databases as the INAHTA has taken on the responsibility for the production of the HTA database.

The search strategy for economic evaluations combined terms capturing the interventions or comparators of interest, the target condition (cystic fibrosis) and the validated CADTH economic evaluations search filter.[191] The search strategy for HRQoL studies was not restricted by treatment, and combined terms capturing the target population with HRQoL terms (adapted from Arber *et al.* 2017).[192] No language (to assess volume of foreign language studies available), setting or country restrictions were applied to the search strategy initially. However, following title and abstract screening, as the number of full texts to examine exceeded 100 publications, the pragmatic decision was taken to limit to UK studies full text search. The EAG does not consider this likely to introduce

substantial bias as UK studies were required the economic model in order to align with the NICE Reference Case.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using pre-defined eligibility criteria. The inclusion and exclusion criteria for each review are outlined in Table 48 for economic evaluations and Table 49 for studies reporting HRQoL data. Additionally, for both searches the EAG reviewed the Company's submission (including results of their SLRs) for additional references.

Table 48. Inclusion criteria: economic evaluations

Criteria	Inclusion	Exclusion
Population	Patients with cystic fibrosis	None
Interventions	The interventions below will be considered: • elexacaftor/tezacaftor/ivacaftor (Trikafta® or Kaftrio®) • lumacaftor/ivacaftor (Orkambi®) • tezacaftor/ivacaftor (Symkevi® or Symdeko®)	• Ivacaftor monotherapy
Comparators	Specified interventions versus each other or ECM.	None.
Outcomes	• Costs per unit of outcome (e.g. ICERs) • QALYs; • LYG.	None.
Study design	Economic evaluations: • Cost-utility analyses • Cost-effectiveness analyses • Cost-minimisation analyses • Cost-benefit analyses • Cost-consequence analyses.	• Budget impact analysis; • Cost-analysis only • Commentaries and letters; • Reviews (systematic and non-systematic); • Study protocols with no results
Report type	• Full text articles • English	• Abstracts with insufficient methodological details

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year;

Table 49. Inclusion criteria: HRQoL studies

Criteria	Inclusion	Exclusion
Population	Patients with CF	None.
Interventions	None.	None.
Comparators	None.	None.
Outcomes	• Preference-based multi-attribute utility values (e.g. EQ-5D, HUI-3, SF-6D)	Outcomes not listed.

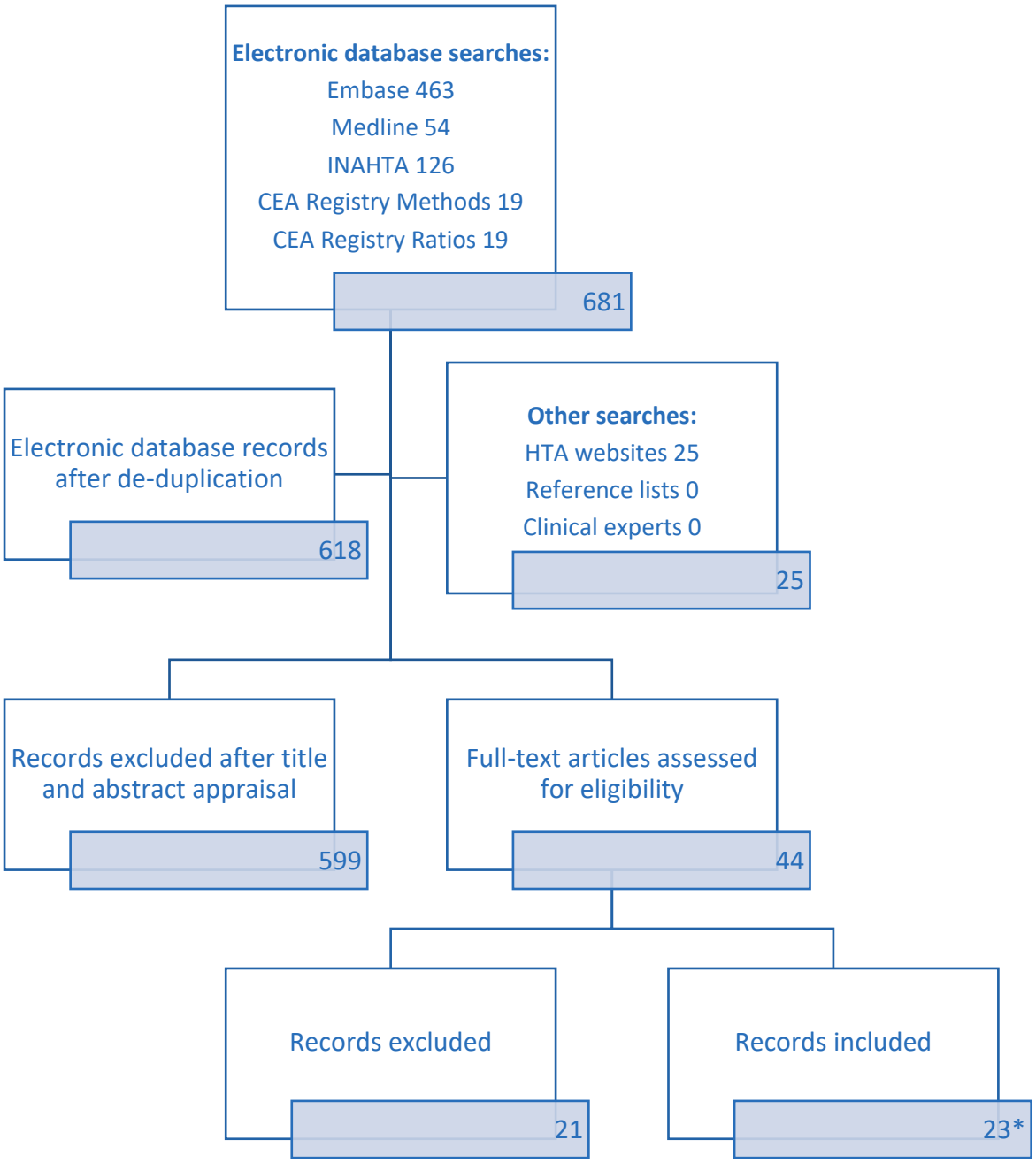
	• Direct utility elicitation tools (TTO, standard gamble, rating scale) • Generic health-related quality of life questionnaires (e.g. SF-36, SF-12). • CFQ	
Study design	• Studies reporting original HRQoL data or mapping studies • UK cost effectiveness studies	• Commentaries and letters; • Reviews (systematic and non-systematic); • Study protocols with no results.
Limits	Publications in English (numbers of relevant non-English studies will be reported).	Non-English studies (numbers of relevant non-English studies will be reported).

Abbreviations: CF, cystic fibrosis; CFQ; cystic fibrosis questionnaire; EQ-5D, EuroQol 5 Dimensions; HRQoL, health-related quality of life; HUI, health utilities index; SF-6D, short-form 6-dimension; SF-12, 12-item short-form health survey; TTO, time trade-off

4.1.2 Results – economic evaluations

The electronic database searches identified 681 records. After the removal of duplicates this left 618 records to be assessed against the inclusion criteria by two independent reviewers. An additional 25 records were identified though searches of HTA websites. After title and abstract assessment, 599 records were excluded, leaving 44 records to be assessed at the full text stage. In total, 23 publications were included; however these were extracted as 18 unique studies due to the inclusion of a summary article of an included study,[193] an additional erratum,[194] and earlier versions of PBAC summary reports being combined. A PRISMA diagram of the included studies in shown in Figure 5.

Figure 5. PRISMA diagram of economic evaluations searches



* Extracted as 18 studies due to studies being combined

Of the 18 unique studies, 15 were from HTA organisations. Only two of the 15 were independent evaluations not based on a Company submission, and both of these were conducted by the Institute for Clinical and Economic Review.[195, 196] The remaining three studies were independent evaluations of LUM/IVA, all conducted from the USA payer perspective.[197-199] Seventeen of the included 18 studies conducted cost-utility analyses, reporting results as incremental cost per QALY (ICER), with

the exception of Dilokthornsakul *et al.* (2017)[197] who reported incremental costs, QALYs and life years but did not report the corresponding ICER. Vadagam *et al.* 2018[199] reported outcomes in terms of cost per absolute $ppFEV_1$.

Interventions and comparators

Of the 18 studies included, the majority assessed the cost-effectiveness of LUM/IVA (11/18)[197-207] while only two assessed TEZ/IVA[208, 209] and three included ELX/TEZ/IVA.[111, 210, 211] The remaining two studies[195, 196] included all three interventions of interest to this research and compared ELX/TEZ/IVA, TEZ/IVA and LUM/IVA all against established clinical management for specified genotypes. The interventions were not compared to each other within these two studies but, due to the recommended start age varying between drugs, they were modelled sequentially in the relevant genotype populations, with patients switching to the 'best available' therapy available for that age. Established clinical management was used as a comparator in all studies but varied in its definition, with many studies not describing it at all. PBAC 2021[211] also compared ELX/TEZ/IVA to TEZ/IVA in F/F and F/RF genotype populations, while CADTH 2022[111] compared ELX/TEZ/IVA to LUM/IVA in the F/F genotype population and IVA monotherapy in patients with the F/RF genotype.

Model structure

The most commonly used model structure was an individual patient simulation model, used in 15 of the 18 studies; these studies were all those based on HTA organisation submissions or reports. All of these studies used the same general structure; applying a Cox proportional hazards model by Liou *et al.* 2001[172] to adjust the underlying CF population baseline mortality for each individual patient based on nine characteristics (age, sex, $ppFEV_1$, annual number of pulmonary exacerbations, prior respiratory infection status, CF-related diabetes, weight-for-age z score, and pancreatic sufficiency status) found to influence CF mortality. All patient simulation models used a lifetime time horizon and the majority used a cycle length of four weeks for the first two years and annual thereafter. ICER 2018[195] used an annual cycle length, whereas ICER 2020[196] did not report the cycle length used. Two studies used a Markov state transition model with an annual cycle length,[197, 198] each with five health states (mild lung disease [$\%FEV_1$ predicted ≥70%], moderate lung disease [40 ≤ %FEV1 predicted <70%], severe lung disease [$\%FEV_1$ predicted <40%], post lung transplantation and death). Sharma *et al.*[198] also included transition health states to represent pulmonary exacerbations and lung

transplant. Vadagam *et al.*[199] was described only described as a decision model with no further details.

Treatment effectiveness

Treatment effectiveness of CFTR modulators was measured through an improvement in $ppFEV_1$ scores in all studies, with an additional impact on pulmonary exacerbations and weight-for-age z score included in all individual simulation models. The treatment effectiveness was sourced from the main clinical trials for the relevant CFTR modulator in each study. As trials for ELX/TEZ/IVA have predominately been compared against other CFTR modulators rather than ECM for F/F, F/RF, and F/Gating genotypes, the three studies of cost effectiveness for ELX/TEZ/IVA (PBAC 2021; CADTH 2021; CADTH 2022) all reported conducting indirect treatment comparisons (ITCs) to inform treatment effectiveness against ECM.

Long term effectiveness varied between studies and was implemented through assumptions made regarding long-term decline in $ppFEV_1$ after the initial trial or extension study duration in relation to the rate of decline modelled for patients on ECM. In HTA submissions, this assumption was deemed largely uncertain and often overly optimistic. Alternatives assumptions were implemented in re-analyses produced by CADTH 2021[210] and 2022[111] for ELX/TEZ/IVA, CADTH 2016[200] and 2018[201] for LUM/IVA and PBAC 2019a[208] for TEZ/IVA, in which the rate of decline of $ppFEV_1$ was equal to that of ECM (see Table 51). In the NICE appraisal for LUM/IVA, the committee noted how it had not been sufficiently justified why USA/Canada data was more relevant to the clinical population in England, resulting in uncertainty. The committee also stated how exploratory analyses should have been undertaken using the $ppFEV_1$ decline for standard of care alone based on the 24-week trial data.

Adverse events

Adverse events were only discussed in six of the included studies. The two assessments conducted by the Institute for Clinical and Economic Review (2018[195] and 2020[196]) stated that adverse events were not explicitly modelled in terms of additional costs or disutilties and they were found to be generally comparable across trial arms. Both CADTH reports for LUM/IVA (2016[200] and 2018[201]) state that adverse events from the TRAFFIC[212] and TRANSPORT[213] trials were included in the model, applied as a cost of a general practitioner visit. This method was also used in NICE TA786.[202] The independent study by Vadagam *et al.*[199] included adverse events that occurred in at least 10% of patients in any treatment group in the TRAFFIC[212] and TRANSPORT[213] trials.

Cost-effectiveness results

All included studies had large ICERs, none of which would be deemed cost-effective using the NICE £20,000–£30,000 threshold. Only four studies were relevant to the UK population; NICE TA786,[202] SMC 2016[206] and SMC 2019a[207] for LUM/IVA, and SMC 2019b[209] for TEZ/IVA. None of the included ICERs in any of these four assessments were below £200,000.

A summary of the included studies is provided in Table 50 with further details in Appendix 9.6.1. All studies were assessed using the Drummond checklist, reported in Appendix 9.2.5. As the majority of the included studies were HTA reports, the quality of the evidence reported varied due to some data being redacted or summarised from a Company submission. We also reviewed any changes made by HTA organisations to the Company submissions base-case assumptions, reported in Table 51.

Table 50. Summary of included economic evaluations

Author, year, country	Perspective, discounting & cost year	Model type	Patient population	Intervention/ Comparator	Treatment effectiveness
Multiple CFTR modulators					
Institute for Clinical and Economic Review (ICER), 2018, USA[195]	**Perspective**: Health care perspective **Discount rate**: 3% for costs and QALYS **Cost year**: 2017	Discrete time microsimulation model (developed in TreeAge®) 1 year time cycle	Patients with CF in both homogenous and heterozygous (gating mutation or RF)	**Interventions:** Multiple analyses of CFTR modulators for different genotype mutations: LUM/IVA, TEZ/IVA and IVA. All are combined with ECM. CFTR modulators were compared with ECM and not directly with each other ECM consists of pulmonary and pancreatic therapies. Individuals with or developing CF related diabetes have oral hyperglycaemic agents, intermittent insulin and chronic insulin	Treatment effect is modelled as an immediate increase in $ppFEV_1$, weight for age z-score, and a decrease in the annual number of acute PEs, sourced from the key trials relevant to the intervention
Institute for Clinical and Economic Review (ICER) 2020, USA[196]	**Perspective**: Health care perspective **Discount rate**: 3% for costs and QALYs **Cost year**: 2019	Microsimulation model (developed in TreeAge) with a lifetime horizon.	Target population is patients both homozygous and heterozygous for the *F508del* mutation	**Interventions:** Multiple analyses of CFTR modulators for different genotype mutations: LUM/IVA, TEZ/IVA and ELX/TEZ/IVA. All are combined with ECM. CFTR modulators were compared with ECM and not directly with each other. Patients started on a CFTR modulator when they were first eligible to receive that modulator as per the marketing authorisation and then switch to a 'more effective' modulator when they become age eligible ECM consists of pulmonary and pancreatic therapies	Treatment effect is modelled as an immediate increase in $ppFEV_1$, weight for age z-score, and a decrease in the annual number of acute PEs. Patients switching CFTR modulators are assumed to experience the net increase in $ppFEV_1$ between the two drugs, based on trial data, where available

Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA)					
CADTH Common Drug Review, 2021, Canada[210]	**Perspective**: Canadian public health care payer **Discount rate:** 1.5% for costs and QALYs **Cost year:** N.R.	Patient-level simulation model with a lifetime horizon (approx. 65 years) Model cycle = four weeks for the first two years and annual thereafter.	Target population is patients with CF aged ≥ 12 years who have at least 1 *F508del* mutation in the CFTR gene. 4 genotypes considered in separate analyses: F/F, F/MF, F/RF and F/G inclusive of R117H	**Intervention:** ELX/TEZ/IVA plus ECM **Comparator:** ECM alone - consisting of recommended medications (such as mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, and corticosteroids) and physiotherapy	Treatment was assumed to impact disease progression through effects relating to $ppFEV_1$, weight for age score, and PE rate. Data on effectiveness was taken from key trials and ITC (Bucher method) undertaken for ECM

CADTH Common Drug Review, 2022, Canada[111]	**Perspective:** Canadian public health care payer **Discount rate:** 1.5% for costs and QALYs **Cost year:** N.R.	Same as earlier submission model structure (CADTH, 2021) Patient-level simulation model with a lifetime horizon (approximately 92 years)	This is an extension of the previously submitted and reviewed submission for those are 12+ focusing on those aged 6-11 years old Target population is patients with CF aged ≥ 6 years who have at least 1 *F508del* mutation in the CFTR gene. 4 genotypes considered in separate analyses: F/F, F/MF, F/RF and F/G inclusive of R117H	**Intervention:** ELX/TEZ/IVA plus ECM **Comparator** 1.ECM for all genotypes - consisting of mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, and corticosteroids) and physiotherapy. 2. LUM/IVA in patients with the F/F genotype, in combination with ECM 3. IVA in patients with the F/RF genotype, or the R117H mutation, in combination with ECM	Treatment impacts disease progression through effects relating to $ppFEV_1$,weight for age score, and PE rate sourced through the relevant clinical trials. Indirect treatment comparison was undertaken on patient level data as placebo-adjusted estimates were required
Pharmaceutical Benefits Advisory Committee (PBAC), 2021, Australia[211]	Perspective: N.R Discount rate: 5% for costs and QALYs Cost year: N.R	individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years	CF patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any)	**Intervention:** ELX/TEZ/IVA plus ECM **Comparator:** 1. TEZ/IVA in the F/F population; 2. TEZ/IVA in the F/RF population; 3. ECM in the F/MF population and the F/not yet characterised population	Treatment effectiveness was measured in terms of change in $ppFEV_1$, weight for age z score and PEs Changes in $ppFEV_1$ and weight for age score for patients on ELX/TEZ/IVA versus TEZ/IVA taken from an ITC conducted of Study 109 and EVOLVE (TEZ/IVA) in the F/F population and an ITC of Study 104 and EXPAND (TEZ/IVA) for the F/RF population
Lumacaftor/Ivacaftor (LUM/IVA)					

National Institute for Health and Care Excellence (NICE) - TA786, 2016[202]	**Perspective**: UK NHS **Discount rate**: 3.5% for costs and QALYs **Cost year**: 2014	Individual patient level micro-simulation model with a lifetime horizon Cycle length of 4 weeks for the first 2 years and 1 year thereafter	Cystic fibrosis patients homozygous for the *F508del* mutation (age 12+)	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM comprising daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, and daily physiotherapy	Main measure of treatment effect was change in $ppFEV_1$. This was taken from the pooled placebo-adjusted mean change from baseline in $ppFEV_1$ measured as the average of weeks 16 and 24 from TRAFFIC and TRANSPORT studies (increases by 2.8 percentage points by week 16 compared to starting $ppFEV_1$ and assumed to remain constant until week 24, irrespective of if they remained on treatment)
Scottish Medicines Consortium (SMC), 2016, Scotland[206]	**Perspective**: Scottish National Health Service **Discount rate**: 3.5% for costs and QALYs **Cost year**: N.R.	Individual patient state-transition microsimulation model Model cycle = four weeks for the first two years and annual thereafter	CF patients aged 12 years and older who are homozygous for the *F508del* mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM	Treatment effectiveness was measured through changes in $ppFEV_1$, PEs and weight for age z score taken from the TRAFFIC and TRANSPORT trials
Scottish Medicines Consortium (SMC), 2019a, Scotland[207]	Perspective: Scottish National Health Service health system Discount rate: N.R. Cost year: N.R.	individual patient state-transition microsimulation model Model cycle = four weeks for the first two years and annual thereafter	CF patients aged 6 years and older and aged 2 to 5 years who are homozygous for the *F508del* mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM	Treatment effectiveness was measured through changes in $ppFEV_1$, PEs and weight for age z score For patients aged 12 years + this data were from a pooled analysis of the TRAFFIC and TRANSPORT studies. For patients aged 6 to 11 years, taken from study 109 and study 011. For patients aged 2 to 5 years, there was no placebo-controlled evidence available.

CADTH Common Drug Review (CDR), 2016, Canada[200]	**Perspective**: Canadian public health care payer **Discount rate:** 1.5% for costs and QALYs **Cost year:** 2015	Patient simulation model with a lifetime horizon (100 years) - cohort of 6000 patients with base-case analysis based on 1000 replications of the simulated population Model cycle = four weeks for the first two years and annual thereafter	CF in patients aged 12 years + who are homozygous for the *F508del*-CFTR mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM consists of mucolytics, pancreatic enzymes, anti-inflammatory medications, and antibiotics for lung infections	Treatment effectiveness data based on TRANSPORT and TRAFFIC trials to inform changes in $ppFEV_1$, PEs and weight for age z score.
CADTH Common Drug Review (CDR), 2018, Canada[201]	**Perspective**: Canadian public health care payer **Discount rate:** 1.5% for costs and QALYs **Cost year:** 2017	Patient simulation model with a lifetime horizon (119 years) - cohort of 6000 patients with base-case analysis based on 1000 replications of the simulated population Model cycle = four weeks for the first two years and annual thereafter.	Target population is patients 6 years of age and older who are homozygous for the *F508del* mutation Includes analyses for patients 6-11 and age 12+ separately	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM consists of nutritional support, airway clearance, and treatment of clinical manifestations such as lung infections	Treatment impacts disease progression through effects relating to $ppFEV_1$,weight for age score, and PE rates. For the first 24 weeks of the model, changes in $ppFEV_1$ is taken from TRAFFIC and TRANSPORT studies for patients aged over 12 and the 809-109 study for patients aged between six and 12
Pharmaceutical Benefits Advisory Committee (PBAC), 2018b, Australia[203]	Perspective: N.R. Discount rate: N.R Cost year: N.R	Individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years and annual thereafter	CF patients aged 12+ homozygous for the *F508del* mutation	**Intervention:** LUM/IVA plus ECM. **Comparator:** ECM	Treatment effectiveness data taken from TRAFFIC & TRANSPORT trials to inform changes in $ppFEV_1$, PEs and weight for age z score
Pharmaceutical Benefits Advisory Committee (PBAC), 2018a, Australia[204]	Perspective: N.R. Discount rate: N.R Cost year: N.R	Individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years and annual thereafter	CF patients aged 6-11 homozygous for the *F508del* mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM	Data from Study 109 informed changes in $ppFEV_1$ for patients ages 6-11 while changes in weight for age z score were informed by TRAFFIC and TRANSPORT trials

Pharmaceutical Benefits Advisory Committee (PBAC), 2019b, Australia[205]	Perspective: N.R. Discount rate: N.R Cost year: N.R	Individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years and annual thereafter	CF patients aged 2–5 years who are homozygous for the *F508del* mutation	**Intervention:** LUM/IVA plus ECM **Comparator** ECM	Data from Study 109 informed changes in $ppFEV_1$ for patients ages 6-11 while changes in weight for age z score were informed by TRAFFIC and TRANSPORT trials
Dilokthornsakul, P., *et al.* 2017, USA[197]	**Perspective:** US payer **Discount rate**: 3% for costs and QALYs **Cost year**: 2016	Markov state transition model with five health states and a lifetime horizon: mild lung disease, moderate lung disease , severe lung disease , lung transplantation and death. Patients entered the model in one of the three health states reflecting lung disease severity Model cycle = 1 year Time horizon = lifetime	CF patients (25+) with homozygous phe508del mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM comprising of pancreatic enzymes, periodic intravenous antibiotics and dornase alfa	Data from TRAFFIC and TRANSPORT trials was used to inform treatment effect on $ppFEV_1$ which determined the probability of moving from moderate to mild health states and severe to moderate. Transition probability table not provided in report
Sharma, D *et al.*, 2018, USA[198]	**Perspective**: USA payer **Discount rate**: 3% for costs and QALYs **Cost year:** 2016	Markov state transition model with five health states and two transition states Model cycle = 1 year Time horizon = 10 years	12 year old CF patients with homozygous *F508del* mutation	**Intervention:** LUM/IVA plus ECM **Comparator:** ECM comprised of antibiotics, pancreatic enzymes, aminoglycosides (inhaled tobramycin as well as intravenously administered aminoglycosides) and DNase	Data from TRAFFIC and TRANSPORT trials informed changes in ppFEV1 and pulmonary exacerbations between the two treatment arms
Vadagam P *et al.*, 2018, USA[199]	**Perspective**: USA health care payer **Discount rate**: 3% for costs and QALYs	Described as a static decision model Time horizon = 1 year	CF patients 12 years + with homozygous *F508del* mutation	**Intervention:** Lumacaftor/ivacaftor plus standard of care **Comparator:** ECM comprised of bronchodilators, inhaled antibiotics, mucolytics (dornase	Efficacy measured a change in ppFEV1 sourced from the TRAFFIC and TRANSPORT trials

	Cost year: 2016			alfa, hypertonic saline), inhaled corticosteroid	
Tezacaftor/Ivacaftor (TEZ/IVA)					
Scottish Medicines Consortium (SMC), 2019b, Scotland[209]	Perspective: Scottish National Health Service health system Discount rate: N.R. Cost year: N.R.	individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years and annual thereafter.	CF patients 12 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation with residual function	**Intervention:** TEZ/IVA plus ECM. **Comparator:** ECM	Treatment effectiveness was measured through changes in $ppFEV_1$, PEs and weight for age z score (heterozygous population only) Data from the EVOLVE trial was used for homozygous patients and the EXPAND trial for heterozygous patients
Pharmaceutical Benefits Advisory Committee (PBACa), 2019, Australia[208]	Perspective: N.R. Discount rate: N.R. Cost year: N.R.	Individual patient state-transition microsimulation model - lifetime time horizon Model cycle = four weeks for the first two years and annual thereafter.	CF patients 12 years and older heterozygous for the *F508del* mutation with residual function	**Intervention:** TEZ/IVA plus ECM **Comparator:** ECM	Treatment effects based on Study 108. Changes in treatment effect over time based on extension study PROGRESS (LUM/IVA for patients homozygous for the *F508del* mutation) and large longitudinal registry analyses

Abbreviations: AE, Adverse events; ECM, Established clinical management; CADTH, Canadian Agency for Drugs and Technologies in Health; CDR, Common Drug Review; CF, Cystic Fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFTR, Cystic fibrosis transmembrane conductance regulator; ESC, Economics subcommittee; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; ICER, Institute for Clinical and Economic Review; LUM/IVA, Lumacaftor/ivacaftor; MF, minimal function; NICE, National Institute of Care and Excellence; N.R., Not reported; ppFEV1, percent predicted forced expiry volume in one second; PBAC, Pharmaceutical Benefits Advisory Committee; PE, Pulmonary exacerbations; RF, residual function; SMC, Scottish Medicines Consortium; TEZ/IVA, Tezacaftor/ivacaftor; F/F, two *F508del* mutations

Table 51. Changes made to Company submission in HTA organisation re-analyses

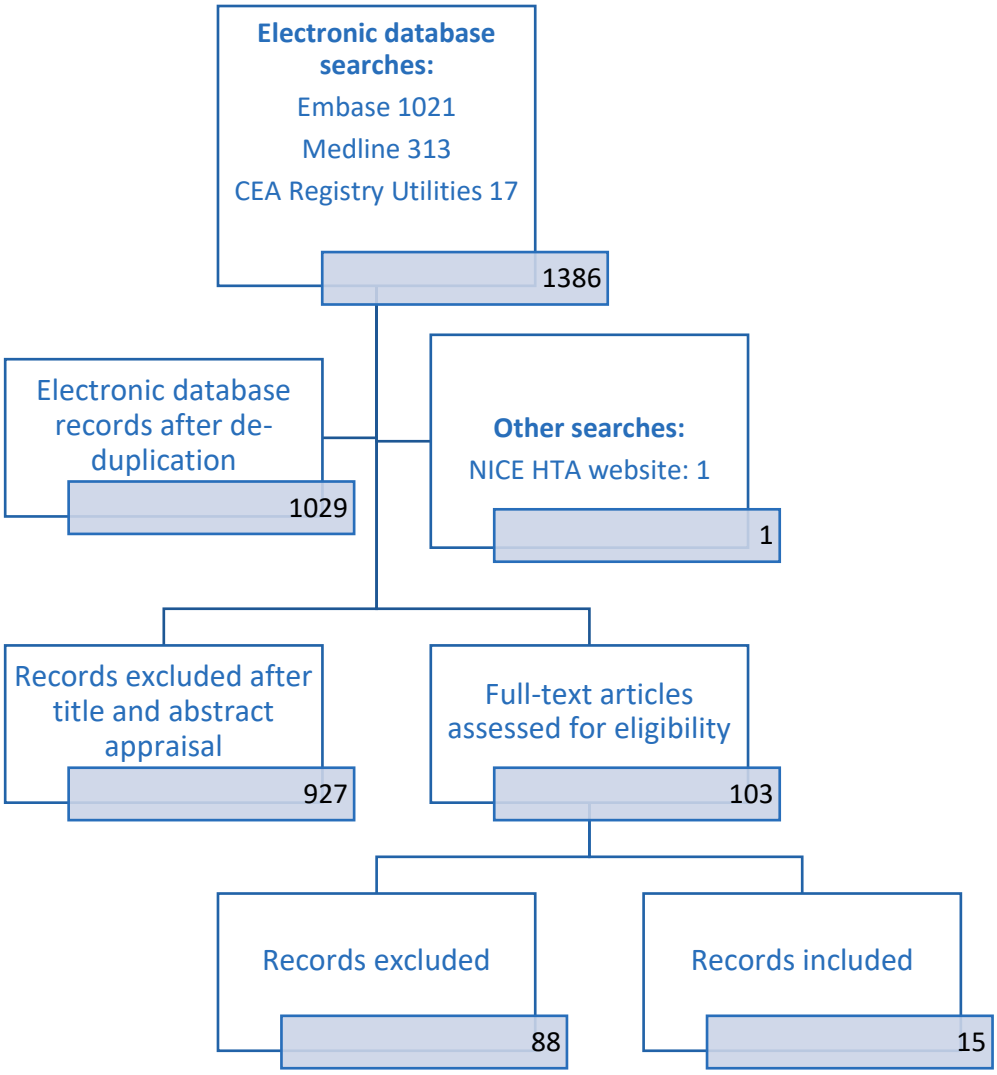
	PBAC 2019a (TEZ/IVA)[208]	CDR 2018 (LUM/IVA)[201]	CDR 2016 (LUM/IVA)[200]	NICE TA786 2016 (LUM/IVA)[202]	CDR, 2022[111]; CDR 2021[210] (ELX/TEZ/IVA and LUM/IVA)
$ppFEV_1$	0% decline in $ppFEV_1$ relative to ECM following the trial period, i.e. decline assumed equal to that of ECM instead of 42% applied by the Company	0% decline in $ppFEV_1$ relative to ECM following the trial period, i.e. decline assumed equal to that of ECM instead of 42% applied by the Company	0% decline in $ppFEV_1$ relative to ECM following the trial period, i.e. decline assumed equal to that of ECM instead of 42% applied by the Company	mean absolute change in $ppFEV_1$ from baseline was based on the 24-week time point data alone rather than the average of the 16-week and 24-week data	0% decline in $ppFEV_1$ relative to ECM following the trial period, i.e. decline assumed equal to that of ECM
Pulmonary exacerbations	Assume 0% reduction in PE instead of 45% applied by the Company (rate ratio 0.55)	Included the effect of $ppFEV_1$% on exacerbations but with no additional relative reduction in PEs compared to ECM	Included the effect of $ppFEV_1$% on exacerbations but with no additional relative reduction in PEs compared to ECM	N.C.	Assume PE rate ratio with modulators vs ECM after acute period is 1
Price reduction	0% price reduction in drug cost following loss of exclusivity	0% reduction in drug cost instead of Company's assumed 82%	0% reduction in drug cost instead of Company's assumed 82%	N.C.	0% price reduction in drug cost following loss of exclusivity
Treatment compliance	N.C.	N.C.	100% compliance assumed instead of Company's 88%, which reduces costs accordingly	96.5% instead of the Company's 90%	100% compliance assumed
Costs	N.C.	N.C.	N.C.	N.C.	Include disease management costs in period of survival benefit for patients on ELX/TEZ/IVA
	N.C.	N.C.	N.C.	N.C.	Equal inpatient and pharmacotherapy costs for both treatment arms
Other	N.C.	N.C.	N.C.	Discontinuation of LUM/IVA after the trial period (24 weeks) included	No utility increment for patients on ELX/TEZ/IVA instead of increment of 0.0785 applied by Company

Abbreviations: ECM, Established clinical management; CDR, Common Drug Review; CF, Cystic Fibrosis; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; ICER, Institute for Clinical and Economic Review; LUM/IVA, Lumacaftor/ivacaftor; NICE, National Institute of Care and Excellence; N.C., No change; ppFEV1, percent predicted forced expiry volume in one second; PBAC, Pharmaceutical Benefits Advisory Committee; PE, Pulmonary exacerbations; TEZ/IVA, Tezacaftor/ivacaftor

4.1.3 Results – HRQoL searches

The electronic database searches identified 1,386 potential publications. Upon removal of duplicates, 1,029 publications were screened against the eligibility criteria at title and abstract stage. After title and abstract assessment, 927 records were excluded, leaving a remaining 103 records to be assessed at full text stage. As previously noted, Following the title and abstract review it was decided that as the number of full texts to examine exceeded 100 publications, the pragmatic decision was taken to limit to UK studies full text search to identify the most relevant papers for this appraisal. Of the remaining 103 records, 15 publications were included. One of these studies is an earlier version of another and therefore details were extracted of 14 individual publications. The PRISMA flow diagram presented in Figure 6 details the inclusion and exclusions of studies at each stage of the review.

Figure 6. PRISMA diagram for HRQoL search



Of the 14 included publications, three were based on HTA submissions, 10 were full-text publications, and one was an abstract which detailed all the required information. The three HTA submissions were NICE technology appraisals for colistimethate sodium powder and tobramycin powder (TA276)[65], lumacaftor and ivacaftor combination therapy (TA398)[202] and an NIHR HTA report for ivacaftor monotherapy.[43] Both the HTA reports for colistimethate sodium powder and tobramycin powder and ivacaftor monotherapy included alternative utility values from previous publications and therefore details were also extracted in Table 52.

Of the 14 included publications, 12 reported EQ-5D data of which four additionally reported CRQ-R or SF-36 data as well. The remaining studies reported only CFQ-R or SF-36 data.

Of the 14 publications, 10 reported heath state utility values (HSUVs) according to ppFEV$_1$, with these percentages generally being grouped into mild (>70%), moderate (40%–70%) and severe (<40%), with some overlap in percentage groupings and severity between publications. The HSUVs assigned to each health state varied considerably between publications; for example, those reported by Acaster *et al.* 2015[214] describe a steady decline from a mild health state with a utility of 0.74 to a severe health state of 0.54, while those using the ivacaftor monotherapy and LUM/IVA clinical trials recorded utility from mild to severe of approximately 0.94 to 0.89, respectfully. Three of the studies devised health states according to occurrence and severity of pulmonary exacerbations.[44, 215, 216] On further investigation into the relationship between ppFEV$_1$ and utility by Tappenden *et al.*[217] in 2013, it was suggested that only one paper by Johnson *et al.*[218] had attempted to examine whether a statistical association exists between FEV$_1$ and EQ-5D utility. This study identified that such a relationship may exist; however, the size of the coefficient was very small and described as unlikely to be clinically meaningful.

A summary of the 14 included publications (reporting 12 unique studies) are provided in Table 52 and detailed data extractions can be found in Appendix 9.6.2.

Table 52. Publications identified in the health-related quality of life literature review

Study	Author, Year	HSUV's used from	Country	Measure	HSUVs according to
1	Acaster 2015[214]	Own study	UK	EQ-5D, CFQ-R	ppFEV$_1$ severity
2	Acaster 2019/22[219, 220]	Own study	UK	CFQ-R	Physical functioning, role functioning, emotion, vitality, breathing difficulty, cough, abdominal pain, body image.
3	Angelis 2015[52]	Own study	UK	EQ-5D-5L, VAS	N/A
4	Bell 2013[221]	Own study	France, UK, Germany, Australia and Ireland	EQ-5D-5L	CF responsible mutation
5	Bradley 2013[215]	Own study	UK	EQ-5D, CFQ-R	Pulmonary exacerbations
6	Cameron 2021 [216](abstract only)	Own study	UK	EQ-5D-5L, TTO	Pulmonary exacerbations
7	Solem 2016[44]	Own study – Uses Ivacaftor clinical trial data	UK	EQ-5D-3L, VAS	ppFEV$_1$, pulmonary exacerbations severity and time from events

8	NICE TA786 2016 (HTA)[202]	TRAFFIC and TRANSPORT clinical trials	N. America, Australia, European Union	EQ-5D-3L, CFQ-R	$ppFEV_1$
9	Tappenden 2013 (HTA)[217]	Bradley 2013	UK	EQ-5D	$ppFEV_1$ (mapped from results of Bradley study)
		Stahl 2005	Sweden	EQ-5D, SF-36	$ppFEV_1$
10	Tappenden 2014[222]	Bradley 2013	UK	EQ-5D	$ppFEV_1$
11	Tappenden 2017[223]	Bradley 2013	UK	EQ-5D	$ppFEV_1$
12	Tappenden 2023[224]	Wildman 2021	UK	EQ-5D-5L mapped to EQ-5D-3L	$ppFEV_1$
13	Whiting 2014 (HTA)[43]	Ivacaftor clinical trial	UK	EQ-5D	$ppFEV_1$
		Gee 2002	UK	SF-36	Disease severity
14	Wildman 2021[225]	Own study	UK	EQ-5D-5L	$ppFEV_1$

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire Revised; EQ-5D, EuroQol 5 Dimensions; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; HRQoL, health-related quality of life; HUI, health utilities index; SF-6D, short-form 6-dimension; SF-36, 36-item short-form health survey; TTO, time trade-off; UK; United Kingdom; VAS, visual analogue scale

4.1.4 Assessment of the Company's submission

In addition to the cost-effectiveness studies identified during the systematic review, the EAG also reviewed the economic models submitted as part of the Company submission. This is discussed in more detail below.

Interventions and comparators

The Company submitted three separate models for the treatments included in the MTA. No full incremental analysis was undertaken by the Company to compare treatments to each other. Treatments were instead each compared against ECM with the addition of ivacaftor monotherapy as a comparator for ELX/TEZ/IVA for patients with F/Gating mutation. This was not included as a comparator in the NICE final scope. The individual treatments used in ECM were not explicitly outlined and are applied in the model based on non-PE related disease management costs only.

Model structure

The three models used an individual patient simulation model, following the same structure as those previously mentioned in Section 4.1.2, based on a Cox proportional hazards (CPH) survival model published by Liou *et al.* 2001.[172] A patient's initial risk of death, referred to as the reference survival curve, is based on an age specific mortality hazard estimated from UK CF Registry data from 1985–2008, with a Weibull model fit to pooled Kaplan-Meier survival data by the Company. The median survival predicted by the Weibull model was [redacted]. Clinical experts to the EAG highlighted that standard care for CF patients, and in turn survival, has improved within the last decade, even prior to the introduction of CFTR modulators. UK CF Registry data shows that in 2013-17, prior to the use of any CFTR modulators, median survival was 47.0 years.[226] The EAG therefore considers that the data used to represent background mortality for CF patients in the Company's models is out of date and does not accurately represent standard of care in the UK without CFTR modulators. The Liou *et al.* 2001[172] survival model was developed based on an analysis of CF patients between the ages of 5.5 to 71 in the United States Cystic Fibrosis Foundation Patient Registry (US CFFPR) between 1993–1998. The purpose of this study was to predict 5-year survival in CF patients based on patient characteristics, whereas the model has been used by the Company to measure the impact of changes in these characteristics over time on survival. The Company notes that although this model was based on historical data, a re-analysis was published by Liou and colleagues in 2020[227] based on US CFFPR data from 1993–2016 that concluded that despite some changes in the coefficients of the model, the original coefficients were still found to be predictive of survival. The main difference found in the updated study is that the intercept of the logistic regression model is higher than in the original model, representing an improvement in overall survival of the population, which may result in the original model predicting survival probabilities that are too low when applied to more recent cohorts. The updated coefficients were not published for the Cox proportional hazards model, only the logistic regression, therefore these were not able to be updated in the Company's model.

Models for ELX/TEZ/IVA and TEZ/IVA include patients aged ≥6 years and LUM/IVA includes patients ≥2 years, based on the stated indications in the marketing authorisations for each treatment.[228-230] However, in the 2–5 age group for LUM/IVA, only age and discontinuation rates are tracked during this time period as $ppFEV_1$ is not used as a clinical measure in younger children. Clinical experts to the EAG confirmed that this was the case in clinical practice as spirometry is not used in these age groups and therefore measurement of $ppFEV_1$ is unavailable.

Treatment effectiveness

Treatment effectiveness was taken from the main trials for each treatment for the corresponding genotypes, with ITCs undertaken for the ELX/TEZ/IVA model (F/F age 6–11 and 12+; F/Gating age 12+; F/RF age 12+) to obtain placebo adjusted estimates (described in further detail in Section 3.2.2.1). When estimates were not available from trials, assumptions were made regarding equivalent treatment effectiveness compared to older age groups or alternative genotypes. In cases where no ITCs were possible, EAG's clinical experts suggested it is reasonable to assume equivalence between CFTRm efficacy between genotypes.

Long term decline in $ppFEV_1$ for the ECM group is based on a retrospective cohort study of patients from the US CFFPR.[3] This study compared annual rates of $ppFEV_1$ decline over 2-year periods between F/F and F/RF genotype patients. Different rates of decline in $ppFEV_1$ from this study for age groups 6–12, 13–17, 18–24 and 25+ are applied in the models. This assumed that for patients who remain alive past 25 years, there is an annual linear decline in $ppFEV_1$ of –1.86 for F/F, F/MF and F/Gating patients, and –1.06 for F/RF patients. Clinical experts to the EAG suggested that after age 30 the rate of decline tends to slow and therefore a linear decline in $ppFEV_1$ may be inappropriate.

The long-term effect of CFTR modulators is applied as a percent reduction of the rate of decline of ECM patients. For ELX/TEZ/IVA, this was 100% reduction in annual rate of decline (i.e., no change over time) based on a *post hoc* analysis of the long-term extension study.[231] The EAG notes that the data used to inform this figure from the long-term extension study is likely to be confounded with the impact of the COVID-19 pandemic, as clinical experts to the EAG suggested that shielding is likely to be responsible for improving/maintaining patient lung function during this time period, as was seen in clinical practice for patients on both ECM and CFTR modulators. Clinical experts also commented that no decline over time in $ppFEV_1$ is implausible as even healthy non-CF patients will experience a decline with age. However, it was suggested by one clinical expert that if ELX/TEZ/IVA is initiated in earlier age groups (age 2 or below), prior to established lung damage, then it may be plausible that $ppFEV_1$ decline could be comparable to healthy non-CF patients.

For LUM/IVA, the long term $ppFEV_1$ decline was assumed to be 42% of the rate of decline for ECM based on propensity score matching patients from the TRAFFIC[212] and TRANSPORT[213] trials, and the PROGRESS extension study to the US CFFPR. For TEZ/IVA, it was assumed to be 61.5% of the rate of decline for ECM based on propensity score matching patients from the EVOLVE and EXTEND trials to the US CFFPR. All studies assumed equal rate of decline for those age 6–11 based on data from patients 12+.

PEs which required antibiotics or hospitalisations are included in the model based on a relationship between $ppFEV_1$ and PE derived from the US CFFPR. A treatment effect of CFTR modulators is only applied for patients age 12+ as the Company state that trials were either not powered to detect a change in PEs in younger age groups or did not collect it as an efficacy outcome. This is deemed a conservative assumption. The treatment effect on PEs for patients aged 12+ is applied through a rate ratio derived in key trials and calibrating for the PEs experienced on CFTRm treatment relative to ECM that accounts for the acute improvement in $ppFEV_1$ seen in the key trials. This is done in order to avoid double counting the impact on $ppFEV_1$ and PEs. This calibrated rate, however, was applied for the lifetime of model. The EAG notes that the treatment effect for ELX/TEZ/IVA may also suffer from confounding due to COVID-19 as noted for $ppFEV_1$. As PEs are measured as a function of age and $ppFEV_1$ in the Company's model, this means that no PEs are assumed to occur in patients aged <6 as $ppFEV_1$ is not tracked in patients aged <6.

Compliance and discontinuations

The Company's models assumed varying compliance rates across the treatments and genotype groups, ranging from [redacted] for the trial duration period. In the post-trial period, a compliance rate of 80% is applied to all modulator treatments for all age groups based on a US admin claims study. This was implemented through a reduction in costs only and no change in treatment effectiveness is applied. The EAG notes that, although the compliance rate in clinical practice may be lower than that observed in the trials, if treatment efficacy is not being adjusted then the same source for compliance and treatment effectiveness should be applied in the model. Discontinuation rates were taken from the key trials and extension studies. Upon discontinuation patients receive the decline in $ppFEV_1$ for ECM, however they retain the acute increase in $ppFEV_1$. Beyond the time period of the extension study for each treatment no further discontinuations were assumed to apply. Clinical experts to the EAG suggested that they still see discontinuations in the longer term due to abnormal liver function tests, bowel function, and hair loss. It was also noted that some patients have discontinued for reasons linked to mental health although it is difficult to establish if this is treatment related.

HRQoL

The Company's models applied health state utilities stratified by $ppFEV_1$ grouping (<40, 40–70, >70). These utility values were based on [redacted]

[redacted] The EAG notes that this is a departure from the NICE Reference Case.[232] The Company stated that a disease specific preference measure was used as the EQ-5D failed to adequately capture meaningful differences in lung function, measured by $ppFEV_1$ in the ivacaftor monotherapy and LUM/IVA trials, which were the only modulator trials to collect EQ-5D data. In addition, the Company state that the high EQ-5D values observed at baseline in the ivacaftor monotherapy and LUM/IVA trial are above that of general population norms for the UK and suggest a ceiling effects in the EQ-5D, reflecting a patient's adaptation to a chronic condition. The EAG notes that a mapping algorithm is available from the CFQ-R to EQ-5D; however only six of the CFTR modulator trials measured scores on all three scales included in the measure, with the remaining studies only reporting the CFQ-R Respiratory domain.

Conclusions

The Company's model makes a number of deviations from the NICE Reference Case[232] including the use of a 1.5% discount rate for health outcomes and the use of non EQ-5D generated utility values. The EAG also notes a number of assumptions made that may be inappropriate or lack clinical validity. Due to these reasons, and a lack of full incremental analysis undertaken by the Company, the EAG undertook an independent analysis of the three included treatments.

4.2 Independent economic assessment

4.2.1 Methods

The systematic review of previously published cost-effectiveness analyses and the Company submission identified that there are no studies which compare all three interventions included within the scope of this appraisal (elexacaftor/tezacaftor/ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor) for the treatment of people with cystic fibrosis (CF) with at least one *F508del* mutation. As such, the EAG developed a *de novo* model that incorporated all three interventions included in the NICE final scope,[100] detailed below.

4.2.1.1 Population(s)

As described in Section 2.1, the population relevant to this MTA is people with CF with at least one *F508del* mutation. Analyses conducted are based on the genotype eligibility criteria specified in the current and expected marketing authorisation for each CFTR modulator combination therapy.[233-235]

Hence, the populations considered for this appraisal are:

- People with CF who are homozygous for the *F508del* mutation;[233-235]
    - This population is relevant for all three combination therapies and established clinical management (ECM).

- People with CF who are heterozygous for the *F508del* mutation and a residual function mutation or a gating mutation in the *CFTR* gene.

    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a residual function mutation is relevant for TEZ/IVA,[234] ELX/TEZ/IVA[235] and ECM, only.

    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a gating mutation is relevant for ELX/TEZ/IVA and ECM, only.[235]

The age patients are eligible to start treatment differs among the three modulator treatments and between genotypes, based on the current and expected marketing authorisation. Section 4.2.1.4 provides further detail on the interventions and the proposed analyses based on age for the cost-effectiveness analyses.

4.2.1.2 Model structure

The EAG developed a patient level microsimulation model which largely followed the structure of the models submitted in the Company submission and used in the previous NICE appraisal for LUM/IVA (TA786),[202] with amendments made where the original assumptions or parameters used were deemed inappropriate (to be discussed in upcoming sections). This is also the same model structure used by ICER in their independent assessments of CFTR modulators[195, 196] and re-analyses of the Company submissions produced by CADTH[111, 200, 201, 210] and PBAC,[208] as described earlier in Section 4.1.2. The EAG explored the use of alternative model structures during the model conceptualisation stage such as a cohort Markov model. However, due to consideration of the following points, it was decided that an individual simulation model was most appropriate to accurately reflect the average costs and benefits of the included treatments within this appraisal:

- The model population, consisting of both adults and children, includes patients with heterogenous characteristics, such as age, body mass index (BMI) and pancreatic sufficiency, which are expected to have a non-linear relationship with model outcomes and therefore a

cohort model using average patient characteristics may result in biased estimates of the average outcomes of the CF population to be modelled.

- $ppFEV_1$ used to measure lung function in CF patients (over the age of 6) is a continuous variable and the use of a cohort Markov state-transition model would require an arbitrary categorisation of the variable to produce defined health states. An individual simulation model allows the impact of all changes in disease progression measured through $ppFEV_1$ to be more accurately captured.
- Previous pulmonary exacerbations are expected to influence both the risk of future exacerbations and survival. A Markov state-transition model would likely require the use of tunnel states in order to incorporate patient history, which may become inefficient.
- A patient simulation model is able to incorporate the correlation between baseline characteristics over time, e.g. $ppFEV_1$ and exacerbations are not independent of each other, and the joint distribution changing over time. This would be challenging to implement in a Markov model resulting in a much more complex structure than modelling individual patients.

Due to the reasons described above, the EAG felt that to most accurately capture the heterogenous population being modelled and incorporate patient history, an individual simulation model was most appropriate.

A Cox proportional hazards model developed by Liou *et al.* 2001[172] is used to predict patient survival based on nine individual characteristics (age, sex, weight-for-age z score, $ppFEV_1$, number of pulmonary exacerbations, *Staphylococcus aureus* infection, *Burkholderia cepacia* infection, pancreatic sufficiency status and CF-related diabetes status [CFRD]). A patient's mortality hazard is updated in each model cycle to reflect changes in the following risk factors included in the Cox proportional hazards function: age, weight-for-age z score, $ppFEV_1$, number of pulmonary exacerbations, and development of CF-related diabetes. The remaining four characteristics do not change through the model lifetime and are set at baseline.

As discussed in Section 4.1.4, the Liou *et al.*[172] model was developed based on a USA cohort and the Company does not appear to have searched for any alternative models relative to the UK. In order to identify if a more relevant model to the UK was available, the EAG ran a targeted search for survival prediction models for the UK and identified Keogh *et al.* 2019.[171] This paper used a dynamic prediction model for survival in CF patients based on UK CF Registry data from 2005–2015 of

patients aged 18 and above. After a review of the paper, the EAG deemed it inappropriate to use these data to predict patient survival in the population of interest for this appraisal, which includes children, as the Keogh *et al.* 2019[171] prediction model has not been validated in younger age groups. Despite the Liou *et al*. 2001[172] model being based on a USA dataset, clinical experts to the EAG suggested that they do not expect to see large differences between the patient populations. Therefore, despite the limitations of Liou *et al.* 2001,[172] as mentioned in Section 4.1.4, the EAG deemed it the best available approach at the time of this appraisal to model CF survival based on individual patients characteristics.

The Cox proportional hazards model is applied to a reference survival curve in the first model cycle to represent mortality for CF patients in the UK, without the use of modulator treatments, reflective of ECM. As discussed in Section 4.1.4, the EAG deemed the reference survival curve used by the Company to be out of date and unreflective of the latest available data on CF survival pre-modulator treatments in the UK. The EAG therefore conducted a targeted search and identified a study conducted by Keogh *et al*. 2018,[236] which used UK CF Registry data from 2011–2015 to provide estimates of survival for CF patients. This study includes survival predictions for patients who are both homozygous and heterozygous for the *F508del* mutation. The EAG notes how these survival estimates will not be impacted by the introduction of ivacaftor monotherapy within the UK as this was not available for the genotypes included in this appraisal at the time of the analyses. As such, the EAG considers this to be the most up to date and relevant representation of CF population average survival for patients in the UK on ECM without modulator treatment.

The steps below detail the flow of patients in the simulation model, conducted for each comparator. The model uses a monthly cycle length for the first two years and annual after this time point.

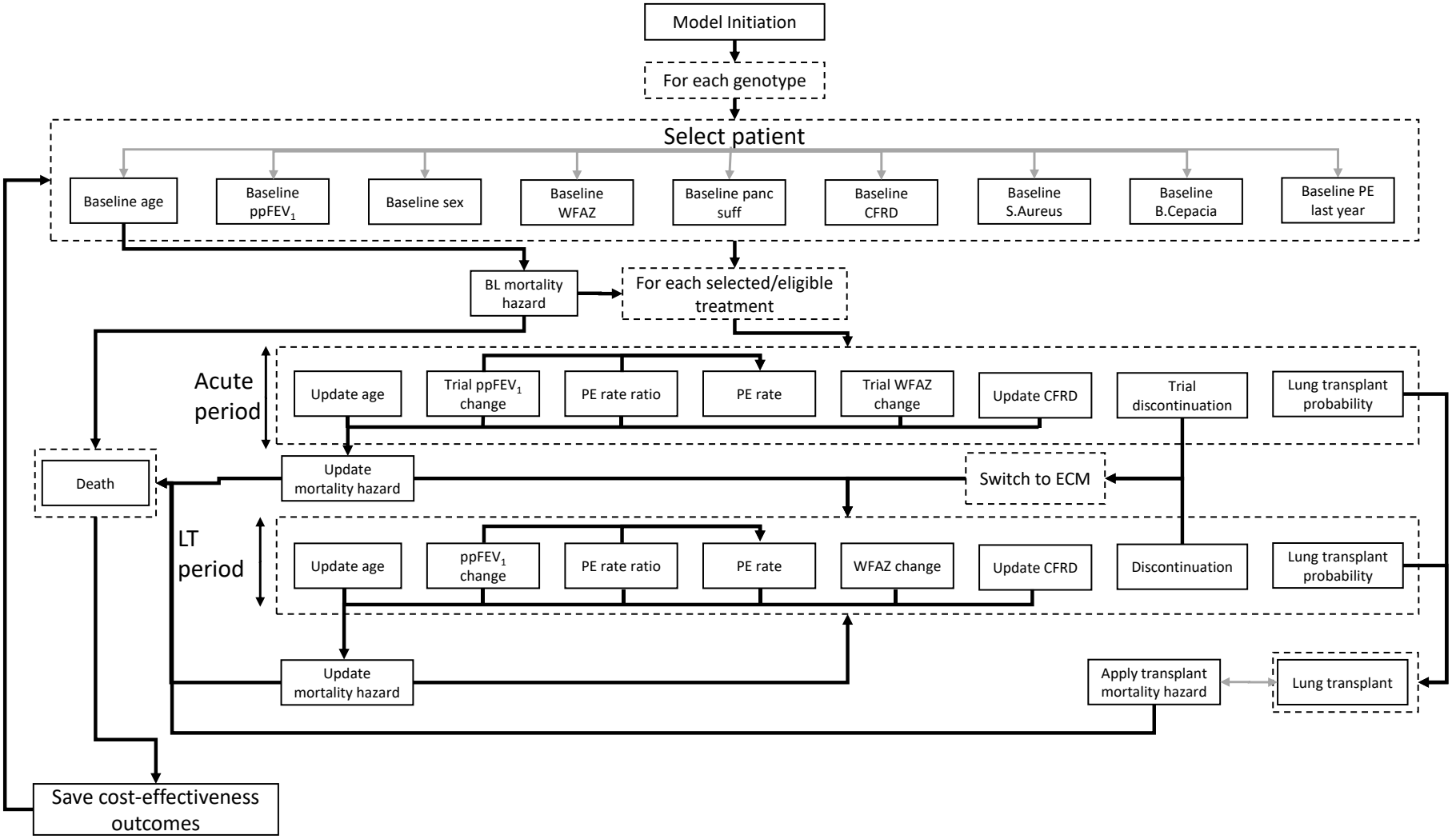
- Based on the relevant trial data, patient characteristics are defined for each individual.
- An age specific mortality hazard is assigned to the patient taken from the reference population survival curves from Keogh *et al.* 2018[236] in the first model cycle, based on patient starting age.
- Patient characteristics for age, $ppFEV_1$, PEs, weight-for-age z score and CFRD status in each model cycle are updated. All other characteristics are assumed to remain the same. The treatment effect of CFTR modulators is captured in the model through changes in patients' weight-for-age z score, $ppFEV_1$ and rate of PEs.

- Changes in patient characteristics since the previous model cycle are incorporated into the Liou *et al.* 2001[172] Cox proportional hazards model, which is used to update the hazard of death.
- Costs and utilities are assigned to each patient in each cycle.
- This process is repeated in each model cycle either until a patient discontinues CFTR modulator treatment (and therefore receives ECM only), has a lung transplant (and receives post lung transplant costs/utilities and risk of death for remaining cycles) or until a patient dies whereby the next patient is then simulated. Total costs and QALYs per patients are calculated.
- Each individual simulated patient is duplicated across every treatment arm of the model and steps 1-6 repeated.
- Average total costs and QALYs are calculated for each treatment arm.

As discussed, patient level models have the advantage of being able to easily incorporate patient heterogeneity over cohort-based models. However, they commonly have significantly longer run times, which is particularly evident in Microsoft Excel®. Therefore, in line with ISPOR good research practice for simulation models,[237] to reduce variance and the number of model runs required, the EAG ensured each population modelled for each treatment was identical through the use of common random numbers. The EAG tested the stability of results by comparing the average cumulative ICERs for each treatment compared to ECM when the model was run with different numbers of patients.

Stability for ELX/TEZ/IVA and TEZ/IVA was considered achieved with a smaller number of patients (~1000 and 1500, respectively) compared to LUM/IVA (2000). This was due to the EAG's efficacy estimates for LUM/IVA being similar to ECM in the long-term, and therefore the likelihood of mortality for individual patients was largely driven by random-number assignment rather than efficacy differences. In the EAG's base-case analysis, beyond the trial period duration, LUM/IVA has the same long term ppFEV$_1$ decline as patients on ECM, therefore resulting in LUM/IVA and ECM having similar model outputs over a lifetime (see 4.2.1.6.2). When the EAG tested this by applying a long-term treatment effect for LUM/IVA relative to ECM, the model stabilised with a smaller number of patients. As noted in NICE TSD 15,[238] a greater number of patients may be required if similar treatments are compared. There were 2000 patients were in the model base-case.

Figure 7. Individual simulation model diagram



Abbreviations: BL, baseline; CFRD, cystic fibrosis related diabetes; ECM, established clinical management, LT, long-term; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; panc suff, pancreaitc sufficiency status; WFAZ, weight-for-age z score

4.2.1.3 Time horizon, perspective and discounting

The time horizon of the model is lifetime (up to a maximum age of 100 years). The perspective of the analysis is the NHS and Personal Social Service (PSS) in England. Costs and QALYs have been discounted at 3.5%, as per the NICE reference case.[239]

4.2.1.4 Interventions and comparators

The interventions of interest as part of this MTA are LUM/IVA, TEZ/IVA and ELX/TEZ/IVA. All three interventions are combined with ECM. As noted in Section 4.2.1.1, the three interventions have marketing authorisation in different CF genotypes and age groups.

In order to compare the modulators against each other and undertake incremental analyses, they must be analysed within common populations. Therefore, the EAG analyses are separated based on genotype, detailed below and shown in Figure 8.

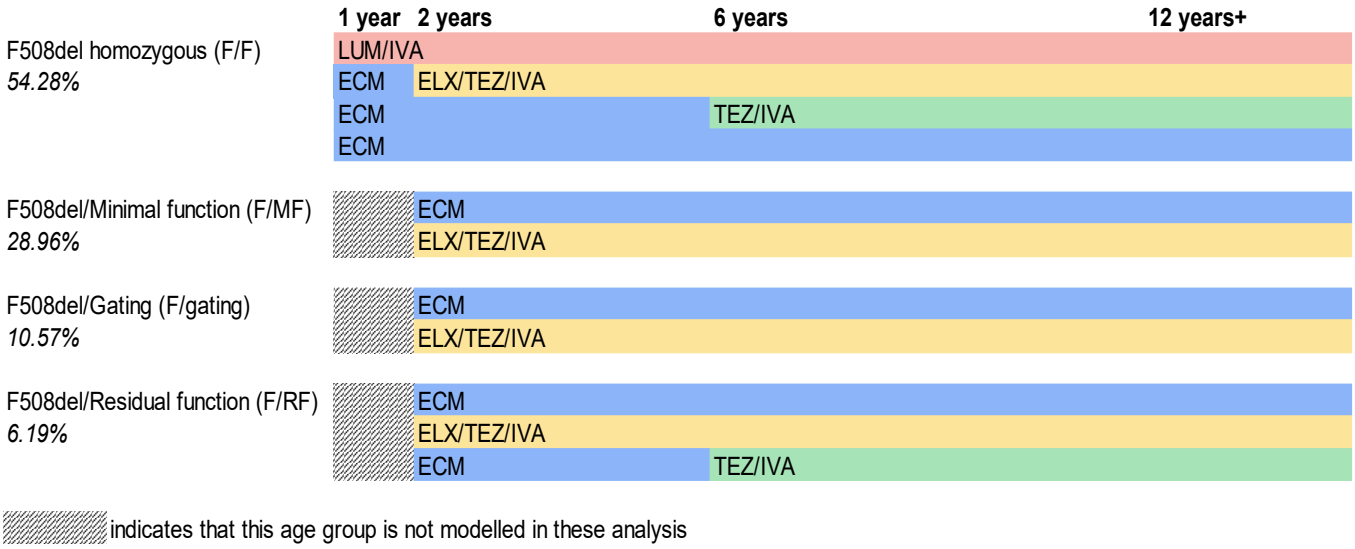
1. F/F population: ECM vs LUM/IVA vs ELX/TEZ/IVA vs TEZ/IVA. Patients will receive LUM/IVA from age 1, in line with the most recent marketing authorisation. In the ELX/TEZ/IVA treatment arm, patients aged 1-2 will receive ECM before switching to ELX/TEZ/IVA aged 2, based on expected marketing authorisation. In the TEZ/IVA treatment arm, patients aged 1–5 will receive ECM before switching to TEZ/IVA aged 6;

2. F/MF population: ECM vs ELX/TEZ/IVA for all patients aged 2+. Patients aged 1–2 are not included in this analysis;

3. F/Gating population: ECM vs ELX/TEZ/IVA for all patients aged 2+. Patients aged 1–2 are not included in this analysis;

4. F/RF population: ECM vs ELX/TEZ/IVA vs TEZ/IVA. In the TEZ/IVA treatment arm, patients aged 2–5 will receive ECM before switching to TEZ/IVA aged 6.

Figure 8. Main EAG analyses based on genotype



Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; ECM, established clinical management

ECM consists of a range of different therapies used to treat CF symptoms and symptoms associated with CF treatments, coordinated by a multidisciplinary team. The treatments used as part of ECM for CF patients can differ depending on lung function and co-morbidities, as described in Section 1.2.1.

4.2.1.5 Patient characteristics

The individual simulation model requires patient profiles that include data on the characteristics included in the Cox proportional hazards model used to estimate mortality, as described in Section 4.2.1.2. Individual baseline characteristics are sourced from either patient level trial data, assumptions or population data from the UK CF Registry, described in detail below. In addition, data are required on how those characteristics change over time, in the absence of CFTR modulators. For patients on ECM, only their age, $ppFEV_1$, pulmonary exacerbations and CFRD status changes within the model lifetime. Further details on the data sources and assumptions used for these variables are described below, excluding age, as this is updated in line with each model cycle.

4.2.1.5.1 Baseline characteristics

Patients' pancreatic sufficiency status is only included from the trials for patients with a F/RF or F/Gating mutation, with patients who are F/F or F/MF assumed to be pancreatic insufficient. Data was not available on changes in pancreatic sufficiency status overtime and so was assumed not to change over the model duration and therefore does not contribute to the risk of mortality. The EAG considers that this is likely a conservative assumption. Respiratory infections are also assumed not to

change over the model duration due to incidence data not being available to inform these changes and therefore do not impact on the mortality hazard equation. Assuming respiratory infections do not change over the patient's lifetime could be considered as a conservative approach as CFTR modulators have been shown to reduce respiratory infections in CF patients.

Patient's CFRD status at baseline was assumed to equal to that of the age-specific prevalence rate reported in the CF Registry Report 2021.[1] Data is only reported for patients aged 10–15 and ≥16, therefore the rates for age 10–15 were applied for patients aged 6–15. The 8.3% of patients in the model aged 6–15 at baseline are randomly assigned as having CFRD, while 35.2% of patients aged ≥16 are assigned as having CFRD. As this parameter is randomly assigned to patients, it assumes that CFRD it not related to other patient characteristics that are included in the model. All patients aged <6 are assumed not to have CFRD. Clinical advisers to the EAG noted that it is possible for patients <6 to have CFRD and there is evidence of impaired blood sugar control in younger age groups. However, younger patients are not screened for CFRD and therefore prevalence rates are not available.

Patients aged ≥6

Patient's aged ≥6 baseline data on age, sex, weight-for-age z score and ppFEV$_1$ were sourced from the various genotype-specific CFTR modulator trials (see Table 53), using the same approach and patient data as that employed by the Company. Patient data were only used from trials where patients had not previously been treated with a CFTR modulator or had undergone a washout period prior to patient screening. As patients with F/Gating mutations in the ELX/TEZ/IVA trials had received either ivacaftor monotherapy or TEZ/IVA previously, and were therefore not CFTR modulator naïve, patient profiles were taken from the ivacaftor monotherapy trials.

When the age distribution of patients for each genotype from the trial data was not reflective of that in the UK population, based on data from the CF registry 2018,[240] a weighted population was created by the Company and used by the EAG. Data used to inform this is shown in Appendix 9.8. This involved either oversampling or undersampling patients in particular age groups to ensure that the patient profiles included in the model from the trials was representative of the UK population.

Table 53 below details the patient numbers and details used in the model for patients aged ≥6 for each genotype.

Table 53. Details of patients used from key CFTR modulator trials in the economic model

Genotype	CTFR modulator trial used	Trial name	Patient ages	Patient numbers from trial	Total patient numbers included in the model post re-weighting
F/F	TEZ/IVA	661-106 (EVOLVE)	≥12	503	-
	LUM/IVA	809-103 and 809-104 (TRAFFIC/TRANSPORT	≥12	1,097	-
	LUM/IVA	809-011B and 809-109	6–11	257	-
	TEZ/IVA	661-113 and 661-115 (EMBRACE) - subset of patients with F/F only	6–11	113	-
	ELX/TEZ/IVA	445-106 - subset of patients with F/F only	6–11	28	-
				1,998	2,019
F/MF	ELX/TEZ/IVA	445-102	≥12	403	-
	ELX/TEZ/IVA	445-106 - subset of patients with F/MF only	6–11	39	-
	ELX/TEZ/IVA	445-116	6–11	121	-
				563	780
F/RF	TEZ/IVA	661-108 (EVOLVE)	≥12	244	-
	TEZ/IVA	661-113 and 661-115 (EMBRACE) - subset of patients with RF/F only	6–11	24	-
				268	289
F/Gating	Ivacaftor monotherapy	770-102 (STRIVE) – patients with *G551D* mutation	≥12	161	-
	Ivacaftor monotherapy	770-103 (ENVISION) - patients with *G551D* mutation	6–11	52	-
	Ivacaftor monotherapy	770-111 (KONNECTION) - patients with a non-*G551D* mutation	≥6	39	-
	Ivacaftor monotherapy	770-110 (KONDUCT) - patients with a *R117H* mutation	≥6	69	-
				321	417

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function

Patients aged <6

The model uses correlated patient characteristics from the trials (sex, weight-for-age z score and $ppFEV_1$). However, $ppFEV_1$ is not a measure that is obtained in clinical practice in patients aged <6, as spirometry is not used in this age group. Therefore, no baseline values of $ppFEV_1$, a key parameter in the survival model, are available from the trial data for this age group. In order to maintain the correlation between a patient's characteristics and have a value of $ppFEV_1$ available for patients aged 1–5 once they turn age 6, patient profiles of those aged 6–9 from each genotype were sampled to create a cohort of patients aged <6. To calculate the number of patients required in each genotype, the proportion of CF patients aged 2–5 for genotypes RF, MF and Gating (9.28%) and 1–5 for F/F genotype (11.98%) was sourced from the CF Registry 2021 by digitising the population pyramid (Figure 1.3, CF Registry Report 2021).[1] The number of patients aged 2–5 required for each genotype was greater than the total number of patients aged 6–9 for each genotype. Hence, in order to generate patients for the 2–5 age group, all patients aged 6–9 were used and additional patients aged 6–9 for each genotype were randomly sampled without replacement until the required number achieved. This method ensured that patients were not resampled more than once unless absolutely necessary. Sampled patients were then randomly assigned an age. Although using patients aged 6 only to sample from may have been more representative of patients aged 1–5, this would have greatly limited the total number of patients available to sample and resulted in many patients being resampled numerous times, therefore limiting the variability between patients. It is important to capture this variability due to the heterogenous patient characteristics in the CF population.

Table 54. Number of patients aged <6 added to total patient cohort

	F/F	F/MF	F/RF	F/Gating
Ages included	1–5	2–5	2–5	2–5
Total number of patients needed to be added	267	80	30	43

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function

4.2.1.5.2 $ppFEV_1$

Once the model has reached the time point equal to the length of trial period from which treatment effectiveness data is taken (see Section 4.2.1.6), patients' $ppFEV_1$ begins to decline. The EAG agrees with the Company that it is correct to model a long-term decline in $ppFEV_1$ related to a patient's age. The Company applied a linear annual rate of decline in $ppFEV_1$, separated by genotype (RF versus all remaining) and stratified by four age groups (6–12; 13–17; 18–24 and 25+) taken from Sawicki 2022.[3] This assumes that the same annual rate of decline for patients aged ≥25, equal to -1.06 for F/RF genotype and -1.86 for all remaining genotypes, is applied for the remainder of a patient's lifetime. In the Company's model, this results in patients on ECM reaching a $ppFEV_1$ of 15 around age 40–50, if remaining alive/not receiving a lung transplant. Clinical advisors to the EAG noted how the rate of decline in $ppFEV_1$ slows over time and the linear decline after age 30 may be slower than that suggested by the Company's approach. The EAG ran a targeted literature search for studies reporting decline in $ppFEV_1$ over time in CF patients. A study[17] was identified reporting on the different methodologies used to model the decline in $ppFEV_1$ and how these can produce inconsistent results. The study applied both linear and non-linear models to CF patients aged >6 years from the USA CFFPR, between the years 2003–2016. The best fitting model was a non-linear, stochastic mixed effects model. The study provided curves of the rate of change in $ppFEV_1$ against age, for the overall CF population (Figure 10) and the homozygous genotype only (Figure 9), which were digitised by the EAG using Engauge Digitizer,[241] to produce an estimate of annual $ppFEV_1$ rate of change for ages 6–75 to apply in the EAG's model. The EAG applied the digitised values from the *F508del* homozygous population for the F/F, F/MF and F/Gating mutations in the model. As evidence has shown that the F/RF group have a slower rate of decline due to a milder form of disease, the digitised values from the overall CF population was applied rather than the homozygous for the F/RF population.

Figure 9. ppFEV$_1$ rate of change for *F508del* homozygous population. Reproduced from Szczesniak *et al.* 2023, Figure 5.

Figure 9 above is reproduced from Szczesniak *et al.* 2023, Figure 5, which graphs the output of the non-linear stochastic mixed-effects model. Figure B, short dashed line curve which represents the homozygous *F508del* population was digitised by the EAG.

Figure 10. Population level ppFEV$_1$ rate of change for CF patients. Reproduced from Szczesniak *et al.* 2023, Figure 2

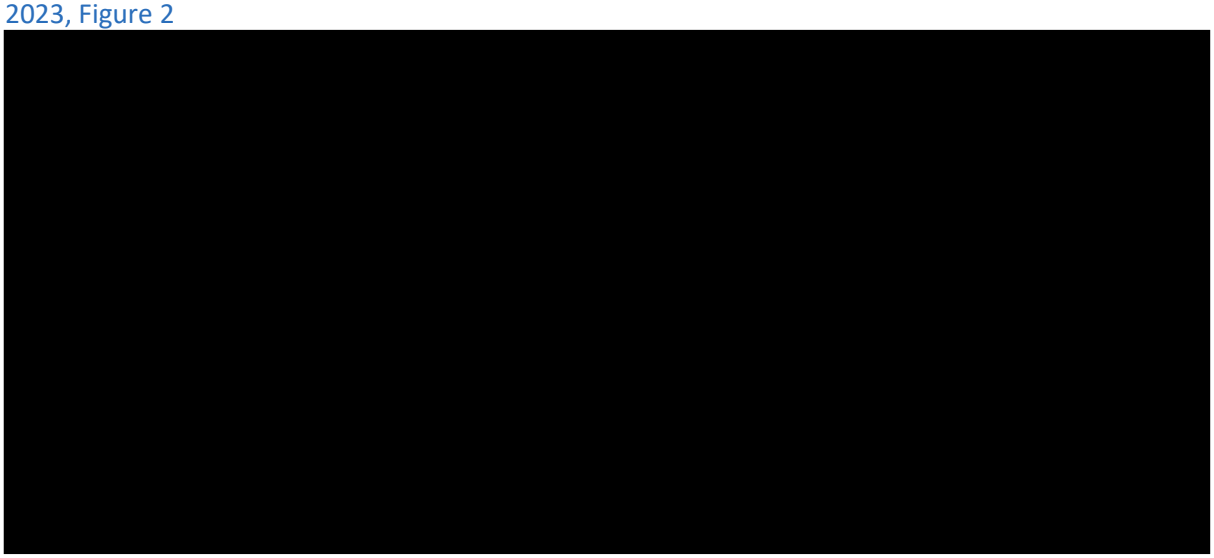


Figure 10 above is reproduced from Szczesniak et al. 2023, Figure 2, which graphs the output of the non-linear stochastic mixed-effects model. Figure D, stochastic model curve (circle symbol with solid line was digitised by the EAG.

4.2.1.5.3 Pulmonary exacerbations

The Cox proportional hazards model includes PEs that require hospitalisations or IV antibiotics. PEs are included in the model as a function of age and ppFEV$_1$. This is based on the formula derived by

Whiting *et al.* [43] in the ivacaftor monotherapy HTA which estimated the association between average annual PE rate and average $ppFEV_1$ for patients aged <18 and aged ≥18, shown below. This was based on data from the US CFFPR 2004 published in Goss *et al*.[242] The equation for <18s is applied to patients aged 6–18 only. PEs are assumed not to occur in patients aged <6. While clinical experts to the EAG considered that all patients are at risk of PEs, the EAG did not include PEs in patients aged <6. This is because the formula used to estimate PE is based on ppFEV1 and age, and ppFEV1 is not measured in clinical practice in younger patients (i.e. those <6). This is a similar assumption used in the Company's model.

$$\text{Average annual PE rate in patients aged 6 to <18} = 8.5938 \times \exp(-0.035 \times ppFEV_1)$$

$$\text{Average annual PE rate in patients aged ≥18} = 3.7885 \times \exp(-0.026 \times ppFEV_1)$$

4.2.1.5.4 CFRD status

Patients aged ≥6 who do not have CFRD at baseline are at risk of developing it over the lifetime of the model. The probability of a patient developing CFRD is based on incidence rates by age and sex, derived from a longitudinal study of the UK CF Registry data from 1996–2005[243], shown in Table 55. The EAG notes that this is historical data and the incidence of CFRD may have changed since this time period. Comparison of UK CF Registry data from 2009 reported that 3.3% of patients aged <16 and 26.8% of patients ≥16 were on treatment for CFRD compared to 8.3% and 35.5%, respectively, in 2021. This suggests that the incidence of CFRD may have increased from 2009 to 2021; however due to a lack of incidence data by age groups for the UK identified by the EAG, the older data was used. The EAG does not expect that this will have a large impact on the ICER.

Table 55. Annual incidence of CFRD by age group and sex

Age group	Male	Female
6–9	0.008	0.016
10–19	0.039	0.060
20–29	0.049	0.071
30–39	0.065	0.072
40–100	0.051	0.029

4.2.1.6 Treatment effectiveness

In the economic model, CFTR modulators are assumed to have a treatment effect on a patient's lung function, measured via $ppFEV_1$, number of PEs and weight-for-age z score. This may be considered a conservative assumption as some evidence has shown that CFTR modulators can also reduce the number of respiratory infections and development of CFRD or pancreatic insufficiency, if initiated at an early age. The initial treatment effect is applied for the duration of the trial period from which the efficacy data was sourced, referred to as the acute period. When relevant head-to-head data from randomised-controlled trial data were available, the EAG used effectiveness data sourced from the relevant trial. When these were not available, the results from the EAGs network meta-analysis (NMAs), described in Section 3.2.2.4. were used, along with assumptions when required. Details on the treatment effects applied in the model for the key clinical inputs are detailed below.

4.2.1.6.1 Acute change in $ppFEV_1$

4.2.1.6.1.1 Age 1–5

As previously noted, patients aged <6 do not have measures of $ppFEV_1$ available as this is not measured in clinical practice. Therefore, patients in the model aged 1–5 have had patient profiles assigned, sampled from patients aged 6–9, including a measure of $ppFEV_1$ at baseline. An acute increase in $ppFEV_1$ for patients aged 1–5 is applied as soon as patients initiate treatment. This increase is assumed to be equal to that of patients aged 6–11, sourced from the clinical trials or NMA data for the relevant genotype (see 4.2.1.6.1.2 for details). Although $ppFEV_1$ would not be measured in clinical practice for patients in this age group, applying this acute increase reflects the

improvement in lung function that patients may experience from initiating treatment at younger ages and avoided decline. No decline in $ppFEV_1$ is applied for patients until age 6 and the impact of any changes in $ppFEV_1$ is not implemented in the Cox proportional hazards model for mortality until patients are aged 6.

4.2.1.6.1.2 Age 6–11

The EAG model inputs for the acute increase in $ppFEV_1$ due to CFTR modulator treatment are shown in Table 56. These are in line with the EAG preferred data sources on clinical effectiveness discussed in detail in Section 3.2.2. An overview of the data used for different genotypes are treatments is described below:

- For the F/F genotype, increases in $ppFEV_1$ were taken from a placebo-controlled RCT for LUM/IVA, and from single-armed trials for ELX/TEZ/IVA and TEZ/IVA, see Section 3.2.2 Table 21, Table 24, and Table 30 for further detail.
- For F/MF genotype, the EAG applied the values observed in the placebo-controlled Phase 3 RCT of ELX/TEZ/IVA, in line with the Company model.
- Direct trial evidence for ELX/TEZ/IVA was not available in the F/Gating population. The EAG assumed an equivalent treatment effect as observed in the F/MF population, which the EAG clinical experts considered reasonable.
- Due to a lack of direct trial evidence for ELX/TEZ/IVA in F/RF population, as described in Section 3.2.2.5.6, the EAG multiplied the treatment effect observed in the F/RF 12+ population by [redacted], the relative reduction observed in the F/MF trial data between 6 to 11 years and 12+ years. For F/RF patients receiving TEZ/IVA, data was used from the single arm estimate of the Phase 3 RCT of TEZ/IVA in children aged 6 to 11.

Table 56. EAG preferred inputs for acute increase in $ppFEV_1$ for patients 6–11. Values also applied to patients aged <6

CFTR modulator treatment	Acute increase in $ppFEV_1$ (95% CI)	Acute period duration (weeks)	Data source
F/F genotype			
LUM/IVA	2.4 (0.4 to 4.4)	24	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA

ELZ/TEZ/IVA	11.2 (7.2 to 15.2)	24	Taken from single-arm estimate of Zemanick 2022
TEZ/IVA	2.8 (1.0 to 4.6)	24*	Taken from single-arm estimate of Davies 2021
F/MF genotype			
ELZ/TEZ/IVA	11.0 (6.9 to 15.1)	24	Mall 2022 (VX19-445-116) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating genotype			
ELZ/TEZ/IVA	11.0 (6.9 to 15.1)	24	Assumed equal to value for F/MF genotype
F/RF genotype			
ELZ/TEZ/IVA	6.776 (4.99 to 8.57) †	8	EAG analysis
TEZ/IVA	2.8 (1.0 to 4.6)	8	Single-arm estimate of Davies 2021

* This trial period was a duration of 8 weeks. To allow comparison across treatments the EAG assumed this treatment effect also applied for 24 weeks

† This CI was inputted by the EAG by applying the same width of that observed in the 12+ population

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; EAG, evidence assessment group, RCT; randomised controlled trial; $ppFEV_1$, percent predicted forced expiratory volume in 1 second

4.2.1.6.1.3 Age 12+

For patients aged 12+, direct trial estimates of the acute increase in $ppFEV_1$ were used when available. No randomised-controlled data were available for ELZ/TEZ/IVA for patients aged ≥12 with either F/F, F/Gating or F/RF populations. Therefore, the EAG conducted their own NMAs to obtain estimates of the acute increase in $ppFEV_1$ in these populations, as described in Section 3.2.2.4. The values obtained from the EAG's NMAs differ very slightly from the Company's estimates, but not enough to be expected to have an impact on the economic model outputs.

Table 57. EAG preferred inputs for acute increase in ppFEV1 for patients 12+

CFTR modulator treatment	Acute increase in $ppFEV_1$ (95% CI)	Acute period duration (weeks)	Data source
F/F genotype			
LUM/IVA	2.83 (1.84 to 3.82)	24	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA.

ELZ/TEZ/IVA	14.20 (12.07 to 16.31)	24	EAG NMA
TEZ/IVA	4.0 (3.1 to 4.8)	24	Taylor-Cousar 2017 (VX14-661-106) Phase 3 placebo-controlled RCT
F/MF genotype			
ELZ/TEZ/IVA	14.3 (12.7 to 15.8)	24	Middleton 2019 (VX17-445-102) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating genotype			
ELZ/TEZ/IVA	15.18 (12.16 to 18.22)	8	EAG NMA
F/RF genotype			
ELZ/TEZ/IVA	8.80 (7.01 to 10.61)	8	EAG NMA
TEZ/IVA	6.8 (5.7 to 7.8)	8	Rowe 2017 (VX14-661-108) Phase 3 placebo-controlled crossover RCT of TEZ/IVA

Abbreviations: EAG, evidence assessment group; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; NMA, network meta-analysis; RCT, randomised controlled trial; CI, confidence interval

4.2.1.6.2 Long term change in $ppFEV_1$

As discussed in Section 3.2.2.6, the long-term effectiveness of CFTR modulator treatments on the change in $ppFEV_1$ is subject to a high degree of uncertainty. This is due to no available RCT evidence outside of the acute phase, a maximum follow-up duration of 144 weeks in non-RCT studies and confounding of long-term data for ELX/TEZ/IVA due to COVID-19 in the managed access agreement (MAA) final analysis data. Therefore, assumptions based on the best data available to the EAG were made to inform the long-term change in $ppFEV_1$ for the three CFTR modulator treatments.

In the EAG base case, a relative reduction in the rate of $ppFEV_1$ decline is applied for ELX/TEZ/IVA and TEZ/IVA. To calculate this relative reduction, the EAG used the Newsome 2022[178] estimate of rate of decline of IVA-treated patients in the UK CF Registry (see Section 3.2.2.6.2). However, Newsome 2022 only reported the absolute reduction in the rate of ppFEV1 decline between IVA treated patients and controls, and did not report the relative reduction in $ppFEV_1$ decline or the absolute slopes for either IVA-treated or control-patients. Hence, in order to estimate the relative reduction in $ppFEV_1$ decline that would have been observed in Newsome 2022[178] the EAG searched for alternative data on the absolute rate of $ppFEV_1$ decline of IVA eligible patients in the UK CF

Registry during the Newsome 2022 study period. Through bibliography searching of a relevant systematic literature review,[244] the EAG identified Newsome 2018.[245]

Newsome 2018[245] reported the absolute rate of ppFEV$_1$ decline of patients who were later treated with IVA in the UK CF Registry, i.e., a cohort similar to the Newsome 2022 cohort as both studies used UK CF registry data of people treated with IVA between 2010 and 2015 (Newsome 2018), and 2008 and 2016 (Newsome 2022). In Newsome 2018, the average annual rate of ppFEV$_1$ decline of patients later treated with IVA in the UK CF Registry was –1.3% (95% CI: –1.9% to –0.6%), over the 3 years prior to treatment. Hence, the EAG estimated a relative reduction in ppFEV$_1$ decline for Newsome 2022 of 0.49/1.3 = 37.7% for people treated with IVA. The EAG applies this value for the relative rate of decline for ELX/TEZ/IVA in their base-case analysis. The EAG considered applying the estimate from data based on ivacaftor monotherapy likely to be conservative. As such, the EAG scaled the 37.7% estimate of the IVA treatment effect by the ratio of the IVA to the ELX/TEZ/IVA acute treatment effect from the EAG's NMA. Using this approach, the estimate for the relative reduction in the long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA is 61.0% (37.7*[15.18/9.38]). The EAG does not consider this value to be conservative, and notes that, as the long-term treatment effect of CFTR modulators on ppFEV$_1$ is applied for a person's lifetime in the economic model, there is a high degree of uncertainty around the most appropriate value. The EAG notes that applying the 37.7% relative reduction directly from the IVA estimate provides a reasonable lower estimate that confers less decision risk, and the EAG has provided a scenario analysis using this value.

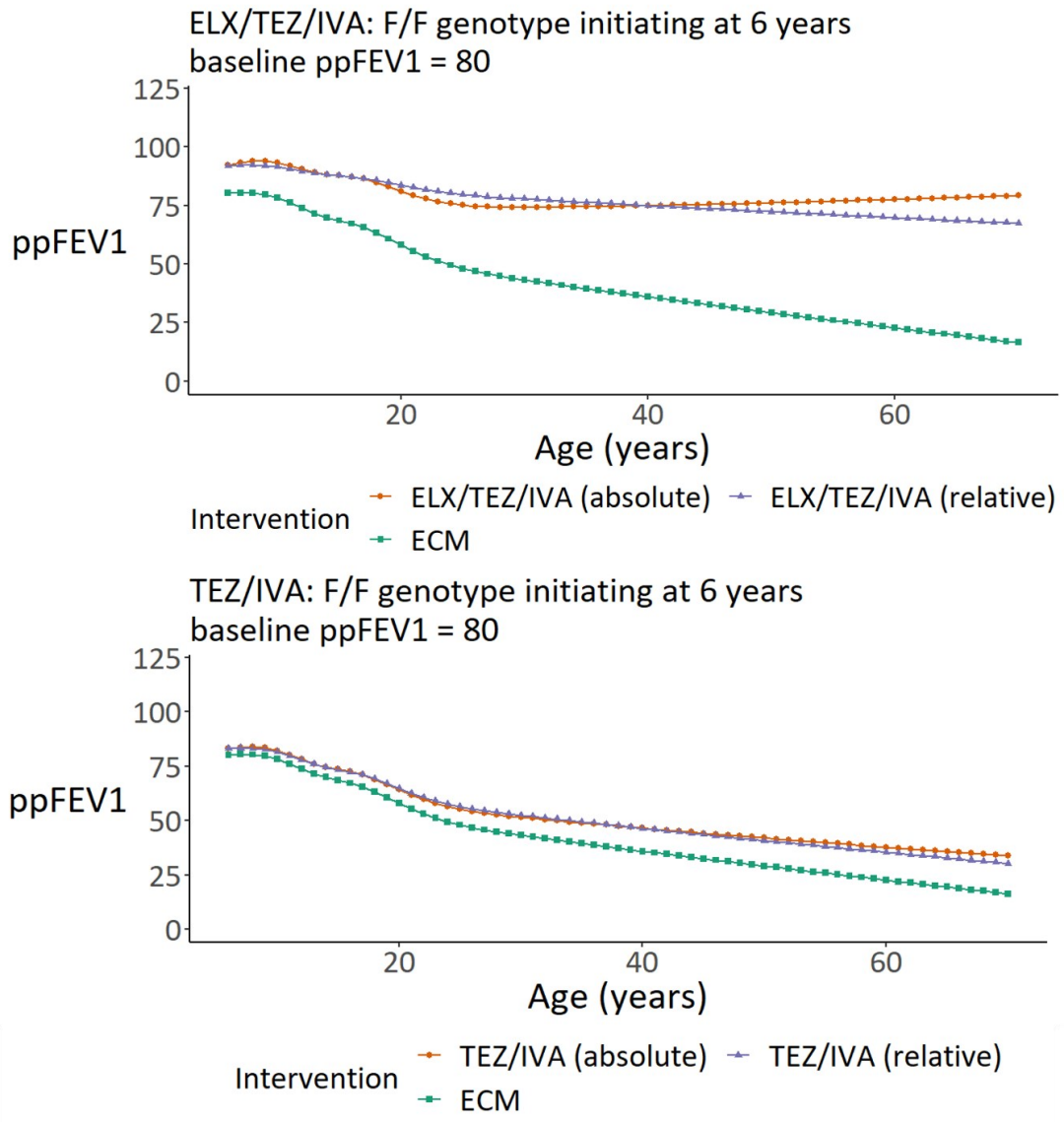
As noted in Section 3.2.2.6, the EAG does not consider the long-term data available for TEZ/IVA and LUM/IVA to provide a reliable estimate of the treatment effect in the post-acute period. For LUM/IVA, the EAG notes that no robust evidence has been presented or identified to suggest that LUM/IVA causes a long-term slowing in the rate of ppFEV$_1$ decline compared to ECM. Therefore, the EAG applied a 0% relative reduction in decline compared to ECM, meaning that in the post-acute period, patients on LUM/IVA have the same annual rate of decline in ppFEV$_1$ as patients on ECM alone. Although the EAG did not identify any robust evidence for a slowing in the reduction in ppFEV$_1$ decline for TEZ/IVA, based on the data observed in the acute period, it is expected that it would have a greater impact than LUM/IVA but smaller than that of TEZ/IVA. Therefore, for TEZ/IVA the EAG applied the ratio of the acute effects observed in the aged 12+ F/F populations for TEZ/IVA (4.0) and ELX/TEZ/IVA (14.2) to the calculated relative reduction in the rate of decline applied to the ELX/TEZ/IVA arm to give a relative reduction in ppFEV$_1$ compared to ECM of 17.2% for TEZ/IVA (see Section 3.2.2.6.3).

The EAG preferred to implement a relative reduction in the rate of $ppFEV_1$ decline, rather than the absolute reduction reported in Newsome 2022,[178] as relative effect measures are less affected by baseline risk than absolute measures, and are therefore usually more transportable and consistent between studies.[246-248] However, to test the sensitivity of the EAG base case to applying an absolute versus relative reduction in $ppFEV_1$, the EAG performed a scenario analysis applying a scaled Newsome 2022 estimate of IVA for ELX/TEZ/IVA (+0.79 per year slower decline than ECM), and scaled this estimate for TEZ/IVA (+0.22 per year slower decline than ECM).

The Newsome 2022 estimate used an linear regression model adjusted for the following covariates: sex, age, ethnicity, smoking status, CFRD, $ppFEV_1$, IV antibiotic use, mucolytic treatment use and bacterial infection.[178] As such, the +0.49 ivacaftor estimate is a population average effect but also a conditional estimate based on each of the covariates in the model, i.e., it is an estimate of the absolute difference in the rate $ppFEV_1$ decline between IVA-treated patients and matched controls with the same baseline $ppFEV_1$, age, etc.

To visualise the impact of applying an absolute or relative reduction in $ppFEV_1$ associated with ELX/TEZ/IVA or TEZ/IVA therapy, Figure 11 displays the modelled long-term rate of $ppFEV_1$ decline of a 6-year old person with CF and an F/F genotype who: i) received ECM only, iii) initiated treatment with a CFTR modulator with the EAG's absolute reduction in rate of $ppFEV_1$ applied, and ii) initiated treatment with a CFTR modulator with the EAG's relative reduction in rate of $ppFEV_1$ applied. The absolute and relative reduction curves produce similar results, but diverge at larger ages. This divergence is due to the modelled non-linear rate decline of $ppFEV_1$ on ECM being lower at higher ages, such that an absolute reduction for ELX/TEZ/IVA provides implausible estimates of $ppFEV_1$ change at higher ages (e.g., suggesting the population average $ppFEV_1$ increases with age).

Figure 11. Absolute and relative reductions in decline of ppFEV1 applied in EAG base case and scenario ages. Simulated for F/F genotype initiating treatment aged 6 years with a baseline $ppFEV_1$ of 80.



4.2.1.6.3 Change in PEs

As trials in younger age groups were either not powered to detect a difference in PEs or did not collect data on PEs, the EAG applied a treatment effect for the impact of CFTR modulators on the rate of PEs (requiring antibiotics or hospitalisation) only for patients aged ≥12. This is considered a conservative assumption and similar to that applied in the Company model.

The treatment effect for patients aged ≥12 is applied as a rate ratio in the model. In NICE TA786 for LUM/IVA, the EAG noted that as the annual rate of PEs is a function of a patients $ppFEV_1$ value, which has a separate treatment effect applied, the observed change in PEs in the model may be caused by the change in $ppFEV_1$ and there is a risk of double counting the treatment effect of CFTR modulators if applying separate treatment effects to both $ppFEV_1$ and PEs. To adjust for this risk of double counting in the Company's MTA submission, calibration techniques were used to derive a rate ratio for PEs when receiving CFTR modulators compared to ECM in order to account for the acute $ppFEV_1$ increase. The EAG applied the same calibration approach; however unlike the Company's analyses, discontinuations were possible during the EAG's calibration. In addition, the rate ratios observed in the trials were based over a 24 week period, therefore, the EAG set the model time horizon to 1 year when undertaking the calibration as this was closest timeframe to that of the trial. The data sources used to inform the initial rate ratio values are described in Table 58, alongside the adjusted value following calibration. The EAG does not believe that any robust evidence was provided to show that the effects of CFTR modulators on the rate of PEs, independent of the $ppFEV_1$ effect, exists beyond the acute period. For both LUM/IVA and TEZ/IVA, the estimated PE event rates from the initial placebo-controlled trials appeared to increase when compared to the observational extension studies, whereas the event rates for ELX/TEZ/IVA long-term extension studies and final analysis of the MAA are likely to be biased due to the protective effect of COVID-19 shielding. Therefore, the EAG's base case analysis only applies the calibrated rate ratio for PEs in the acute period. No further separate treatment effect on PEs beyond that applied through the effect on $ppFEV_1$ is applied in the long-term.

Table 58. Change in the rate of pulmonary exacerbations for patient's aged 12+

CFTR modulator treatment	PEs rate ratio (uncalibrated)	PEs rate ratio (calibrated)	Data source for uncalibrated rate ratio
F/F genotype			
LUM/IVA	0.44	[redacted]	Wainwright 2015 (VX12-809-103) and (VX12-809-104) Phase 3 placebo-controlled RCTs of LUM/IVA in participants aged 12+ years
ELZ/TEZ/IVA	0.22	[redacted]	Assumed equivalent to patients with F/MF genotype

TEZ/IVA	0.53	[redacted]	Taylor-Cousar 2017 (VX14-661-106) Phase 3 placebo-controlled RCT in people with CF aged 12+ with F/F genotype
F/MF genotype			
ELZ/TEZ/IVA	0.22	[redacted]	Middleton 2019 (VX17-445-102) was a placebo-controlled Phase 3 RCT of ELX/TEZ/IVA, F/MF patients
F/Gating genotype			
ELZ/TEZ/IVA	0.22	[redacted]	Assumed equivalent to patients with F/MF genotype
F/RF genotype			
ELZ/TEZ/IVA	0.22	[redacted]	Assumed equivalent to patients with F/MF genotype
TEZ/IVA	0.54	[redacted]	Rowe 2017 (VX14-661-108) Phase 3 placebo-controlled crossover RCT in people with CF aged 12+ with F/RF genotype

Abbreviations: CF; cystic fibrosis; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function, RCT, randomised controlled trial; PE, pulmonary exacerbation

4.2.1.6.4 Change in weight-for-age z score

A treatment effect on a patient's weight-for-age z score (mean increase) is applied during the acute period, in line with the trial durations, in which patients on CFTR modulators experience an increase in the weight-for-age z score from baseline. It is assumed that no decline in weight-for-age z score is experienced over a patient's lifetime. The EAG's clinical experts noted that there are many complexities associated with a patient's weight while on CFTR modulators. These treatments have been shown to help patients maintain weight but also potentially gain excessive weight long term due to following previous advice of a high calorie diet before CFTR modulator treatments were available. Therefore, the EAG considers it a reasonable assumption to have no decline in weight-for-

age z score over a patient's lifetime. Further details on the treatment effectiveness on weight-for-age z score are provided below.

4.2.1.6.4.1 Age 1–5

As described in Section 3.2.2.1.3, trial data for LUM/IVA was available for F/F genotype patients aged 1–2 and aged 2–5. In patients aged 1–2 an increase in weight-for-age z score of 0.06 was observed. A higher increase was observed in patients aged 2–5, with an absolute increase of 0.13 or 0.20 when placebo adjusted. The ELX/TEZ/IVA trial observed an increase in weight-for-age z score for patients aged 2–5 with either F/F or F/MF genotype that was [redacted] than that observed for LUM/IVA, with an absolute increase of [redacted]. As no change beyond the acute increase is assumed over the patient's lifetime in the model, only applying an acute increase of [redacted] for ELX/TEZ/IVA patients starting aged 2–5 was considered overly conservative by the EAG as this would not capture the long-term benefits expected from ELX/TEZ/IVA. Therefore, the EAG applied the values observed in patients aged 6–11 for patients aged 1–5 for both LUM/IVA and ELX/TEZ/IVA. These are described and listed in the following section.

4.2.1.6.4.2 Age 6–11

The EAG model inputs for the acute increase in weight-for-age z score due to CFTR modulator treatment are shown in Table 59. These are in line with the EAG's preferred data sources on clinical effectiveness discussed in detail in Section 3.2.2.1 and clinically plausible assumptions when required. An overview of the data used for different genotypes are treatments is described below.

- For the F/F genotype, estimates were sourced from direct trial evidence for LUM/IVA and ELX/TEZ/IVA. The trial estimates for TEZ/IVA showed a decrease in weight-for-age z score relative to ECM which the EAG considered implausible and therefore applied a value of 0.
- For F/MF genotype, the EAG applied the values observed in the placebo-controlled Phase 3 RCT for ELX/TEZ/IVA.[134]
- Direct trial evidence for ELX/TEZ/IVA was not available in the F/Gating population. The EAG assumed an equivalent treatment effect as observed in the F/MF population, which the EAG's clinical experts considered reasonable.
- Due to a lack of direct trial evidence for ELX/TEZ/IVA F/RF population, as described in Section 3.2.2.5.6, the EAG took the midpoint of the treatment effect observed in the 12+

F/RF population when multiplied by [redacted] and [redacted], the observed reduction in weight-for-age z-score treatment effect between the 12+ years and 6 to 11 years groups in the F/MF and F/F genotypes. For F/RF patients receiving TEZ/IVA, the same assumption made for F/F patients was applied, with zero increase in weight-for-age z score.

Table 59. EAG preferred inputs for acute increase in weight for age z score for patients 6–11. Values also applied to patients aged <6

CFTR modulator treatment	Acute increase in weight-for-age z score (95% CI)	Acute period duration (weeks)	Data source
F/F genotype			
LUM/IVA	[redacted]	24	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA
ELZ/TEZ/IVA	[redacted]	24	Taken from single-arm estimate of Zemanick 2022
TEZ/IVA	0	24	EAG assumption
F/MF genotype			
ELZ/TEZ/IVA	[redacted]	24	Mall 2022 (VX19-445-116) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating genotype			
ELZ/TEZ/IVA	[redacted]	24	Assumed equal to value for F/MF genotype
F/RF genotype			
ELZ/TEZ/IVA	[redacted]	8	Assumptions
TEZ/IVA	0	8	EAG assumption

* This trial period was a duration of 8 weeks. To allow comparison across treatments the EAG assumed this treatment effect also applied for 24 weeks

† This CI was inputted by the EAG by applying the same width of that observed in the 12+ population

Abbreviations: CI, confidence interval; EAG, evidence assessment group; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; RCT, randomised controlled trial

4.2.1.6.4.3 Age 12+

Direct trial evidence informed the treatment effectiveness estimates for the LUM/IVA F/F genotype and TEZ/IVA F/F and F/RF populations. Treatment effectiveness estimates for ELX/TEZ/IVA were sourced from the EAG's NMAs, described in further detail in Section 3.2.2.4. The weight-for-age z score model inputs for patients aged ≥12 are shown below in Table 60.

Table 60. EAG preferred inputs for acute increase in weight for age z score for patients aged 12+

CFTR modulator treatment	Acute weight-for-age z score (95% CI)	Acute period duration (weeks)	Data source
F/F genotype			
LUM/IVA	[redacted]	24	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA.
ELZ/TEZ/IVA	[redacted]	24	EAG NMA
TEZ/IVA	[redacted]	24	Taylor-Cousar 2017 (VX14-661-106) placebo-controlled Phase 3 RCT of TEZ/IVA
F/MF genotype			
ELZ/TEZ/IVA	[redacted]	24	Middleton 2019 (VX17-445-102) placebo controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating genotype			
ELZ/TEZ/IVA	[redacted]	8	EAG NMA
F/RF genotype			
ELZ/TEZ/IVA	[redacted]	8	EAG NMA
TEZ/IVA	[redacted]	8	Rowe 2017 (VX14-661-108) Phase 3 placebo-controlled crossover RCT of TEZ/IVA

Abbreviations: CI, confidence interval; EAG, evidence assessment group; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; NMA, network meta-analysis, RCT, randomised controlled trial

4.2.1.7 Treatment discontinuation

4.2.1.7.1 Acute period discontinuations

Annual treatment discontinuation rates were calculated for the acute period, corresponding to the appropriate trial duration, based on the number of discontinuations recorded in the trial. Further detail on the rates and data sources used for each of the three CFTR modulator treatments is detailed below. The discontinuation rates used by the EAG for the acute period are the same as those applied by the Company, with the exception of patients aged 2–5 on ELX/TEZ/IVA as this age group was not included in the Company's model. Upon discontinuing CFTR modulator treatments, patients receive ECM only, with the associated costs and annual ppFEV$_1$ decline. Clinical experts to the EAG noted that upon stopping treatment with CFTR modulators, they observe patients rapidly decline and feel worse in a short time frame. Based on this, the EAG assumes that both the acute increase in ppFEV$_1$ and weight-for-age z score is lost upon discontinuation.

4.2.1.7.1.1 ELX/TEZ/IVA

The rate of discontinuations for patients aged 2–5 was taken from Study 445-111,[159] the Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5. As data was only available for F/F and F/MF patients, the same rate was also applied for patients with F/Gating and F/RF genotypes. In patients aged 6–11, pooled data for both F/F and F/MF patients aged 6–11 in Zemanick 2021[135] (VX18-445-106) was used to calculate the discontinuation rate for F/F patients due to the small sample size. These data were assumed to also apply to patients with F/Gating and F/RF genotypes due to lack of data in these patient groups. For patients with F/MF genotype, discontinuation data was calculated directly from Mall 2022 (VX19-445-116),[134] the placebo-controlled Phase 3 RCT of ELX/TEZ/IVA in children with CF aged 6 to 11 with an F/MF CF genotype. For discontinuation rates for patients aged 12+, the genotype specific trials with the longest durations were used, as reported in Table 61.

Table 61. ELX/TEZ/IVA acute period discontinuation rates

Genotype	Acute period (weeks)	Annual rate of discontinuations	Source
Age 2–5			
F/F	24	[redacted]	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/MF	24	[redacted]	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/Gating	24	[redacted]	Assumed equal to F/F and F/MF

F/RF	24	[redacted]	Assumed equal to F/F and F/MF
Age 6–11			
F/F	24	0.067	Zemanick 2021 (VX18-445-106) phase 3 non-randomised trial of ELX/TEZ/IVA
F/MF	24	0.036	Mall 2022 (VX19-445-116) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating	24	0.067	Assumed equal to F/F
F/RF	24	0.067	Assumed equal to F/F
Age 12+			
F/F	24	0.025	Sutharsan 2022 (VX18-445-109) TEZ/IVA-controlled Phase 3 RCT of ELX/TEZ/IVA in people with CF aged 12+
F/MF	24	0.033	Middleton 2019 (VX17-445-102) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA aged 12+ with an F/MF CF genotype
F/Gating	8	0.049	Barry 2021, active controlled Phase 3 RCT. F/RF or F/Gating
F/RF	8	0.049	Barry 2021, active controlled Phase 3 RCT. F/RF or F/Gating

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; RCT, randomised controlled trial

4.2.1.7.1.2 TEZ/IVA

Discontinuation rates for patients aged 6–11 on TEZ/IVA were taken from Davies 2021,[139] the Phase 3 RCT for patients aged 6–11, genotype F/F and F/RF. For patients aged 12+, discontinuation rates were calculated from the two main RCT trials for each genotype, shown in Table 62.

Table 62. TEZ/IVA acute period discontinuation rates

Genotype	Acute period (weeks)	Annual rate of discontinuations	Source
Age 6–11			
F/F	8	0.121	Davies 2021, phase 3 RCT for patients aged 6–11
F/RF	8	0.121	Davies 2021, phase 3 RCT for patients aged 6–11
Age 12+			
F/F	24	0.143	Taylor-Cousar 2017, phase 3 RCT for patients aged 12+, F/F
F/RF	24	0.081	Rowe 2017, phase 3 RCT for patients aged 12+, F/RF

Abbreviations: F/F, *F508del* homozygous; RF, residual function; RCT, randomised controlled trial

4.2.1.7.1.3 LUM/IVA

Acute period discontinuation rates for LUM/IVA (F/F genotype only) were taken from the main RCT evidence available for each age group. The EAG assumed that the rate of discontinuations seen in patients aged 2–5 was also applicable for patients aged 1–2. The rates applied in the model are shown in Table 63.

Table 63. LUM/IVA acute period discontinuation rates

Age	Acute period (weeks)	Annual rate of discontinuations	Source
1–5	24	0.149	McNamara 2019 (VX15-809-115) Phase 3 non-randomised
6–11	24	0.13	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA
12+	24	0.152	Wainwright 2015[42]

Abbreviations: LUM/IVA, lumacaftor ivacaftor; RCT, randomised controlled trial

4.2.1.7.2 Long-term discontinuations

Data from modulator treatments extension studies were used to inform the discontinuation rates beyond the acute period. The longest extension study data available was over 144 weeks for ELX/TEZ/IVA F/F and F/MF genotypes, while all other studies had a maximum of 96 weeks data available. Extension study data were not available for ELX/TEZ/IVA for patients aged 6–11 with F/Gating and F/RF genotypes. Therefore, the long-term rate of discontinuations was assumed equal to that for the F/F and F/MF genotype population. No long-term data are available for ELX/TEZ/IVA for patients aged 2–5, therefore the EAG assumed long-term discontinuation rates for this age group are equal to that observed in patients aged 6–11.

Clinical experts to the EAG noted that discontinuations from CFTR modulators are still observed in clinical practice beyond the time frame of the extension studies; however, one clinical expert noted that they would not expect to see discontinuations from CFTR modulator treatment beyond 5 years. Therefore, the EAG applied the discontinuation rate calculated from the extension studies for 5 years in the post-acute phase, with no further discontinuations assumed to occur beyond this time. As modulator treatments became available commercially, while clinical trials were ongoing, some

patients discontinued from the trials for this reason. The EAG excluded all discontinuations due to commercial availability of the drugs in their calculations of the annual discontinuation rates. All other reasons for discontinuation were included in the calculated rates. The calculated annual rates for each treatment are shown in Table 64.

Table 64. Long term annual discontinuation rates

Genotype/age group	Study period (weeks)	Annual rate of discontinuations	Source
ELX/TEZ/IVA			
Age 2–11			
F/F	96	0.026	Ratjen 2021[148]
F/MF	96	0.026	Ratjen 2021[148]
F/Gating	96	0.026	Assumed equal to F/F and F/MF population
F/RF	96	0.026	Assumed equal to F/F and F/MF population
Age 12+			
F/F	144	[redacted]	Griese 2022[147]
F/MF	144	[redacted]	Griese 2022[147]
F/Gating	96	[redacted]	Study 445-110[149]
F/RF	96	[redacted]	Study 445-110[149]
TEZ/IVA			
Age 6–11			
F/F	96	[redacted]	Sawicki 2022[151]
F/RF	96	[redacted]	Sawicki 2022[151]
Age 12+			
F/F	96	[redacted]	Flume 2021[150]
F/RF	96	[redacted]	Flume 2021[150]
LUM//IVA			
1–5	96	0.06	McNamara 2019
6–11	96	0.035	Chilvers 2021[153]
12+	96	0.152	Konstan 2017[152]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function

4.2.1.8 Compliance

Compliance rates based on pill counts during the key clinical trials for each genotype and age group were applied for the acute period, corresponding to the appropriate trial duration. The sources and

assumptions made for acute period compliance rates are the same as those applied for discontinuation rates, as previously described in Section 4.2.1.7.1. Further detail on the rates and data sources used for each of the three CFTR modulator treatments is detailed in Table 65. As no data on both long-term compliance and treatment effectiveness was available for the three included CFTR modulators, the EAG assumed 100% compliance following the acute period. As the impact of compliance in the model is only through a reduction in costs, applying a lower compliance rate beyond the trial period would not account for any differences in efficacy that result from lower compliance. The EAG is aware that compliance in the real world may be lower than 100% but based on clinical expert opinion to the EAG it is expected to remain high due to the quick decline in health experienced by patients when they discontinue. The EAG has conducted a scenario analysis (Section 4.2.2.4), which utilises an alternative long-term compliance rate based on the Company's latest estimate from the data collection agreement.[164]

Table 65. Compliance rates applied during the acute period

Genotype	Acute period (weeks)	Compliance rate applied in acute period	Source
ELX/TEZ/IVA			
Age 2–5			
F/F	24	[redacted]	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/MF	24	[redacted]	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/Gating	24	[redacted]	Assumed equal to F/F and F/MF
F/RF	24	[redacted]	Assumed equal to F/F and F/MF
Age 6–11			
F/F	24	[redacted]	Zemanick 2021 (VX18-445-106) phase 3 non-randomised trial of ELX/TEZ/IVA
F/MF	24	[redacted]	Mall 2022 (VX19-445-116) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA
F/Gating	24	[redacted]	Assumed equal to F/F
F/RF	24	[redacted]	Assumed equal to F/F
Age 12+			
F/F	24	[redacted]	Sutharsan 2022 (VX18-445-109) TEZ/IVA-controlled Phase 3 RCT of ELX/TEZ/IVA in people with CF aged 12+
F/MF	24	[redacted]	Middleton 2019 (VX17-445-102) placebo-controlled Phase 3 RCT of ELX/TEZ/IVA aged 12+ with an F/MF CF genotype
F/Gating	8	[redacted]	Barry 2021, active controlled Phase 3 RCT. F/RF or F/Gating

F/RF	8	[redacted]	Barry 2021, active controlled Phase 3 RCT. F/RF or F/Gating
TEZ/IVA			
Age 6–11			
F/F	8	[redacted]	Davies 2021, phase 3 RCT for patients aged 6–11
F/RF	8	[redacted]	Davies 2021, phase 3 RCT for patients aged 6–11
Age 12+			
F/F	24	[redacted]	Taylor-Cousar 2017, phase 3 RCT for patients aged 12+, F/F
F/RF	24	[redacted]	Rowe 2017, phase 3 RCT for patients aged 12+, F/RF
LUM/IVA			
1–5	24	[redacted]	McNamara 2019 (VX15-809-115) Phase 3 non-randomised
6–11	24	[redacted]	Ratjen 2017 (VX14-809-109) placebo-controlled Phase 3 RCT of LUM/IVA
12+	24	[redacted]	Wainwright 2015[42]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; RCT, randomised controlled trial

4.2.1.9 Lung transplantation

In line with the Company's models and based on UK clinical guideline for transplantation, patients are eligible for lung transplant in the model once their ppFEV$_1$ falls below 30%. Clinical experts to the EAG noted how patients would usually be referred for a transplant once their ppFEV$_1$ started to drop below 40%. However, as the referral and waiting list process can take up to 1–2 years it is likely that patients ppFEV$_1$ will be around 30% or lower by the time of transplant. The Company apply a probability of lung transplant based on data from the CF Registry report 2021,[1] in which 5 patients out of the 78 evaluated received a lung transplant (6.4%). The EAG notes that this value is much lower than in 2019 and there is a potential for this value to be impacted by the COVID-19 pandemic. In response to clarification questions, the Company also stated that the lower number of transplants in 2021 may be a result of CFTR modulators. As a value for lung transplant in the model is required that represents the impact without CFTR modulators, the EAG applied the values from the CF Registry 2019 report. The exact number of patients aged <16 receiving a bi-lateral lung transplant in 2019 was not available and was reported for age <5 only. Due to this, the probability of transplant in the EAG model included only those aged >16. This resulted in a probability of 20.3% (49/241). This is applied as a one-off probability in the model cycle in which a patients ppFEV$_1$ reaches below 30.

Following lung transplantation, the CPH model for mortality is no longer implemented and a separate post lung transplant mortality is applied. The Company used international data on survival post lung transplant for CF patients, collected between 1992-2017. Survival post lung transplant may differ across countries and health care systems and therefore the EAG believed a UK specific source would be more appropriate. The NHS annual report on Cardiothoracic Organ Transplantation 2021/22[249] provides post lung transplant 1- and 5-year survival rates for cystic fibrosis and bronchiectasis patients. The EAG converted these survival rates into annual 1 year and post 1 year mortality probabilities, equal to 13.1% and 9.1% respectively.

4.2.1.10 Adverse events

The EAG included the adverse events (AEs) that were either highlighted by the EAG's clinical experts as problematic for patients or were reported as AEs of special interest across the clinical trials, namely: rash events and liver adverse events. For liver adverse events, the EAG identified increased alanine aminotransferase and increased aspartate aminotransferase as those that were reported consistently between clinical trials noted in Section 3.2.2.4, and therefore were included in the economic model. The EAG's clinical experts also noted how CFTR modulators may be associated with an increased risk of cataracts, lens opacities and hypertension. The rates of cataracts, lens opacities and hypertension reported across the clinical trials was low and most events occurred in patients aged ≥12. Therefore, although noted as clinically important, cataracts, lens opacities and hypertension are not included in the economic model. Clinical experts noted how liver-related AEs may incur costs through increased monitoring but may also lead to CFTR modulator discontinuation. The EAG applied a cost of a GP visit for all liver-related AEs and rash events.

Due to the three different treatments being included in the model, there was no common ECM arm from the clinical trials to assess AEs. As the model requires a common ECM arm to compare all three CFTR modulator treatments to, the difference between the placebo arm and treatment arm of the trials used for each included AE was calculated. AEs were then applied in the CFTR modulator treatment arms of the model as a difference from ECM that could either be positive or negative. In cases where the rate of AEs in the treatment arm was negative, i.e., the adverse event rate was higher in the placebo arm, the EAG capped the rate at zero. This decision was made as the EAG considered it implausible that CFTR modulators would reduce the rate of rash or liver events in people with CF and considered lower values in the CFTR modulator arms to be reflective of sampling variance in small samples rather than a treatment effect.

In line with the clinical efficacy data used, the EAG calculated AE rates from placebo controlled RCT data, when available. When comparative RCT data was not available, the EAG either applied the placebo arm from a different CFTR modulator treatment, conducted within the same age group, or assumed equal rates of AEs within the same intervention and age group but across genotypes. For TEZ/IVA patients aged 6–11, although placebo-controlled comparative data were available in Davies 2021,[139] the control arm of the study consisted of 10 patients only. Therefore, the EAG compared the treatment arm of Davies 2021[139] to the placebo arm of Mall 2022,[134] the placebo-controlled trial of patients aged 6–11 for ELX/TEZ/IVA. Further details on the sources used for the calculated absolute annual rates of AEs are shown below in Table 66.

Table 66. Included annual rates of adverse events

	Alanine aminotransferase increased	Aspartate aminotransferase increased	Rash events	Source
	Absolute annual rate			
ELX/TEZ/IVA				
2-5 all genotypes	[redacted]	[redacted]	[redacted]	Treatment arm AEs taken from Study VX20-445-111. Placebo arm AEs taken from Stahl 2021 (placebo-controlled trial in LUM/IVA age 2–5)
6-11 all genotypes	[redacted]	[redacted]	[redacted]	Mall 2022. Data from patients F/MF assumed to apply to all genotypes
12+ all genotypes	[redacted]	[redacted]	[redacted]	Middleton 2019. Data from patients F/MF assumed to apply to all genotypes
TEZ/IVA				
6-11 F/F, F/RF	[redacted]	[redacted]	[redacted]	Treatment arm AEs taken from Davies 2021. Placebo arm AEs taken from Mall 2022 (placebo-controlled trail in ELX/TEZ/IVA age 6–11, F/MF genotype
12 + F/F	[redacted]	[redacted]	[redacted]	Taylor-Cousar 2017
12+ F/RF	[redacted]	[redacted]	[redacted]	Rowe 2017
LUM/IVA				
1 to 5 F/F	[redacted]	[redacted]	[redacted]	Stahl 2021. Data from patients aged 2–5 also assumed to apply to patients aged 1
6 to 11 F/F	[redacted]	[redacted]	[redacted]	Ratjen 2017. Placebo-controlled RCT patients aged 6–11
12+ F/F	[redacted]	[redacted]	[redacted]	Wainwright 2015

* [redacted]

† Event was recorded as not reported in the clinical trial

Abbreviations: AE, adverse events; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; F/F, *F508del* homozygous; MF, minimal function; RF, residual function; RCT, randomised controlled trial

4.2.1.11 Health-related quality of life

Utility values were required in the economic model based on ppFEV$_1$, disutility of PEs and following post lung transplant. The EAG applied a reduction in HRQoL with age, as per the general population, based on the Health Survey for England (HSE) EQ-5D-3L general population value set. This value set only provide general population utility values for individuals aged 16+. Therefore, the EAG applied a conservative assumption, assuming no decline in HRQoL due to age prior to age 16 in the model.

The Company's models also applied a treatment specific utility increment for patients [redacted] An additional increment of 0.03 in the ELX/TEZ/IVA model only for carers of children aged 6–11 was also applied in the Company's model. This was based on a study of 25 carers using the Care-Related Quality of Life measure (CarerQoL). [redacted] Based on the small sample size, it is unclear if all carers have the same experience and how long the carer impact should apply for. Due to a lack of reliable estimates, carer HRQoL was not included in the EAG base case analyses, however this was explored in a scenario analysis (Section 4.2.2.4).

4.2.1.12 HRQoL stratified by ppFEV$_1$ value

The economic model was constructed to capture the main benefits of treatment for CF and, as such, utility values that reflect changing ppFEV$_1$ were required. The systematic literature review undertaken by the EAG, described in Section 4.1.3, identified 5 individual studies (reported in 10 separate studies) that reported HRQoL values stratified by ppFEV$_1$ grouping, all of which used EQ-5D. One of these studies was the NICE TA786 for LUM/IVA, which reported the trial collected EQ-5D-3L values. This was the only key trial of the three CFTR modulators included in the current MTA that collected EQ-5D data. In the current MTA submission and the previous NICE appraisal for LUM/IVA, the Company stated that the generic measure of HRQoL failed to capture meaningful differences in lung function. It was also stated that the high utility values observed in the trial reflects patients' adaptation to life with a chronic disease and limits the ability to detect treatment benefit. During TA786, the committee stated that there was no evidence to suggest that the EQ-5D was inappropriate and that it generally captured the effects of having CF. It was also noted how benefits

in HRQoL can be captured by avoiding any decrements, such as reduced PEs. A utility decrement for PEs is applied in the Company's models.

The NICE Reference Case stipulates that the EQ-5D is the preferred measure for HRQoL and any departures from this must provide, "qualitative empirical evidence on the lack of content validity for the EQ-5D" and this should be derived from a synthesis of peer-reviewed literature. The EAG does not consider that the Company has provided a robust argument that EQ-5D is an inappropriate tool for use in CF.

In line with the NICE Reference Case, the EAG used the utility values sourced from the LUM/IVA clinical trials in the base-case. However, an adjustment was made to the trial values. The utility values from the LUM/IVA trial were available for patients split across four $ppFEV_1$ groups: ≥90, 70 to <90, 40 to<70, <40. The EAG replaced the utility value for the ≥90 category with the general population values for the mean age of the population being modelled as it was deemed that this group was most reflective of the general population's lung function. The CF Registry Report only provides the median age of the population, which in 2021 was 21. This is largely in line with the mean age of all patients included in the modelled cohort (21.9). The general population utility value for males and females (weighted according to the CF Registry sex split, 53.2% males) was sourced from HSE EQ-5D-3L general population value set, which was equal to 0.925. The relative reduction in utility value from ≥90 to 70 to <90, was estimated from the LUM/IVA trial (0.933/0.951 = 0.981) and this was applied to the general population utility value assigned by the EAG to ≥90 (0.925 x 0.981 = 0.908). A similar, step-wise process was used for the subsequent $ppFEV_1$ categories, shown in Table 67. In the EAG's model the utility value for the groups 70 to <90 was applied for all patients with a $ppFEV_1$ of ≥70.

Table 67. EAG applied EQ-5D value

$ppFEV_1$ grouping	LUM/IVA trial value	Relative difference compared to ≥90 group	Updated values used in EAG model
≥90	0.951	-	-
70 to <90	0.933	0.981	0.908
40 to<70	0.906	0.953	0.882
<40	0.878	0.923	0.854

Abbreviations: $ppFEV_1$, percent predicted forced expiratory volume in 1 second; EAG, evidence assessment group; LUM/IVA, lumacaftor ivacaftor

The EAG's preference is to use utility values measured directly from the clinical trials, as this is the same source of evidence on effectiveness data. In a scenario analysis the Company applied utility values from Acaster 2015,[214] which reported EQ-5D values classified by $ppFEV_1$ grouping. This study was also identified in the EAG's systematic literature review. The EAG notes that the Acaster *et al.* study included adult patients who had a self-reported CF diagnosis and $ppFEV_1$ value and may potentially suffer from selection bias. The EAG used the values reported in this study in a scenario analysis to explore the impact on the ICER. A separate scenario analysis is also included using utility values from the Company's model. This uses the [redacted] The EAG notes that, although the values for each $ppFEV_1$ group are lower than the EQ-5D values applied in the EAG base case, the reduction in utility when moving from $ppFEV_1$ 70-40 to ≤40 is the same between the Company's and the EAG's utility values. It is also noteworthy that the EAG model applies an age-adjustment to utility values over the lifetime of the model, whereas this was not included in the Company's model.

4.2.1.12.1 Disutility of pulmonary exacerbations

The EAG identified two UK based studies in the review of utility values (section 4.1.3) that also reported on the disutility of pulmonary exacerbations. Bradley 2013[16] reported disutility values for major exacerbation (0.174) and minor exacerbation (0.015). This study was conducted in adult CF with *Pseudomonas aeruginosa* infections who were taking nebulised or oral antibiotics and therefore may not be as applicable to the whole population in the MTA. Tappenden *et al.* 2023[224] applied a disutility for days on IV antibiotics based on trial data of patients aged ≥ 16 years who are taking inhaled mucolytics or antibiotics. The EQ-5D-3L disutility related to each IV day was 0.12. Additionally, the Company applied disutility associated with a PE based on a study assessing the impact of PEs on HRQoL using data from the ivacaftor monotherapy clinical trial. This collected EQ-5D-3L data from patients aged ≥12 with a G551D mutation. Based on data reported in this study, a disutility of 0.07 was applied for 30 days for each PE.

In line with using the trial data from LUM/IVA for utility values stratified by $ppFEV_1$, the EAG used the disutility associated with PEs from the ivacaftor monotherapy clinical trial, as applied by the Company. This included patients from age 12, unlike the other sources available for UK data.

4.2.1.12.2 Post lung transplant

Numerous studies identified in the EAG's systematic literature review of previous economic evaluations applied a post lung transplant utility of 0.81, including the Company's MTA submission. The data used to calculate this figure is sourced from a study by Anyanwu 2001.[250] This study collected data from patients post lung transplant from UK lung transplant centres during 1998. In the ivacaftor monotherapy HTA, Whiting *et al.*[43] used the data from bi-lateral lung transplant patients (79 patients) from the Anyanwu *et al.*[250] study as this was said to most likely reflect CF transplant patients. They calculated the weighted average post-transplant utility based on the reported data at the different follow up time points to give an EQ-5D utility of 0.81

The value of 0.81 is lower than the EAG's utility value used for patients with a $ppFEV_1$ of < 40% (0.854), which does not seem clinically plausible. The value of 0.81 applied for post lung transplant is similar to the value used by the Company (0.8) and by Tappenden *et al.* 2023[224] (0.83) for $ppFEV_1$ ≥70. A recently published systematic literature review[251] on HRQoL for CF patients following post lung transplant found that up to 5 years post lung transplant patients HRQoL is equal to that of general population and the HRQoL following transplant for CF patients is greater than or equal to that of other indications requiring lung transplant. Due to these reasons, the EAG apply the utility value post lung transplant equal to the value used for patients with $ppFEV_1$ ≥70 (0.908).

4.2.1.13 Resource use and costs

The economic model includes costs related to drug acquisition, ECM costs, pulmonary exacerbations, monitoring costs related to CFTR-modulators and lung transplantation. Further detail is provided in the following section on each of these costs.

4.2.1.13.1 CFTR modulator acquisition costs

The drug acquisition costs included in the model based on list price are given in Table 68 and were obtained from the BNF.[252] Treatment regimens based on age group and weight for each of the CFTR-modulator combinations are described in Section 1.3.1. The annual cost of each CFTR-modulator combination therapy by age group is presented in Table 69. PAS prices were provided by NICE to the EAG and used in the final model results presented in this report but only list prices are presented below.

The EAG notes that while the strength of dose for each CFTR-modulator combination therapy varies by age and weight, the pack price of the different strengths available is the same. Additionally, for each CFTR-modulator combination therapy, the number of units per day for the treatment regimen irrespective of strength of dose required is the same (see Table 69).

Table 68. CFTR-modulator acquisition costs (source: British National Formulary)[252]

Treatment	Strength*	Pack size	List price	
			Pack price	Cost per unit
LUM/IVA	75 mg / 94 mg sachet	56	£8,000.00	£142.86
	100 mg / 125 mg sachet			
	150 mg / 188 mg sachet			
	100 mg / 125 mg tablets	112	£8,000.00	£71.43
	200 mg / 125 mg			
TEZ/IVA	50 mg / 75 mg tablets	28	£6,293.91	£224.76
	100 mg / 150 mg tablets			
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]
	37.5 mg / 25 mg / 50mg tablets	56	£8,346.30	£149.04
	75 mg / 50 mg/ 100 mg tablets			
Ivacaftor	[redacted]	[redacted]	[redacted]	[redacted]
	75 mg tablets	28	£7,000.00	£250.00
	150 mg tablets			

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; mg, milligram; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor

*The order of the strength of the tablets reflects the order of the associated combination therapy. For example, for the LUM/IVA strength of 100 mg / 125 mg represents lumacaftor 100 mg and ivacaftor 125 mg.

** Proposed list price for ELX/TEX/IVA + IVA granules for the 2 to 5 years age group.

Table 69. CFTR-modulator acquisition costs per year according to dose

Treatment	Age group	Units per day	Annual cost
LUM/IVA	1 to 5 years	Two sachets per day (one sachet every 12 hours)	£104,357.14
	6 years +	Four tablets per day (two tablets every 12 hours)	£104,357.14

TEZ/IVA	6 years +	One tablet of TEZ/IVA in the morning and one tablet of IVA in the evening.	£173,414.31
ELX/TEZ/IVA	2 to 5 years	[redacted]	[redacted]
	6 years +	Two tablets of ELX/TEZ/IVA in the morning and one tablet of IVA in the evening.	£200,187.00
Abbreviations: ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; IVA, ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor			

4.2.1.13.2 Established clinical management costs

Drug costs

Due to the nature of CF causing a wide range of symptoms and associated illnesses (e.g. respiratory infections, pancreatic insufficiency, CFRD), management is multidisciplinary and so there is no one standard treatment applied to all patients. However, as described in Section 1.2.1 (Table 3), a set of therapies are commonly used to treat the symptoms of CF, such as antibiotics, inhaled bronchodilators/corticosteroids and mucoactive therapies. Clinical experts to the EAG highlighted that the use of these treatments may differ between patients based on their lung function, as measured by ppFEV$_1$. In a targeted search, the EAG identified a recent study by Granger 2022,[162] which used UK CF Registry data to explore treatment usage in CF patients pre- and post-introduction of ivacaftor monotherapy. This study provides the proportion of patients taking the most common therapies used to treat CF symptoms as part of ECM, split by patients ppFEV$_1$ status (<60, 60-80, >80), shown in Table 70.

The EAG used the reported proportions of each treatment for patients who were ineligible for ivacaftor monotherapy in 2018 to represent the most recent ECM treatment usage. The treatments included were inhaled antibiotics, dornase alfa, hypertonic saline solution, azithromycin, flucloxacillin and supplementary feeding (both oral and gastrostomy). One of the EAG's clinical experts (senior dietician) advised that the costs and dosages associated with supplementary feeding is extremely variable between both patients and centres within the UK. Due to this, the EAG is unable to apply an average cost of supplementary feeding and therefore has excluded this from the overall ECM costs. Inhaled antibiotics was reported as a single broad category, however numerous

types of inhaled antibiotics are available, each with an individual cost. Therefore, the EAG used data available in the CF Registry 2018 report[253] on the proportion of each inhaled antibiotic used to calculate an overall weighted cost of inhaled antibiotics, see Appendix 9.9. The proportion of patients in each of the three $ppFEV_1$ groups could then be applied to each treatment to provide an ECM treatment cost, based on a patients $ppFEV_1$. The EAG notes that the three $ppFEV_1$ groups used for ECM drug costs differ to that used for other disease management costs and utility values. As the patient level simulation model includes $ppFEV_1$ as a continuous measure, it allows this additional granularity in costs to be incorporated. Further detail on the costs and resource use applied is provided in Table 70.

The dosage used for each drug was informed by Tappenden 2023,[224], which was identified during the EAG's HRQoL systematic literature review (Section 4.1.3). The EAG assumed that the dosage for all treatments is the same for adults and children as this was found to be the case for the majority of the drugs included. For the treatments included, where the dosage details available differ between adults and children, this was a very low cost and therefore the EAG do not expect this to have a large impact on overall costs. The costs of treatment assumes full adherence and that treatment is prescribed as per the recommended guidelines.

The EAG notes that a confidential comparator price is available for colistimethate dry powder, which makes up a proportion of the inhaled antibiotics dugs costs. As the impact on the ICERs was negligible, publicly available eMIT and list prices (sourced from BNF[252]) have been used. The study used to inform ECM resource use by $ppFEV_1$ grouping also explored the difference in usage between patients eligible for ivacaftor and those not eligible. Clinical experts to the EAG noted that it is currently unknown if other treatments can be reduced while taking CFTR modulators, as the data are not currently available on the impact on CFTR modulator efficacy when not taken in combination with ECM. Therefore, the EAG base case assumed equal ECM drug costs between patients on ECM alone and CFTR modulators. However, a scenario analysis is included which uses the weighted average reduction of resource use reported by Granger 2022[162] between patients eligible for ivacaftor and those not eligible from 2018, calculated by the EAG. This results in a 23% reduction in ECM drug costs for patients on CFTR modulator treatments. An additional scenario applies a reduction of 40%, based on the maximum reduction observed across any single resource use component within Granger 2022 (hypertonic saline).[162] The EAG notes that an ongoing study (CF STORM)[188] is being conducted to estimate the impact the reducing or stopping treatment of nebulised mucoactive therapies, while on treatment with ELX/TEZ/IVA, on decline in lung function.

This will hopefully provide evidence in place of the current assumption in any future modelling. The EAG also notes that the Cystic Fibrosis Dietitians Specialist Group of the British Dietetic Association (CF BDA), highlighted how treatment with CFTR modulators has led to reduced prescribing of oral nutritional supplements and the removal of gastronomy feeding tubes in some patients. While these costs could not be incorporated in the ECM costs as noted above, the EAG's scenario analyses represent a reduction in all ECM costs.

Healthcare costs

In addition to drug costs, patients with CF will regularly come into contact with numerous healthcare professionals, as part of the multidisciplinary approach to disease management. Costs for healthcare were taken from Tappenden 2023[224] who reported CF disease management costs split by $ppFEV_1$ grouping ($ppFEV_1$ > 70% = £3,368; $ppFEV_1$ 40–69% = £3,774; $ppFEV_1$ < 40% = £3,320). Tappenden 2023 used healthcare resource use data for CF patients collected using a standardised resource use questionnaire, as part of a trial to assess adherence to inhaled medications. This included resource use associated with hospitalisations not due to PEs requiring IV antibiotics, GP visits, hospital-based consultant visits, nurses, physiotherapists, psychologists, dieticians, occupational therapists, radiographers, social workers and visits to Accident and Emergency (A&E). Resource use was costed using NHS Reference Costs 2021/22.[239]

Table 70. Annual ECM costs by $ppFEV_1$ group

Treatment	Cost per year	Proportions taking treatment			Total cost			Source/Assumptions
		ppFEV1 > 80%	ppFEV1 > 60–80%	ppFEV1 < 60%	ppFEV1 > 80%	ppFEV1 > 60–80%	ppFEV1 < 60%	
Inhaled Antibiotics	£12,086.13	0.49	0.59	0.7	£5,922.20	£7,130.82	£8,460.29	CF Registry 2018 report, see Appendix 9.7 for further detail
Dornase alfa	£6,043.84	0.73	0.8	0.8	£4,412.01	£4,835.08	£4,835.08	Tappenden 2023, Pulmozyme 2.5mg; daily dose: 2.5mg
Hypertonic saline solution	£173.75	0.37	0.4	0.42	£64.29	£69.50	£72.98	Tappenden 2023, 6% or 7% inhalation solution; daily dose: 8ml
Azithromycin	£99.53	0.4	0.59	0.71	£39.81	£58.72	£70.67	Tappenden 2023, Azithromycin 250mg tablets; daily dose: 250mg
Flucloxacillin	£48.29	0.31	0.27	0.22	£14.97	£13.04	£10.62	Tappenden 2023, Flucloxacillin 250mg or 500mg capsules; daily dose:1g
					£10,453.28	**£12,107.15**	**£13,449.63**	

Abbreviations: CF, cystic fibrosis; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; g, grams; mg, milligrams; ml, millilitre

4.2.1.13.3 Costs of pulmonary exacerbations

In the economic model, as PEs occur as a function of age and ppFEV$_1$, patients with a lower ppFEV$_1$ are more likely to have a greater number of PEs each year and therefore incur greater costs. Clinical experts to the EAG noted that although the cost of PEs may differ between ppFEV$_1$ groups (>70, 40-70, <40), this is largely due to the greater number of PE events occurring and that a standard course of 14 days on IV antibiotics is common practice. One clinical expert did note that for some patients with poorer lung function, who are not responding to a standard course, IV antibiotics may be given for a three-week period instead. As the EAG did not have data available on the number of patients who may require a longer course of treatment, the cost of each pulmonary exacerbation event in the model consisted of 14 days inpatient stay in hospital, receiving IV antibiotics. The unit cost for inpatient stay and IV drugs used in hospital to treat PEs was taken from Tappenden 2023,[224] shown in Table 71.

Table 71. Cost per pulmonary exacerbation event

Resource	Unit cost	Resource use (days)	Total cost	Source
Inpatient stay (per day)	£410.75	14	£5750.50	Tappenden 2023. Cost per non-elective bed-day, weighted by FCEs and average length of stay, assumed interventions for bronchiectasis (codes DZ12C to DZ12F)
IV drugs in hospital	£27.82	14	£389.48	Tappenden 2023. Costs consists of Ceftazidime 3g ,Tobramycin 481-560mg, Sodium chloride 0.9% and Heparin 50units in 5ml.
Total cost per PE event			**£6139.98**	Calculated

Abbreviations: IV, intravenous; PE, pulmonary exacerbations; g, grams; mg, milligrams; ml, millilitre; FCE, finished consultant episode

4.2.1.13.4 Monitoring costs

Monitoring costs for liver function tests (bilirubin, aspartate transaminase [AST] and alanine transaminase [ALT]) and ophthalmologist visits are applied to all patents on CFTR modulator treatments, in line with guidance in the Summary of Product Characteristics (SmPC). Clinical experts to the EAG noted how children will have ophthalmology visits annually while on CFTR modulators, whereas adults will require them in the initial year only. Therefore, the EAG applies the cost of ophthalmology visits each year for patients aged ≤18. This differed to the Company's models in

which costs are only applied in the initial year of treatment for all patients. For all patients in the model, in the year of initiating treatment, both an initial and follow-up ophthalmology visit are included. Clinical experts also stated that monitoring for liver function is applied every three months in the first year of initiating treatment, and annually thereafter. Costs were sourced from NHS Reference Costs 2021/22,[239] as shown in Table 72.

Table 72. Annual monitoring costs associated with CFTR modulators

Treatment	Unit cost	Resource use	Total cost	Source
Monitoring costs, initial year of treatment, age ≤18				
Liver function tests	£1.85	4	£7.40	NHS Reference costs 2020/21. Directly Accessed Pathology Services. Clinical biochemistry. DAPS04
Initial ophthalmologist visit (age≤18)	£225.47	1	£225.47	NHS Reference costs 2020/21. Consultant led. Paediatric Ophthalmology. Non-Admitted Face-to-Face Attendance, First. WF01B
Follow-up ophthalmologist visit (age≤18)	£187.64	1	£187.64	NHS Reference costs 2020/21. Consultant led. Paediatric Ophthalmology. Non-Admitted Face-to-Face Attendance, Follow-up. WF01A
Total monitoring costs	-	-	**£420.51**	Calculated
Monitoring costs, subsequent years, age ≤18				
Liver function tests	£1.85	1	£1.85	NHS Reference costs 2020/21. Directly Accessed Pathology Services. Clinical biochemistry. DAPS04
Follow-up ophthalmologist visit (age≤18)	£187.64	1	£187.64	NHS Reference costs 2020/21. Consultant led. Paediatric Ophthalmology. Non-Admitted Face-to-Face Attendance, Follow-up. WF01A
Total monitoring costs	-	-	**£189.49**	Calculated
Monitoring costs, initial year of treatment, age >18				
Liver function tests	£1.85	4	£7.40	NHS Reference costs 2020/21. Directly Accessed Pathology Services. Clinical biochemistry. DAPS04
Initial ophthalmologist visit (age>18)	£213.13	1	£213.13	NHS Reference costs 2020/21. Consultant led. Ophthalmology. Non-Admitted Face-to-Face Attendance, First. WF01B
Follow-up ophthalmologist visit (age>18)	£166.35	1	£166.35	NHS Reference costs 2020/21. Consultant led. Ophthalmology. Non-Admitted Face-to-Face Attendance, Follow-up. WF01A

Total monitoring costs	-	-	**£386.88**	Calculated
Monitoring costs, subsequent years, age >18				
Liver function tests	£1.85	1	£1.85	NHS Reference costs 2020/21. Directly Accessed Pathology Services. Clinical biochemistry. DAPS04
Total monitoring costs	-	-	**£1.85**	Calculated
Abbreviations: NHS, National Health Service				

4.2.1.13.5 Cost of lung transplantation

The cost of lung transplant is taken from NHS Reference Costs 2020/21[239] and was calculated as the weighted average of elective inpatient, non-elective inpatient long stay and non-elective inpatient short stay lung transplant costs. Once patients have had a lung transplant in the model, they no longer receive the treatment costs and disease management costs associated with CF. Instead, costs associated with post-lung transplant were taken from Anyanwu 2002,[254], which reported post lung transplant follow up costs up to 15 years. The EAG used the reported costs associated with bi-lateral lung transplant. The reported costs had been discounted at 6%, therefore the EAG reversed the discounting and inflated costs to 2021 prices using the NHS cost inflation index (NHSCII),[255], shown in shown in Table 73.

Table 73. Lung transplant and follow up costs

Resource	Cost	Source
Lung transplant	£91,778	NHS Reference Costs 2020/21. Weighted average of lung transplant elective inpatient, non-elective inpatient long stay and non-elective inpatient short stay (DZ01Z)
Post lung transplant annual follow up cost (first year)	£27,612.78	Anyanwu 2002, inflated to 2021
Post lung transplant annual follow up cost (second year)	£11,503.97	
Post lung transplant annual follow up cost (third year)	£11,218.50	
Post lung transplant annual follow up cost (years 4-10)	£9,917.49	
Post lung transplant annual follow up cost (years 11+)	£8,112.75	
Abbreviations: NHS, National Health Service		

4.2.1.14 List of assumptions

The EAGs economic model employs a number of assumptions, with the main ones detailed below in Table 74.

Table 74. EAG base case assumptions

EAG base case assumptions	Justification
An individual's baseline mortality is equal to the marginal population mortality. This assumes that any given patients' characteristics at baseline are the same as that of the general CF population	A baseline mortality hazard is required to apply the Cox proportional hazards model to which is not available for each patient. This simplifying assumption is applied in line with Company's validation exercise which found this approach provided a better survival prediction to observed data
Baseline characteristics are based on patients combined from the main CFTR modulator trials for each specific genotype	Data on individual patients were required for the individual simulation model to maintain the correlation between specific characteristics. These data were only available to the EAG from the trial data
Patients' pancreatic sufficient status and respiratory infections do not change over time and therefore do not contribute to the risk of mortality	Lack of data available to inform these parameters changing over time and the effect of CFTR modulator treatments. Deemed a conservative assumption
No pulmonary exacerbations in patients aged <6	PEs are included as a function of $ppFEV_1$ which is not tracked in patients aged. Clinical experts stated that PEs can still occur in <6 and so this is deemed a conservative assumption
No CFRD in patients aged <6	Lack of data available as patients aged <6 are not screened for CFRD.
No decline in a patient's weight-for-age z score	Clinical experts noted that a patient's weight can fluctuate over a patient's lifetime but can be very variable and person-specific. This simplifying assumption is therefore deemed to be conservative.
No treatment effect on the rate of PEs for patients aged <12	Lack of available data. Deemed a conservative assumption
The relative reduction in the rate of $ppFEV_1$ decline compared to ECM is equal to 61.0% per year for patients on ELX/TEZ/IVA following the acute period, applied for the lifetime.	Based on a study of ivacaftor monotherapy due to a lack of unconfounded long-term data for ELX/TEZ/IVA
The relative reduction in the rate of $ppFEV_1$ decline compared to ECM is equal to 17.2% per year for patients on TEZ/IVA following the acute period, applied for the lifetime	Lack of robust long-term evidence beyond the trial period. Therefore applied the ratio of the acute effects observed in the aged 12+ F/F populations for TEZ/IVA and ELX/TEZ/IVA to the absolute reduction used for ELX/TEZ/IVA
Same rate of decline in $ppFEV_1$ as ECM following the acute period for patients on LUM/IVA	Lack of robust long-term evidence showing a continued treatment effect

No independent treatment effect of PEs beyond the acute period	Lack of available evidence on the long-term effect of CFTR modulators on PEs separate to the effect of $ppFEV_1$
No further discontinuations beyond 5 years on treatment with CFTR modulators	Based on clinical expert opinion
CFTR modulator compliance rates from the key trials of efficacy data are applied in the acute period. Assumed 100% after this point	Data on compliance should come from the same source as effectiveness. No long-term data on both compliance and effectiveness were available to inform longer term assumptions.
AEs included are those that were highlighted by the EAG's clinical experts or were reported as AEs of special interest across the clinical trials	Numerous AEs were inconsistently reported across the different trials. Data were not available on how long these AEs may have occurred for. As a standard set of AEs was required for the ECM arm to compare all modulator treatments to, only those reported consistently and highlighted by clinical experts were included
Patients are eligible for lung transplant once their $ppFEV_1$ reaches 30	In line with UK clinical guidelines
Treatments included in ECM costs are inhaled antibiotics, dornase alfa, hypertonic saline solution, azithromycin, flucloxacillin only	Clinical experts highlighted how there is no standard treatment for patients with CF as care is multidisciplinary and individualised. Average resource use across $ppFEV_1$ groups was only available for the included treatments.
All ECM and pulmonary exacerbation treatment costs are the same for adults and children	The majority of the included treatments for ECM use the same dosage for adults and children. For those where dosage may differ, the difference in cost of treatment was very small
Treatment costs for pulmonary exacerbations does not differ across $ppFEV_1$ value	Clinical experts highlighted that there is a usual standard course of treatment of 2 weeks IV antibiotics. Although some patients with worse lung function may sometimes require a longer course, data was not available to the EAG on the number of patients this applies to.
Utility values based on $ppFEV_1$ taken from LUM/IVA trial of patients aged 12+ are assumed to apply to all treatment arms	The LUM/IVA trial was the only CFTR modulator trial included in the MTA to collect EQ-5D values
Disutility due to PEs applied for 30 days	In line with clinical trial data for ivacaftor monotherapy. No other EQ-5D data associated with PEs was collected from the included CFTR modulator trials
Utility value for post lung transplant equal to utility of patients with $ppFEV_1$ 70-90	EAG identified systematic review of HRQoL in CF patients post lung transplant found after 5 years CF patients generally have HRQoL equal to general population. As a conservative assumption the EAG applies the same value as those with $ppFEV_1$ 70-90 as clinical experts noted that patients do still have CF and any associated co-morbidities.

Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; EAG, evidence assessment group; ECM, established clinical management; EQ-5D, euroqol-5-dimension; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; PE, pulmonary exacerbations, TEZ/IVA, Tezacaftor/ivacaftor; HRQoL, health related quality of life; $ppFEV_1$, percent predicted forced expiratory volume in 1 second

Table 75 also provides a comparison of the key differences between the EAG and Company model assumptions/data sources.

Table 75. Comparisons of EAG and Company model key base case assumptions

Company base case	EAG base case
Baseline mortality based on Weibull model fit to UK CF Registry data 1985-2008	Baseline mortality based on a published flexible parametric spline model fit to UK CF Registry data 2011-2015
ECM decline in $ppFEV_1$ with age based on linear decline model, stratified by age group	ECM decline in $ppFEV_1$ with age based on non-linear decline model
Relative reduction in the rate of ppFEV1 decline compared to ECM long-term: ELX/TEZ/IVA = 100% TEZ/IVA = 61.5% LUM/IVA = 42%	Relative reduction in the rate of ppFEV1 decline compared to ECM long-term: ELX/TEZ/IVA = 61.0% TEZ/IVA = 17.2% LUM/IVA = 0%
Pulmonary exacerbation treatment effect (rate ratio) applied for patients' lifetime	Pulmonary exacerbation treatment effect (rate ratio) applied for duration of trial period
No discontinuations beyond the trial period	No discontinuations past 5 years on treatment
Retain acute increase of ppFEV1 and WFAZ upon discontinuation	Lose acute increase of ppFEV1 and WFAZ upon discontinuation
Compliance rate of 80% applied to all modulator treatments beyond the trial period	Compliance rate 100% beyond the trial period
[redacted]	Utility values based on EQ-5D collected in LUM/IVA clinical trial
[redacted]	No additional treatment specific utility increments applied
Reduction in ECM costs for inpatients stay and pharmacotherapy for patients on CFTR modulator treatments	No reduction in any ECM costs for patients on CFTR modulator treatments
1.5% discount rate for QALYs	3.5% discount rate for QALYs

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; EAG, evidence assessment group; ECM, established clinical management; EQ-5D, euroqol-5-dimension; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; PE, pulmonary exacerbations, TEZ/IVA, Tezacaftor/ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; QALY, quality adjusted life years; WFAZ, weight for age z score

4.2.2 Results

4.2.2.1 Deterministic results

A summary of the deterministic cost-effectiveness results are presented in Table 76. As described in Section 4.2.1.4, the three CFTR modulator treatments included in this multiple technology appraisal (MTA) have marketing authorisation in different genotype populations and age groups. As the three modulators must be analysed within common populations to undertake incremental analyses, the EAG analyses are separated based on genotype. Pairwise (against ECM only) and fully incremental results are presented in Table 76Table 76. Deterministic base case results compared against ECM only and Table 77. For the full incremental analysis, interventions are ordered with respect to their total cost. Interventions with higher incremental costs and lower incremental QALYs than their predecessor are considered to be dominated, by their predecessor, and are therefore removed from consideration in the final ICER calculations. When interventions have both a higher cost and QALYs then their predecessor, the ICER is calculated between those two treatments. All ICERs shown include confidential PAS prices for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA provided by NICE to the EAG.

Table 76. Deterministic base case results compared against ECM only

Population	Absolute			Incremental			ICER (compared to ECM)	NHB*
	Costs	QALY	LY	Costs	QALY	LY		
F/F genotype								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Calculated with a £30,000 willingness to pay threshold

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; NHB, net health benefit, ECM, established clinical management

Table 77. Full incremental deterministic base case results

Population	Absolute			Incremental			ICER (incremental)
	Costs	QALY	LY	Costs	QALY	LY	
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management

In addition to base case cost-effectiveness results, Table 78 reports clinical outcomes of interest for the EAGs base case analysis.

Table 78. Key clinical outcomes from EAG base case

	ppFEV$_1$ change	WFAZ change	Annual rate of PE	Total lung transplants	Median age of death (years)
F/F genotype					
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF genotype					

ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating genotype					
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF genotype					
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; established clinical management; PE, pulmonary exacerbations; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; WFAZ, weight for age z score

Figure 12 to Figure 15 shows the model predicted median survival curves for each genotype.

Figure 12. F/F population model predicted survival

Figure 13. F/MF population model predicted survival

Figure 14. F/Gating population model predicted survival

Figure 15. F/RF population model predicted survival

Severity modifier

As outlined in the National Institute for Health and Care Excellence (NICE) methods guide,[31] "*the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS*". The thresholds of quality-adjusted life-year (QALY) weightings for severity are shown in Table 79.

Table 79. QALY weighting for severity modifier

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Abbreviations: QALY, quality-adjusted life-year

The EAG calculated the absolute and proportional QALY shortfall using a published calculator by the University of York.[256] The tool calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The source of the general population EQ-5D-3L data used in the calculator is from the Heath Survey for England (HSE) 2014 and uses the model to estimate general population HRQoL norms by Hernandez Alava 2022,[257] as recommended by the NICE decision support unit (DSU).

Table 80 shows the mean age and sex distribution of each genotype in the EAG model and lifetime QALYs for patients without CF. The corresponding QALY weight for each population is also shown.

Table 80. QALY shortfall calculations

	F/F	F/MF	F/Gating	F/RF
Mean age (years)	20.15	20.91	20.71	28.61
Female (%)	51	51	52	55
QALYs with CF	[redacted]	[redacted]	[redacted]	[redacted]
QALYs without CF	22.67	22.52	22.51	21.10
Absolute shortfall	[redacted]	[redacted]	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1	1	1	1

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; CF, cystic fibrosis; QALY, quality adjusted life year

As shown in Table 80, a severity modifier of 1 is applied to all genotypes. In order for a severity modifier of 1.2 to apply, the remaining lifetime QALYs for patients with CF would need to be 10.6 for F/F genotype, 10.5 for F/MF and F/Gating genotypes and 9 for F/RF genotype patients.

4.2.2.2 Probabilistic results

Table 81 and Table 82 presents the results of the probabilistic base case cost-effectiveness results. The EAG notes that although some of the probabilistic ICERs are higher than the deterministic, these do not differ substantially.

Table 81. Probabilistic base case results compared against ECM only

Population	Absolute			Incremental			ICER (compared to ECM)	NHB*
	Costs	QALY	LY	Costs	QALY	LY		
F/F genotype								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IVA/TEZ/ELX	[redacted]							
F/MF								
ECM	[redacted]							
IVA/TEZ/ELX	[redacted]							
F/Gating								
ECM	[redacted]							
IVA/TEZ/ELX	[redacted]							
F/RF								
ECM	[redacted]							
TEZ/IVA	[redacted]							
IVA/TEZ/ELX	[redacted]							

*Calculated with a £30,000 willingness to pay threshold

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; NHB, net health benefit, ECM, established clinical management

Table 82. Probabilistic full incremental base case results

Population	Absolute			Incremental			ICER (incremental)
	Costs	QALY	LY	Costs	QALY	LY	
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						

TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management

4.2.2.3 One-way sensitivity analysis

Deterministic sensitivity analysis was conducted by varying key model parameters between the upper and lower values of the expected value used in the deterministic base case. The key model parameters include:

- CFRD prevalence/incidence for age and sex subgroups
- Baseline CF mortality by sex
- The $ppFEV_1$ limit required for a patient to be eligible for lung transplant
- Probability of death from lung transplant in year 1 and 2
- Change in $ppFEV_1$ for ECM patients by age
- Lowest possible $ppFEV_1$ limit for patients
- Parameters determining rates of PE in ECM patients
- Acute and long-term change in $ppFEV_1$ for CFTRm treatments for age subgroups
- Acute changes in PE rate for CFTRm treatments for age subgroups
- Acute changes in WFAZ rate for CFTRm treatments for age subgroups
- Acute and post-acute changes in discontinuation rate for CFTRm treatments for age subgroups
- Health state, concomitant medication and PE costs
- Health state utility.

Inputs affecting individual subgroups across genotypes were varied separately. Inputs that were separate across genotypes were varied concomitantly.

CFRD prevalence/incidence, baseline mortality, risk of death in the years following transplant, change in $ppFEV_1$ for ECM patients, CFTRm efficacy inputs, health state costs and health state utilities were varied individually for each treatment by their 95% confidence intervals (CIs). No estimates of precision were available for the $ppFEV_1$ limit required for transplant eligibility, the lowest possible $ppFEV_1$ limit for patients, parameters determining rates of PE in ECM patients (which

uses a formula based on age and ppFEV$_1$), therefore the standard error (SE) was assumed to equal +/- 20% of the mean value or were varied at an individually determined fixed interval.

The below subsections present the results of the DSA for the top 10 parameters for the total cystic fibrosis population for each genotype.

The key drivers of changes in the ICER vs ECM in all genotype populations were inputs for health state utility and ppFEV$_1$ change. This is because of the long-time horizon and high survival ensures health state utility remains relevant and change in ppFEV$_1$ is a significant driver of mortality risk for patients in the model. Inputs affecting baseline mortality or PE also had a notable impact on the ICER, although substantially less than the other key drivers. Costs are noticeably absent, largely due to the highest cost items (drug acquisition costs) not being varied due to certainty in the price.

F/F genotype

Figure 16. Tornado diagram for ELX/TEZ/IVA F/F genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio® (ELX/TEZ/IVA); Lt, long term; Mort, mortality; PEx, pulmonary exacerbation; Util, utility.

Figure 17. Tornado diagram for TEZ/IVA F/F genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Lt, long term; Mort, mortality; PEx, pulmonary exacerbation; Sym, Symkevi® (TEZ/IVA); Util, utility.

Figure 18. Tornado diagram for LUM/IVA F/F genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Lt, long term; Mort, mortality; Ork, Orkambi® (LUM/IVA); PEx, pulmonary exacerbation; Util, utility.

Table 83. DSA results: F/F genotype – ECM vs CFTRm therapies (PAS prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
ELX/TEZ/IVA **Base case ICER: £[redacted]**					
1	UtilFev70	[redacted]	[redacted]	NE	NE
2	Kaf12<=AgeFevLtChange	[redacted]	[redacted]	NE	NE
3	UtilFev40	[redacted]	[redacted]	NE	NE
4	rngFev	[redacted]	[redacted]	NE	NE
5	CfMortBlMale	[redacted]	[redacted]	NE	NE
6	CfMortBlFemale	[redacted]	[redacted]	NE	NE
7	UtilFev70_40	[redacted]	[redacted]	NE	NE
8	PexOverAgecutA	[redacted]	[redacted]	NE	NE
9	Kaf12<=AgeFevAcuteChange	[redacted]	[redacted]	NE	NE
10	PexOverAgecutB	[redacted]	[redacted]	NE	NE
TEZ/IVA **Base case ICER: £[redacted]**					
1	Sym12<=Age<100FevLtChange	[redacted]	[redacted]	NE	NE
2	UtilFev70	[redacted]	[redacted]	NE	NE
3	UtilFev70_40	[redacted]	[redacted]	NE	NE
4	UtilFev40	[redacted]	[redacted]	NE	NE
5	Sym12<=Age<100FevAcuteChange	[redacted]	[redacted]	NE	NE
6	rngFev	[redacted]	[redacted]	NE	NE
7	PexOverAgecutA	[redacted]	[redacted]	NE	NE
8	SymAge<12FevAcuteChange	[redacted]	[redacted]	NE	NE
9	CfMortBlFemale	[redacted]	[redacted]	NE	NE
10	SymAge<12DiscPAcuteChange	[redacted]	[redacted]	NE	NE

LUM/IVA Base case ICER: £[redacted]					
1	UtilFev70	[redacted]	[redacted]	NE	NE
2	UtilFev70_40	[redacted]	[redacted]	NE	NE
3	UtilFev40	[redacted]	[redacted]	NE	NE
4	Ork12<=AgeFevAcuteChange	[redacted]	[redacted]	NE	NE
5	TranFevlim	[redacted]	[redacted]	NE	NE
6	Ork6<=Age<12FevAcuteChange	[redacted]	[redacted]	NE	NE
7	PexOverAgecutB	[redacted]	[redacted]	NE	NE
8	CfMortBlFemale	[redacted]	[redacted]	NE	NE
9	OrkAge<6FevAcuteChange	[redacted]	[redacted]	NE	NE
10	Ork12<=AgeWfazAcuteChange	[redacted]	[redacted]	NE	NE

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio®; Lt, long term; Mort, mortality; Ork, Orkambi®; PEx, pulmonary exacerbation; Sym, Symkevi®; Util, utility.

F/MF genotype

Figure 19. Tornado diagram for ELX/TEZ/IVA F/MF genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio®; Lt, long term; Mort, mortality; Ork, Orkambi®; PEx, pulmonary exacerbation; Sym, Symkevi®; Util, utility.

Table 84. DSA results: F/MF genotype – ECM vs CFTRm therapies (PAS prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
ELX/TEZ/IVA **Base case ICER: £[redacted]**					
1	UtilFev70	[redacted]	[redacted]	NE	NE
2	Kaf12<=AgeFevLtChange	[redacted]	[redacted]	NE	NE
3	rngFev	[redacted]	[redacted]	NE	NE
4	UtilFev40	[redacted]	[redacted]	NE	NE
5	CfMortBlFemale	[redacted]	[redacted]	NE	NE
6	UtilFev70_40	[redacted]	[redacted]	NE	NE
7	PexOverAgecutA	[redacted]	[redacted]	NE	NE

8	CfMortBlMale	[redacted]	[redacted]	NE	NE
9	PexUnderAgecutB	[redacted]	[redacted]	NE	NE
10	Kaf12<=AgeFevAcuteChange	[redacted]	[redacted]	NE	NE

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio®; Lt, long term; Mort, mortality; Ork, Orkambi®; PEx, pulmonary exacerbation; Sym, Symkevi®; Util, utility.

F/Gating genotype

Figure 20. Tornado diagram for ELX/TEZ/IVA F/Gat genotype (PAS prices)

[redacted]

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio® (ELX/TEZ/IVA); Lt, long term; Mort, mortality;; PEx, pulmonary exacerbation; Util, utility.

Table 85. DSA results: F/Gat genotype – ECM vs CFTRm therapies (PAS prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
ELX/TEZ/IVA **Base case ICER: £[redacted]**					
1	UtilFev70	[redacted]	[redacted]	NE	NE

2	Kaf12<=AgeFevLtChange	[redacted]	[redacted]	NE	NE
3	rngFev	[redacted]	[redacted]	NE	NE
4	UtilFev40	[redacted]	[redacted]	NE	NE
5	UtilFev70_40	[redacted]	[redacted]	NE	NE
6	Kaf12<=AgeFevAcuteChange	[redacted]	[redacted]	NE	NE
7	PexOverAgecutA	[redacted]	[redacted]	NE	NE
8	CfMortBlFemale	[redacted]	[redacted]	NE	NE
9	CfMortBlMale	[redacted]	[redacted]	NE	NE
10	PexUnderAgecutB	[redacted]	[redacted]	NE	NE

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio®; Lt, long term; Mort, mortality;; PEx, pulmonary exacerbation; Util, utility.

F/RF genotype

Figure 21. Tornado diagram for ELX/TEZ/IVA F/RF genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio® (ELX/TEZ/IVA); Lt, long term; Mort, mortality; PEx, pulmonary exacerbation; Util, utility.

Figure 22. Tornado diagram for TEZ/IVA F/RF genotype (PAS prices)

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV, percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Lt, long term; Mort, mortality; PEx, pulmonary exacerbation; Sym, Symkevi® (TEZ/IVA); Util, utility.

Table 86. DSA results: F/RF genotype – ECM vs CFTRm therapies (PAS prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
ELX/TEZ/IVA **Base case ICER: £[redacted]**					
1	UtilFev70	[redacted]	[redacted]	NE	NE
2	Kaf12<=AgeFevLtChange	[redacted]	[redacted]	NE	NE
3	rngFev	[redacted]	[redacted]	NE	NE
4	UtilFev40	[redacted]	[redacted]	NE	NE
5	UtilFev70_40	[redacted]	[redacted]	NE	NE
6	Kaf12<=AgeFevAcuteChange	[redacted]	[redacted]	NE	NE
7	CfMortBlFemale	[redacted]	[redacted]	NE	NE
8	PexOverAgecutA	[redacted]	[redacted]	NE	NE
9	TranFevlim	[redacted]	[redacted]	NE	NE
10	CfMortBlMale	[redacted]	[redacted]	NE	NE
TEZ/IVA					

Base case ICER: £[redacted]					
1	UtilFev70	[redacted]	[redacted]	NE	NE
2	Sym12<=Age<100FevLtChange	[redacted]	[redacted]	NE	NE
3	UtilFev70_40	[redacted]	[redacted]	NE	NE
4	UtilFev40	[redacted]	[redacted]	NE	NE
5	Sym12<=Age<100FevAcuteChange	[redacted]	[redacted]	NE	NE
6	rngFev	[redacted]	[redacted]	NE	NE
7	CfMortBlFemale	[redacted]	[redacted]	NE	NE
8	SymAge<12DiscPAcuteChange	[redacted]	[redacted]	NE	NE
9	PexOverAgecutA	[redacted]	[redacted]	NE	NE
10	PexUnderAgecutB	[redacted]	[redacted]	NE	NE

Abbreviations: BL, baseline; CF, cystic fibrosis; ECM, established clinical management; FEV,,percent predicted forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; Kaf, Kaftrio®; Lt, long term; Mort, mortality; Ork, Orkambi®; PEx, pulmonary exacerbation; Sym, Symkevi®; Util, utility.

4.2.2.4 Scenario analysis

The EAG ran a number of scenarios to test alternative assumptions made in the model. These are described in Table 87.

Table 87. EAG scenario analyses

	Base case	Scenario analysis
Clinical parameters		
1	Long-term decline in ppFEV$_1$ modelled as a relative reduction in decline compared to ECM	Long-term decline in ppFEV$_1$ modelled as an absolute reduction compared to ECM
2	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e., same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline for each CFTR modulator based on Company estimates. This would apply the value for ELX/TEZ/IVA based on the CF Registry Final Analysis ([redacted] and reported rates for TEZ/IVA (61.5%) and LUM/IVA (42%) from the Company models

3	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e., same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline for ELX/TEZ/IVA based on the CF Registry Final Analysis ([redacted] [AR data only]), EAG base case assumptions for TEZ/IVA and LUM/IVA
4	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e., same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline based on lower bound estimates calculated by the EAG of 37.7% for ELX/TEZ/IVA and 10.63% for TEZ/IVA
5	Both an indirect effect (through ppFEV$_1$) and direct treatment effect on pulmonary exacerbations applied	No separate treatment effect on pulmonary exacerbations applied. The effect on pulmonary exacerbations is therefore only due to the treatment effect on ppFEV$_1$ (indirect treatment effect)
6	Direct treatment effect on pulmonary exacerbations applied for the trial period only	Direct treatment effect on pulmonary exacerbations applied for the observed period equal to the long-term extension studies
7	No discontinuations beyond 5 years on treatment	No discontinuations beyond the observed extension study period (96 weeks or 144 weeks) as applied in the Company's model
8	100% long-term compliance for CFTR modulators after the acute period	93% long-term compliance for CFTR modulators after the acute period
HRQoL		
9	Health state utility values (EQ-5D-3L) sourced from the LUM/IVA clinical trial	Health state utility values taken from Acaster 2015 (EQ-5D). Same as those applied in Company scenario analysis
10	Pulmonary exacerbation disutility applied for 30 days	Pulmonary exacerbation disutility applied for 14 days
11	Health state utility values (EQ-5D-3L) sourced from the LUM/IVA clinical trial	Company model utility values based on CFQ-R utility values
12	No carer QoL utility values included	Inclusion of utility increment for carers of patients aged <12 on ELX/TEZ/IVA
Costs		
13	No difference in ECM medication costs between patients on CFTR modulators and ECM alone	Reduction in ECM medication costs for patients on CFTR modulator treatments of 23%
14	No difference in ECM medication costs between patients on CFTR modulators and ECM alone	Reduction in ECM medication costs for patients on CFTR modulator treatments of 40%

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; CF, cystic fibrosis; QALY, quality adjusted life year; ECM, established clinical management; CFTR, cystic fibrosis transmembrane regulator; QoL, quality of life

The results of the scenario analyses are presented separately for each genotype and are presented as full incremental ICERs. As only ELX/TEZ/IVA has marketing authorisation for F/MF and F/Gating genotypes, the ICERs presented are equivalent to pairwise versus ECM. Across all genotypes, none of the implemented scenario analyses resulted in an ICER below the £20,000–£30,000 WTP threshold.

F/F genotype population

	Absolute			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Base case							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 1: LT ppFEV$_1$ decline absolute reduction							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 5: No separate PE treatment effect							

ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Lower long-term CFTR modulator compliance							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: EQ-5D values from Acaster 2015*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: CFQ-R utility values from company model							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						

*Severity modifier of 1.2 applied. Fully incremental ICERs without a severity modifier are £[redacted] £[redacted] and £[redacted] for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, respectively

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

F/MF population

	Absolute			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Base case							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 1: LT $ppFEV_1$ decline absolute reduction							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 2: Company's estimates of LT $ppFEV_1$ decline on modulator treatments							
ECM	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 3: LT $ppFEV_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 4: LT $ppFEV_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds							
ECM	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 5: No separate PE treatment effect							
ECM	[redacted]						

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Lower long-term CFTR modulator compliance							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: EQ-5D values from Acaster 2015*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: CFQ-R utility values from company model							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

F/Gating population

	Absolute			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	

Base case							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 1: LT ppFEV$_1$ decline absolute reduction							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments							
ECM	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 5: No separate PE treatment effect							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 6: PE treatment effect applied for extension study period							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 7: No discontinuation beyond the extension study period							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 8: Lower long-term CFTR modulator compliance							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 9: EQ-5D values from Acaster 2015*							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 10: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 11: CFQ-R utility values from company model							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						

Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

F/RF population

	Absolute			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Base case							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: LT $ppFEV_1$ decline absolute reduction							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Company's estimates of LT $ppFEV_1$ decline on modulator treatments							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: LT $ppFEV_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: LT $ppFEV_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: No separate PE treatment effect							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 6: PE treatment effect applied for extension study period							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 7: No discontinuation beyond the extension study period							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 8: Lower long-term CFTR modulator compliance							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 9: EQ-5D values from Acaster 2015							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 10: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 11: CFQ-R utility values from company model							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

Additional exploratory analysis

As noted in Section 1.3.2, clinical experts suggested that ELX/TEZ/IVA may prevent any further lung decline from occurring if initiated in the youngest population treatable (<2). The EAG wanted to run an incident population of patient 2 years old through the model to explore the effect of assuming no lung decline for patients on ELX/TEZ/IVA when all patients start treatment at age 2 (potentially prior to any irreversible lung or pancreatic damage), although clinicians suggested treatment may need to be initiated at a younger age to prevent any damage). However, due to limitations of the model (see Section 4.2.3.3) this was not possible. The EAG instead implemented an additional exploratory scenario in the prevalent population. In this scenario, patients treated with ELX/TEZ/IVA received the acute increase in $ppFEV_1$ and no further decline. In addition, the direct treatment effect of ELX/TEZ/IVA on PEs is assumed to apply for a patient's lifetime. The ongoing CF-STORM study is currently exploring whether reducing usage of nebuliser treatments, when taken alongside ELX/TEZ/IVA, results in any significant decline in lung function. As this additional scenario is applying optimistic assumptions regarding the impact of ELX/TEZ/IVA, it also implements a 40% reduction in the costs of ECM medication costs for patients on CFTR modulator treatments.

As this exploratory scenario essentially assumes that patients lung function decline is restored to normal, a 1.5% discount rate for both costs and benefits is applied. Although the EAG believes the 1.5% discount rate may be applicable in this exploratory scenario, this is only the case if the assumption that avoiding further lung decline throughout a patient's life would equate to living in full or near full health. The EAG notes that this is a liberal assumption and the ICERs presented below would be higher if this did not apply.

Both the pairwise (against ECM only) and fully incremental results are provided below. The EAG notes that due to the use of the 1.5% discount rate applied in this scenario, a severity modifier of 1.2 is applicable. The EAG notes that despite applying liberal assumptions on the effectiveness of ELX/TEZ/IVA in the long-term for all patients in the prevalent population and a severity weighting of 1.2 applied, the ICERs are still not considered cost-effective.

Table 88. Additional exploratory scenario analyses, pairwise results

Population	Absolute			Incremental			ICER (no severity weighting)	ICER (severity weighting applied)
	Costs	QALY	LY	Costs	QALY	LY		
F/F genotype								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; NHB, net health benefit, ECM, established clinical management

Table 89. Additional exploratory scenario analyses, fully incremental analysis results

Population	Absolute			Incremental			ICER (no severity weighting)	ICER (severity weighting applied)
	Costs	QALY	LY	Costs	QALY	LY		
F/F genotype								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; NHB, net health benefit, ECM, established clinical management

4.2.2.5 Model validation

A health economist was responsible for the specification and development of the MTA model. A second health economist was responsible for validating model assumptions and performing a detailed quality assurance of the MTA model. A health economist, not involved in the MTA project, performed an independent review of the MTA model, including face validity checks and black and white box testing of the model.

The EAG's clinical experts were involved with validating key assumptions in the model to ensure clinical validity of model inputs and outputs as well as peer review of the report.

4.2.3 Discussion

4.2.3.1 Summary of key results

The purpose of this MTA was to assess the cost-effectiveness of elexacaftor/tezacaftor/ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor for the treatment of people with cystic fibrosis (CF) with at least one *F508del* mutation. All results shown in this report are based on PAS prices for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA.

All three CFTR modulator treatments have marketing authorisation for F/F patients, however the age at which these treatments are available to patients differs. LUM/IVA has marketing authorisation for patients aged ≥1, TEZ/IVA aged ≥6 and ELX/TEZ/IVA has aged ≥2 (expected marketing authorisation will be granted by time of publication for 2–5 year olds). Therefore, in the economic model, any

patients who start the model in each arm before the marketing authorisation age for that specific treatment receives ECM only. None of the ICERs in the base case results were below the NICE recommend willingness to pay (WTP) threshold of £20-000–£30,000. The base case full incremental analysis results suggest that ELX/TEZ/IVA is the most cost-effective of the three modulator treatments in the F/F population, with an ICER of [redacted]. LUM/IVA was the least cost-effective with an ICER of £[redacted] This was a result of small incremental QALY gains, as the EAG base case assumes the same long-term decline in $ppFEV_1$ as ECM on LUM/IVA, and large incremental costs due to the high acquisition costs of CFTR modulator treatments.

In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Base case deterministic results were similar across the two populations when compared to ECM, with ICERs of [redacted] and [redacted] respectively.

In the F/RF population, both TEZ/IVA and ELX/TEZ/IVA have marketing authorisation. The full incremental results suggest that ELX/TEZ/IVA is the most cost-effective of the two treatments, producing both higher costs and higher QALYs than TEZ/IVA, with a resulting ICER £[redacted] compared to the TEZ/IVA ICER of £[redacted]

ELX/TEZ/IVA had the greatest impact on the annual rate of pulmonary exacerbations (PE), $ppFEV_1$ decline, improvement in median survival and rate of lung transplants in every genotype. This translated into greater improvements in both life years (LYs) and quality adjusted life years (QALYs) than LUM/IVA and TEZ/IVA.

The EAG ran a range of scenarios to test the impact on the ICER of alternative assumptions and data inputs for key parameters. Across all genotypes, none of the implemented scenarios resulted in an ICER below the NICE willingness to pay (WTP) threshold of £20,000–£30,000.

Scenario 1 examined the consequences of applying an absolute rather than relative reduction in the rate of $ppFEV^1$ decline for ELX/TEZ/IVA. This reduced the ICERs, however the EAG does not consider applying an absolute reduction of 0.79 (ELX/TEZ/IVA) to older patients to be clinically plausible. This is because the assumed rate of decline for older patients using the non-linear model of Szczesniak is already close to 0.79, (0.70 or smaller for F/F, F/MF and F/Gating individuals from aged 40, and 0.61 or smaller for F/RF from aged 40). As such, applying the absolute reductions in $ppFEV_1$ for these age groups is likely to overestimate the reduction in $ppFEV_1$ decline that these individuals would

experience, i.e., the EAG considers the estimated relative reduction (61.0% of the ECM reduction) to be more transportable to these individuals than the absolute reduction (ECM reduction +0.79).

Across all populations, the assumptions on the long-term effectiveness of CFTR modulator treatments on $ppFEV_1$ decline had one of the greatest impacts. The EAG considers the two scenarios changing the long-term effectiveness assumptions further in line with the Company's estimates (scenario 2 and 3), to be optimistic and likely to overestimate the effect of CFTR modulators, as previously discussed. Scenario 2 applied the relative reduction in the long-term rate of $ppFEV_1$ decline based on the Company's analyses. This applied a rate of 42% for LUM/IVA, 61.5% for TEZ/IVA, both taken from the Company models, and [redacted] for ELX/TEZ/IVA, calculated by the EAG from the Final Analysis of the Data Collection Agreement of UK CF Registry Data. Based on the full incremental analysis, this resulted in reduced ICERs in all genotypes for LUM/IVA and TEZ/IVA. However, in the F/F and F/RF genotype populations, the ICER for ELX/TEZ/IVA increased. Although the LYs and QALYs increased compared to base case for TEZ/IVA and ELX/TEZ/IVA in both of these genotypes, the effect was more prominent in the TEZ/IVA treatment arm, which resulted a higher ICER for ELX/TEZ/IVA when compared to TEZ/IVA.

Scenario 3 changed the assumptions made on the long-term effectiveness of ELX/TEZ/IVA only, applying the relative rate of decline of [redacted] calculated from Final Analysis of the Data Collection Agreement of UK CF Registry Data,[164] while keeping the rates for LUM/IVA and TEZ/IVA the same as the EAG base case. The calculated rate of decline is based on the mixed effects model which estimates the annual rate of change in $ppFEV_1$ using data captured during annual reviews only. This was a planned sensitivity analysis undertaken as part of the Final Analysis. This analysis excludes encounter data as this was not available in the historical comparison cohort. The EAG preferred this sensitivity analysis as it was considered plausible that data collected at encounters may include more measurements during periods of clinical instability than data collected at annual reviews. However, the EAG considers that the most appropriate analysis, that was not provided by the Company, would have included all available data and appropriately modelled the impact of review type on $ppFEV_1$, rather than analysing subsets of the data. Scenario 4 used a LT rate of decline for ELX/TEZ/IVA of 37.7% and TEZ/IVA of 10.63%. These were derived by applying the relative rate of decline calculated for IVA from Newsome 2022 as the relative rate of decline for ELX/TEZ/IVA, which was then scaled by the ELX/TEZ/IVA:TEZ/IVA acute treatment effect in the F/F population (37.7*4/14.2). The EAG notes these estimates are likely conservative in the short-term, but as the estimates are applied for a person's lifetime in the economic model, they offer estimates that confer a lower decision risk given

the uncertainty associated with applying relative rates of decline for time periods much longer than currently available data provide.

Both scenarios 5 and 6 changed the assumptions on the direct treatment effect of CFTR modulators on PEs. Scenario 4 assumed no separate direct treatment effect on PEs, therefore the effect on PEs is only due to the treatment effect on ppFEV$_1$. This had a minimal impact on the ICERs across all genotypes, with the largest impact observed in LUM/IVA F/F genotype. Scenario 5 extended the time period that the direct treatment effect on PEs was applied for from the acute trial period to that of the long-term extension studies. This also had a minimal impact on the ICERs, except for LUM/IVA (F/F genotype) which resulted in a reduction in the ICER of [redacted]. As the incremental QALYs are so small for ECM compared to LUM/IVA, this small increase in incremental QALYs, alongside a reduction in costs, has a large impact on the resulting ICER. However, relative to the base-case ICER for LUM/IVA, this change only equates to [redacted] decrease.

Clinical experts stated that CFTR modulators are generally well tolerated yet they do see patients discontinue treatment for various reason beyond the first few years on treatment. Therefore, the EAG's base case assumed no further discontinuations after 5 years on treatment. Scenario 7 explored the impact of changing this time period to the observed extension study period only (96 weeks or 144 weeks), as applied in the Company's models. This reduced the ICERs across all genotypes.

Scenario 8 applied a 93% compliance rate for all CFTR modulator treatments beyond the trial period. This had the greatest impact on the ICERs for both LUM/IVA (≈ -£100,000) and TEZ/IVA (≈ -£45,000-55,000). The ICERs for ELZ/TEZ/IVA reduced in the range of ≈£20,000–£35,000 across the different genotypes. The EAG notes that, although compliance rates may be lower outside of clinical trials, any reduction in efficacy may not be fully accounted for. In addition, clinical advisors to the EAG noted that when patients stop taking modulator treatments, particularly ELX/TEZ/IVA, they may quickly feel the loss in benefits and therefore resume treatment quickly and therefore clinical experts expect high adherence.

Scenario 9 applied alternative EQ-5D values from Acaster 2015.[214] These values were lower than those applied in the EAG base case. This resulted in lower incremental QALYs across all comparisons, and therefore higher ICERs. However, the EAG notes that the total QALYs on ECM in this scenario are

lower and therefore a severity modifier of 1.2 applies to genotypes F/F, F/MF and F/gating. Due to the higher average age in the F/RF population, the severity modifier did not apply to this age group. The inclusion of a severity modifier therefore results in lower overall ICERs. The utility values applied in this scenario are based on 401 UK participants with a self-reported clinical diagnosis of CF, 18 years or above. Therefore, there is potential selection bias in the recruitment of this study. The EAG notes that the alternative utility values resulted in a change in the magnitude of the ICERs for all genotypes and CFTR modulator treatments, but not in the direction of the results.

Reducing the duration of the disutility value applied for PEs to 14 days from 30 days (scenario 10) did not have a substantial impact on any of the ICERs.

Scenario 11 applied the utility values from the Company's model based on the CFQ-R data. The EAG notes that as with scenario 9, this resulted in in lower incremental QALYs across all comparisons, and therefore higher ICERs, with this being one of the most influential scenarios. In contrast to scenario 9 using Acaster utility values, however, the use of the Company's CFQ-R values did cause the severity modifier to apply.

The EAG is aware of the high impact on the life of carers of patients with CF. The EAG was unable to source appropriate EQ-5D data that measured the decrement on carers QoL due to CF. The Company [redacted] Due to the resulting increase in QALYs for patients on ELZ/TEZ/IVA, this resulted in lower ICERs for all genotypes, ranging from a reduction of [redacted] in the F/F population to [redacted] in the F/RF population.

Scenarios 13 and 14 explored the impact of reduced costs of ECM medications due to CFTR modulator use. It was highlighted to the EAG by clinical experts that the impact of a reduction in the use of concomitant medications due to CFTR modulators is currently unknown and being explored in ongoing studies. The impact was greatest on the F/MF and F/gating populations but was not a significant factor.

The EAG also implemented an additional exploratory scenario to investigate the impact of ELX/TEZ/IVA preventing any long-term lung decline post treatment initiation. This exploratory scenario also assumes that the direct treatment effect of ELX/TEZ/IVA on the rate of pulmonary exacerbations last for a lifetime. Although this scenario resulted in lower ICERs for ELX/TEZ/IVA

compared to the base case, they were still not below the £30,000 threshold, despite a severity modifier of 1.2 being applied, a 1.5% discount rate and highly optimistic assumptions regarding the long-term effectiveness of ELX/TEZ/IVA.

4.2.3.2 Generalisability of results

The perspective of the analysis reflects NHS England and therefore results are generalisable to CF patients in England. When available, the EAG used the most up to date evidence reflective of the population in England. Clinical experts consulted by the EAG confirmed that the populations included in clinical trials used to inform the baseline characteristics of the modelled population and effectiveness evidence can be generalised to the UK population. In addition, as the EAG analyses utilises CF Trust data, results are inherently generalisable to patients in the UK. However, the population included in the clinical trials excluded patients with a baseline ppFEV$_1$ of lower than 40. Therefore, the modelled population excludes those with patients with the worst lung function and results may not be generalisable to these patients.

The EAG analyses are based on the prevalent population including all ages of patients, with a mean age of 21. Clinical experts to the EAG noted that if ELX/TEZ/IVA is initiated in very young patients, such as age 1 to 2, this may avoid long-term lung damage and could potential provide "near normal" lifetime lung function. Therefore, an incident CF population that begins treatment prior to any irreversible lung or pancreatic damage may experience greater benefits in treatment with ELX/TEZ/IVA. However, this was not able to be modelled in the EAG's model.

4.2.3.3 Strengths and limitations of analysis

A key strength of the EAG's analysis is that all three interventions in the final NICE scope are included within the same economic model and compared against each other in an incremental analysis. The EAG analysis follows the NICE final scope and incorporates the current and expected marketing authorisations for the three included modulator treatments.

The EAG's base case cost-effectiveness results differ largely from the Company's models. However, due to the EAG separating their analyses based on genotype and including younger age groups to reflect recent marketing authorisation, the results are not directly comparable. Due to the EAG being required to compare patients across all three treatments when they are eligible to start different modulator therapies at different ages, the EAG model includes some patients on ECM prior to being able to start TEZ/IVA and ELX/TEZ/IVA, in line with their marketing authorisation. As the Company

submitted separate models for each modulator therapy, compared only with ECM, this was not a feature in the Company's models.

Nonetheless, there are other fundamental differences between the EAG's approach and the Company's models which are driving the differences in cost-effectiveness. The EAG used a more recent baseline mortality hazard based on UK CF Registry data from 2011–2015,[236] which included survival estimates for male and female patients with either *F508del* homozygous or heterozygous. Therefore, the EAG was able to use separate baseline mortality hazards based on a patient's sex and genotype. In addition, the EAG applied a non-linear decline in ppFEV$_1$ over time for patients on ECM, which resulted in a slower rate of decline for patients aged 25+ than that applied in the Company's models using a linear decline. This was in line with the EAG's clinical experts who suggested you would expect to see a slower rate of decline for patients after age 30 than that suggested from the Company's approach.

The EAG's model predicts a median age of death for patients on ECM ranging from 45–50, depending on genotype. The EAG's clinical experts stated they expect median survival for patients on ECM to be mid 40s and therefore the EAG's model predicted value is in line with this. This is also very similar to the estimated survival age beyond which 50% live as reported by Keogh 2018[236] based on UK CF Registry data for patients conditional on being alive until age 20 (46.8 for males *F508del* heterozygous). As the average age of patients in the model is 21, this comparison also provides further validation of the EAG's model to predict ECM survival. The median survival for ECM patients from the Company's model for ELX/TEZ/IVA was 38 years old, which the EAG deemed too low based on recent advances in treatment and care for CF patients prior to the use of CFTR modulators and on comparison to recent estimated median survival in the UK CF Registry. The Company's baseline mortality hazard is based on UK CF Registry data from 1985-2008 and clinical experts to the EAG noted how care, and in turn survival, has improved since this time. Therefore, the EAGs approach better reflects survival under current care. Combined with the use of a non-linear decline in ppFEV$_1$ over time, this explains the difference between the EAG and Company's median predicted survival.

Despite the strengths of the EAG's approach, there were a number of limitations that required assumptions to be made within the analyses. A key uncertainty in the model due to a lack of long-term data is on treatment effectiveness for each CFTR modulator over a patient's lifetime, as discussed in Section 3.3.3. Therefore, assumptions using the best available evidence were made by

the EAG. As shown in the EAG's scenario analyses, the ICERs were most sensitive to these assumptions.

The model structure uses an individual microsimulation model, in which a Cox proportional hazards (CPH) model developed by Liou *et al.* 2001[172] is used to predict patient survival based on nine baseline characteristics and demographic variables. The CPH model was based on a historical USA dataset and has not been validated on the UK population. However, clinical experts advising the EAG stated that they would not expect there to be significant differences between the two populations. The CPH model was not developed or validated to assess the impact on mortality due to changes in an individual's characteristics over time, such as an acute increase in $ppFEV_1$. Therefore, it is unknown what the impact of using the model in this way would be on changes to other covariates in the model. In addition, the patient population used to develop the CPH model had a mean age of 18 and it is likely that a small number of patients aged >50 were included in the sample. As $ppFEV_1$ is not a clinical outcome measured in patients aged <6, these patients were also not included in the dataset used to develop the CPH. If the prediction of mortality is substantially different for younger or older ages, then the current model used may inaccurately predict survival for these patients. When the EAG attempted to model an incident population (all start aged 2) to explore the effect of ELX/TEZ/IVA providing a lifetime benefit and preventing any future decline in lung health if started at a young age, the model overestimated survival for patients on ECM and therefore plausible estimates of cost-effectiveness in the scenario were not possible to obtain. Despite these limitations of the model structure, the EAG notes that the models median predicted survival for ECM in the EAG's base case is in line with clinical experts opinion and recent data from the CF Registry.

Data on changes in infection rates over time were not able to be included in the model due to a lack of available data on prevalence rates, and therefore how these may change over time with age or following treatment with CFTR modulators. Clinical experts noted that respiratory infections are associated with decline in lung function and that there is some evidence of CFTR modulators reducing *Pseudomonas* prevalence. It is unknown what the impact of changes in infections over time might be on the cost-effectiveness results, but this may have underestimated the benefits of CFTR modulator treatments.

When data were not available, assumptions were made regarding the best available evidence to apply. For patients aged <6 in the model, when evidence was not available from clinical trials or lacked face validity, the EAG assumed equal efficacy as patients aged 6–11. This is likely to be a

conservative assumption as younger patients may receive greater benefit long term as less lung damage has occurred and treatment may also prevent infections in very young patients developing. In addition, patient level data were not available for patients aged <6. Therefore, a subset of patients with the same characteristics as individuals aged 6–8 was created in order to be able to model these patients. Although this involved resampling patients already in the patient population, using individuals aged 6-8 ensured that patients as similar in age as possible to the cohort being created were used, without overly reducing the number of patients available to sample from, and the resulting heterogeneity in characteristics.

The NICE reference case states that health related quality of life (HRQoL) should be measured using the EQ-5D, with data taken directly from the trials being the preferred source of data. Unfortunately, EQ-5D data was only collected in one of the CFTR modulator trials (LUM/IVA).[42] Therefore, the EAG applied the values obtained from patients within the LUM/IVA study to all treatment arms in the model. This was based on *F508del* homozygous patients aged ≥12 and therefore these values were assumed to also be representative of *F508del* heterozygous patients aged <12.

The model structure uses an individual patient simulation model developed in Microsoft Excel®. When testing different common random number sets, which were used to reduce variance and model run times, there was still some variation in the ICER for LUM/IVA; however the EAG did not deem this to change the overall conclusions. In addition, due to the significant run time of the model and requirements of deterministic and probabilistic sensitivity analyses to be completed, running a greater number of patients was not possible. This is a common limitation with patient level simulation models[238] and future research could look to adapt this model into a faster processing computer package.

A consideration for clinical practice that could not be explored within the MTA was treatment sequencing. In the EAG model, patients are treated with ECM until eligible to start each CFTR modulator, based on age. In clinical practice, patients may start on a CFTR modulator at the youngest age possible, such as LUM/IVA and then switch to a different CFTR modulator once they reach the age at which a more effective treatment holds marketing authorisation (i.e. TEZ/IVA or ELX/TEZ/IVA). In addition, patients who discontinue a CFTR modulator in the model move to ECM only. If more than one CFTR modulator was available in routine clinical practice, patients may be started on another upon discontinuation.

5 Assessment of factors relevant to the NHS and other parties

The Evidence Assessment Group (EAG) considers that all factors relevant to the National Health Service (NHS) and other parties are captured within the clinical and cost-effectiveness analyses.

However, the EAG analyses are based on the prevalent population including all ages of patients, with a mean age of 21. Clinical experts to the EAG noted that if ELX/TEZ/IVA is initiated in very young patients, such as age 1 to 2, this may avoid long-term lung damage and could potential provide “near normal” lifetime lung function. Therefore, the incident CF population may experience greater benefits in treatment with ELX/TEZ/IVA.

6 Discussion

6.1 Statement of principle findings

This multiple technology appraisal (MTA) evaluated the clinical and cost effectiveness of lumacaftor/ivacaftor (LUM/IVA), tezacaftor-ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for treating cystic fibrosis compared to each other and established clinical management (ECM) in England and Wales. The populations considered within the scope of this appraisal followed the current or expected marketing authorisation of each intervention:

- LUM/IVA: people with CF aged 1+ years who were homozygous for the *F508del* mutation (F/F genotype);
- TEZ/IVA: people with CF aged 6+ years who were homozygous for the *F508del* mutation (F/F genotype) or had one F508del copy heterozygous with an eligible residual function mutation (F/RF genotype);
- ELX/TEZ/IVA: people with CF aged 2+ years who were homozygous for the *F508del* mutation (F/F genotype) or had one *F508del* copy heterozygous with an eligible residual function mutation (F/RF genotype), minimal function mutation (F/MF genotype) or gating mutation (F/Gating genotype).

The EAG's clinical experts stated that a person with CF should be treated with a CFTR modulator as soon as they become eligible. To assess the clinical effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, the EAG focused on three clinical outcomes used to predict survival for people with CF: acute and long-term changes in $ppFEV_1$; the rate of pulmonary exacerbations; and weight-for-age z-score. Treatment with ELX/TEZ/IVA was associated with large and statistically significant increases in $ppFEV_1$ and increase in weight-for-age z-score across CF genotypes and ages where $ppFEV_1$ is recorded. In the EAG's microsimulation, this translated into a predicted survival benefit for the prevalent population of CF individuals recruited in clinical trials of [redacted] and [redacted] years in comparison to ECM in the F/F, F/Gating, F/MF and F/RF genotypes, respectively. Effect sizes were attenuated in the F/RF population, which is likely due to the F/RF genotype being associated with a milder CF phenotype at baseline. While not measured consistently across clinical trials and genotypes, ELX/TEZ/IVA reduced the rate of pulmonary exacerbations requiring IV antibiotics relative to LUM/IVA, TEZ/IVA and ECM.

Compared to ELX/TEZ/IVA, LUM/IVA and TEZ/IVA had smaller but still statistically significant increases in ppFEV$_1$ and reductions in pulmonary exacerbations compared to ECM, when reported. While LUM/IVA was associated with a statistically significant, but small, acute increase in weight-for-age z-score compared to ECM, TEZ/IVA was not associated with a statistically significant increase in weight-for-age z-score compared to ECM during the acute phase of the clinical trials.

Despite no validated minimum clinically important differences for ppFEV$_1$, weight-for-age z-score or pulmonary exacerbations, the EAG's clinical experts considered the effect sizes associated with ELX/TEZ/IVA to be clinically meaningful, and like to be associated with increased survival and a reduced rate of pulmonary exacerbations in people with CF. As ppFEV$_1$ and weight-for-age z-scores predict survival, the EAG considers the smaller response to LUM/IVA and TEZ/IVA to also likely be clinically meaningful, but notes the magnitude of the effects are considerably smaller than for ELX/TEZ/IVA. This is visible in the results of the EAG's patient simulation model, in which the incremental life years gained was [redacted] years in comparison to ECM in the F/F genotype for LUM/IVA, and [redacted] and [redacted] years in comparison to ECM in the F/F and F/RF genotypes for TEZ/IVA, respectively.

The EAG considers the key clinical trials of CFTR modulators to have good generalisability to clinical practice in England and Wales, and notes that acute effects similar to those observed in clinical trials have also been observed in the UK CF Register following the managed access agreements. The EAG considers there to be some uncertainty about the generalisability of the trial results to people with ppFEV$_1$<40% and ppFEV$_1$ ≥90%, who were excluded from clinical trials of people aged 12+ years. However, the EAG notes that:

- For people with ppFEV$_1$ ≥90%: the effects of CFTR modulators are likely more visible in the prevention of long-term lung decline rather than acute effects on ppFEV$_1$ and pulmonary exacerbations;

- For people with CF and ppFEV$_1$ <40%: these individuals have advance lung disease and may be candidates for transplant. There is real-world evidence that such patients experience acute increases in ppFEV$_1$ in-line with the magnitude observed for people with ppFEV$_1$ >40% for ELX/TEZ/IVA, although the response is more uncertain for LUM/IVA and TEZ/IVA. However, if CFTR modulator therapies are approved for routine commissioning in England

and Wales they would be initiated prior to an individual's $ppFEV_1$ declining to less than 40% in the incident population.

The major outstanding uncertainty following the clinical evaluation in this MTA concerns the long-term effectiveness of CFTR modulator therapies. Where uncontrolled long-term data are available, follow-up is often limited to 2 to 4 years, meaning that the effects of CFTR combination therapies over a lifetime are highly uncertain. The EAG considers this uncertainty to be heightened for ELX/TEZ/IVA, in which the majority of long-term data are from uncontrolled clinical trials and real-world data, where data collection windows overlapped substantially with the COVID-19 pandemic. In the absence of robust data from ELX/TEZ/IVA, TEZ/IVA or LUM/IVA to inform the long-term effectiveness of CFTR modulator combination therapies, the EAG considered data from a long-term study of IVA monotherapy in people with CF and gating mutations to be the most robust source of data that could approximate the long-term rate of $ppFEV_1$ decline for people treated with ELX/TEZ/IVA compared to ECM, namely a relative reduction of 37.7%, which the EAG scaled up to 61.0% based on the ratio of the ELX/TEZ/IVA:IVA acute treatment effect. The EAG scaled this decline down for TEZ/IVA based on the relative magnitude of the acute effect of TEZ/IVA compared to ELX/TEZ/IVA, as the placebo-controlled phase and open label extension studies of TEZ/IVA were consistent with some slowing of the rate of decline of $ppFEV_1$ compared to ECM. For LUM/IVA, the EAG did not apply a slowing of the rate of decline of $ppFEV_1$ compared to ECM.

The National Institute of Health and Care Excellence (NICE) typically considers interventions a cost-effective use of the National Health Service (NHS) resources if the incremental cost-effectiveness ratio (ICER) sits below a £20,000–£30,000 threshold. None of the EAG's base case ICERs (both pairwise versus ECM alone or full incremental results) would be considered to be cost-effective.

The differences in the clinical effectiveness between the three modulator treatments was observed in the cost-effectiveness results, with ELX/TEZ/IVA having the lowest ICERs when compared to LUM/IVA or TEZ/IVA in the populations in which more than one CFTR modulator is available. The difference between LUM/IVA and TEZ/IVA in the F/F population were less substantial, in line with the outcomes observed in the clinical data. ELX/TEZ/IVA also had the most substantial difference in clinical outcomes predicted by the economic model, namely the annual rate of pulmonary exacerbations, proportion of patients requiring lung transplant and change in both $ppFEV_1$ and WFAZ score.

For the F/F population, all three modulator treatments have marketing authorisation. The ICERs from the full incremental analysis within the population were [redacted] for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA respectively.

In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Base case deterministic results were similar across the two populations when compared to ECM, with ICERs of [redacted] respectively.

In the F/RF population, both TEZ/IVA and ELX/TEZ/IVA have marketing authorisation. The full incremental results suggest that ELX/TEZ/IVA is the most cost-effective of the two treatments, producing both higher costs and higher QALYs than TEZ/IVA, with a resulting ICER of [redacted] compared to the TEZ/IVA ICER of [redacted]

The EAG ran a range of scenarios to explore the impact of different assumptions. The EAG notes that in all analyses, incremental QALYs were relatively small for TEZ/IVA and LUM/IVA, with high incremental costs, resulting in sensitive ICERs. This was seen with changes in magnitude of the ICERs but not direction of results, with all scenario analyses resulting in the same conclusions as the base case analysis.

The key drivers of cost-effectiveness for all genotype populations were the long-term assumptions of the treatment effect of CFTR modulators on $ppFEV_1$ decline. As discussed above, this is also the main outstanding uncertainty following the clinical evaluation in this MTA. When applying the long-term rate of decline in $ppFEV_1$ (relative to ECM) for LUM/IVA and TEZ/IVA from the Company's analyses and the calculated rate of decline from the Final Analysis of the Data Collection Agreement of UK CF Registry Data, the full incremental analysis ICERs showed the greatest impact for LUM/IVA in the F/F population. The increase in incremental QALYs was greater for LUM/IVA and TEZ/IVA than ELX/TEZ/IVA in the F/F population, resulting in a higher ICER when compared to TEZ/IVA in the full incremental analysis when compared to the base case results. In the F/MF and F/Gating populations, in which only ELX/TEZ/IVA has marketing authorisation, the ICERs were reduced. Despite the scenarios on the long-term effectiveness having the most significant impact on the ICERs, none of these fell below the cost-effective range of £20,000–£30,000 per QALY gained. In addition, the EAG notes that the rates applied in these scenarios are considered by the EAG to be overly optimistic of the long-term effectiveness. However, due to the high uncertainty of the long-term effectiveness of

the CFTR modulators, the EAG deems these scenarios to potentially provide a lowest estimate of the likely ICERs achieved.

The EAG notes that the use of alternative assumptions around the direct treatment effect of CFTR modulators on pulmonary exacerbations (PEs) and discontinuations to have a minimal impact on the ICERs.

The use of alternative utility values was explored, using EQ-5D values which were lower than those applied in the EAG base case. This resulted in lower incremental QALYs across all comparisons, and therefore higher ICERs.

6.2 Strengths and limitations of the assessment

A strength of the EAG's clinical analyses is the combination of the EAG's systematic literature review and unpublished data provided by the Company through Study CSRs and *ad hoc* analyses to have relatively complete outcome data for the key acute clinical parameters of interest, with consistent outcome definitions between studies. Due to the availability of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA through managed access agreements in the UK, and other countries, in years prior to this MTA, the EAG was able to:

- Use real-world data on the use of CFTR modulators to inform the clinical and cost-effectiveness modelling, and;
- Receive input from clinical experts with years of experience of treating patients with CFTR modulators.

The EAG notes the contribution of the UK CF Registry in providing a rich source of data on over 99% of people with CF in the UK – in particular, the enriched data collection that was part of the Data Collection Agreement. However, despite the availability of real-world evidence in the UK and elsewhere, analyses of these data were limited due to the uncertain impact of the COVID-19 pandemic on clinical outcomes and lung function of people with CF. The EAG notes additional uncertainty due to the serial nature of uptake of CFTR modulators: the EAG's clinical experts considered that most eligible patients would have moved from treatment with ECM only to LUM/IVA or TEZ/IVA once available, and then subsequently to ELX/TEZ/IVA. As the real-world uptake of CFTR modulator therapies was rapid and widespread once available, contemporaneous control cohorts were unavailable.

The key strength of the EAG's economic assessment is that all three CFTR modulator interventions in the NICE final scope are included within the same economic model and compared against each other in a fully incremental analysis. The EAG analysis follows the NICE final scope and incorporates the current and expected marketing authorisations for the three included modulator treatments. Due to this, the EAG's cost effectiveness results are not directly comparable to the Company's due to including additional age groups. A further strength of the EAG's analysis compared to the Company's is that it follows the NICE reference case.

The EAG's economic model uses a baseline mortality hazard which is specific to the *F508del* population, based on a published flexible parametric cubic spline model fit to UK CF Registry data 2011-2015. The use of a flexible parametric model can provide a better fit to the data that may not be achievable with standard parametric survival models.

In addition, the EAG applied a non-linear decline in $ppFEV_1$ over time for patients on ECM, which resulted in a slower rate of decline for patients aged 25+ than that applied in the Company's models using a linear decline. This was in line with the EAG's clinical experts who suggested you would expect to see a slower rate of decline for patients after age 30 than that suggested from the Company's approach.

The EAG's model predicts a median age of death for patients on ECM ranging from 45–50, depending on genotype, which is in line with the EAG's clinical experts opinion on expecting median survival for patients on ECM to be mid-40s. For the F/F population, the Company's model for ELX/TEZ/IVA predicted a median survival of [redacted] which the EAG's clinical experts suggested was too low.

A key limitation of the EAG's economic analysis, which also applies to the Company's economic models, is the use of a Cox proportional hazards model (CPH) developed using historical data applied to a population in the United States (US). This model was not developed or validated to assess the impact on mortality due to changes in an individual's characteristics over time but instead to predict mortality based on a set of patient characteristics measured at one point in time. In addition, further patient characteristics that are not included in the CPH may be important predictors of survival. Despite these limitations of the model structure, the EAG notes that the models median predicted survival for ECM is in line with clinical experts opinion and recent data from the CF Registry.

Further limitations of the EAG's economic analysis include a lack of EQ-5D data from clinical trials for each CFTR modulator treatment, meaning EQ-5D data from the LUM/IVA trial was applied to all populations. Patient level data were not available for patients aged <6 included in the model, therefore patients aged 6–8 were resampled and assumed to represent patients <6. In clinical practice, these patients may be healthier as less lung damage may have occurred. Therefore, the benefit of CFTR modulator treatment may be greater than that modelled in these patients.

6.3 Uncertainties

As noted in Section 6.1, the major outstanding uncertainty following the clinical evaluation in this MTA concerns the long-term effectiveness of CFTR modulator therapies. Where uncontrolled long-term data are available, follow-up is often limited to 2 to 4 years, meaning that the effects of CFTR combination therapies over the lifetime are highly uncertain, and heightened for ELX/TEZ/IVA, in which the majority of long-term data are from uncontrolled clinical trials and real-world data that overlapped with the COVID-19 pandemic. The EAG notes the following additional uncertainties in the clinical evidence-base of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the:

- Lifetime AE profile of CFTR modulators, including regarding liver disease, cataracts, lens opacities, hypertension and adverse effects on a person's mental health;
- Long-term probability of developing different lung infections;
- Co-adherence to ECM medications for people treated with CFTR modulators, and the effects of discontinuing CFTR modulators;
- Clinical meaningfulness of acute changes in $ppFEV_1$ and weight-for-age z score, especially for LUM/IVA and TEZ/IVA where the effect sizes are small;
- Impact of CFTR modulator therapy on a person's HRQoL, and their carer's, as EQ-5D was not measured in most clinical trials;
- Long-term effectiveness of CFTR modulators, in particular ELX/TEZ/IVA, in young children and people with little existing lung damage, a subgroup of patients for which the long-term clinical outcomes of treatment with ELX/TEZ/IVA might be the most positive.

The above clinical evidence-based uncertainties all apply to the cost-effectiveness analysis. An additional key uncertainty related to the economic model is the application of the Liou 2001[172] Cox proportional hazards (CPH) model to predict mortality. As the data used to develop this model did not include patients aged <6 or >62, it is uncertain how the model performs in predicting survival for these ages. In addition, as previously noted, the CPH model was not developed to predict changes in

a patient's characteristics over time but instead to predict a person's mortality hazard based on their current characteristics. Whilst it may not be incorrect to use the CPH model in this way, further validation should be undertaken on this.

7 Conclusions

7.1 Implications for service provision

As a result of this multiple technology appraisal (MTA) multiple treatments for cystic fibrosis (CF) may be made available to patients in routine commissioning. However, there is currently a lack of both clinical and cost-effectiveness data on sequences of CFTR modulator treatments. In clinical practice, patients may start on a CFTR modulator at the youngest age possible, such as lumacaftor/ivacaftor [LUM/IVA] and then switch to a different CFTR modulator once they reach the age at which a more effective treatment holds marketing authorisation (i.e. tezacaftor/ ivacaftor [TEZ/IVA] or elexacaftor/tezacaftor/ivacaftor [ELX/TEZ/IVA]). In addition, if more than one CFTR modulator was available in routine clinical practice, patients may be started on another upon discontinuation.

The economic evaluation undertaken as part of the MTA showed that the fully incremental analyses resulted in ICERs ranging between £[redacted]. The high drug acquisition costs of CFTR modulators may be a barrier to the availability of these treatments in routine commissioning.

7.2 Suggested research priorities

As discussed in Section 6.3, a number of uncertainties remain regarding the clinical evidence base of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA, which therefore impact on the cost effectiveness analysis. The following priorities for future clinical research are suggested:

- Further data collection and statistical modelling of concerning the long-term effects of CFTR modulators on the rate of ppFEV$_1$ decline, frequency of pulmonary exacerbations and changes infection in infection status of people with CF. This should include an assessment of the impact of any changes in co-adherence to non-CFTR modulator therapies for CF. The EAG notes that for ELX/TEZ/IVA, the Data Collection Agreement would likely have provided sufficient evidence to resolve some of this uncertainty had the COVID-19 pandemic not occurred. The EAG also considers that further analysis of the existing data using an expanded contemporaneous control cohort may resolve some of the outstanding uncertainty

regarding the impact of the COVID-19 on changes in ppFEV$_1$ for people not treated with CFTR modulators;

- Further data collection on the long-term adverse event profile of CFTR modulators, including mental health outcomes and the development of cataracts, lens opacities and hypertension;
- Long-term follow-up of young children treated with ELX/TEZ/IVA, or people treated with ELX/TEZ/IVA prior to the development of significant lung and/or pancreatic damage. Such individuals may have the most positive long-term clinical outcomes following ELX/TEZ/IVA treatment, but long-term data are not yet available for these individuals, especially those initiating at 2 years. is warranted and may address this key uncertainty. In addition, the impact of co-adherence to ECM medications and the effects of discontinuing CFTR modulators should be explored further in future research.

Regarding survival and economic modelling of therapies to treat CF, further validation should be performed of the Cox proportional hazards model used to model the impact of changes in patient characteristics over time on survival in the UK population. In particular, future research should focus on the prediction of survival for younger patients, in light of changes to the landscape of CF care with CFTR modulator treatments.

8 References

1. Cystic Fibrosis Trust. UK Cystic Fribrosis Registry: 2021 Annual Data Report. 2022.
2. Schluter DK, Southern KW, Dryden C, Diggle P, Taylor-Robinson D. Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: a UK CF registry-based study. *Thorax* 2020; **75**: 123-31.
3. Sawicki GS, Konstan MW, McKone EF, Moss RB, Lubarsky B, Suthoff E, et al. Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation. *Pulmonary Therapy* 2022: 1-11.
4. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nat Rev Dis Primers* 2015; **1**: 15010.
5. Ward CL, Omura S, Kopito RR. Degradation of CFTR by the ubiquitin-proteasome pathway. *Cell* 1995; **83**: 121-7.
6. Desai M, Hine C, Whitehouse JL, Brownlee K, Charman SC, Nagakumar P. Who are the 10%? - Non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies. *Respiratory medicine* 2022; **199**: 106878.
7. Medicine AfCBaL. Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK 2nd Version. 2014.

8. National Institue for Health and Care Excellence. Cystic fibrosis: diagnosis and management (NG78), 2017. Available from: https://www.nice.org.uk/guidance/ng78. Date accessed: December 2022.
9. Hoo ZH, Wildman MJ, Curley R, Walters SJ, Campbell MJ. Rescue therapy within the UK Cystic Fibrosis Registry: An exploration of predictors of intravenous antibiotic use amongst adults with CF. *Respirology* 2018; **23**: 190-7.
10. Caley L, Smith L, White H, Peckham DG. Average rate of lung function decline in adults with cystic fibrosis in the United Kingdom: Data from the UK CF registry. *J Cyst Fibros* 2021; **20**: 86-90.
11. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in Cystic Fibrosis. *J Cyst Fibros* 2017; **16 Suppl 2**: S70-S8.
12. Norris AW, Ode KL, Merjaneh L, Sanda S, Yi Y, Sun X, et al. Survival in a bad neighborhood: pancreatic islets in cystic fibrosis. *J Endocrinol* 2019.
13. Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med* 2013; **3**: a009746.
14. Smith S, Rowbotham N, Davies G, Gathercole K, Collins SJ, Elliott Z, et al. How can we relieve gastrointestinal symptoms in people with cystic fibrosis? An international qualitative survey. *BMJ Open Respir Res* 2020; **7**.
15. Cystic Fibrosis Trust. UK Cystic Fribrosis Registry: 2019 Annual Data Report. 2020.
16. Bradley JM, Blume SW, Balp MM, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J* 2013; **41**: 571-7.
17. Szczesniak R, Andrinopoulou ER, Su W, Afonso PM, Burgel PR, Cromwell E, et al. Lung Function Decline in Cystic Fibrosis: Impact of Data Availability and Modeling Strategies on Clinical Interpretations. *Ann Am Thorac Soc* 2023.
18. Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, et al. Data Resource Profile: The UK Cystic Fibrosis Registry. *Int J Epidemiol* 2018; **47**: 9-10e.
19. National institute for Health and Care Excellence (NICE). Data Collection Agreement. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement 06 April 2022]. Date accessed: 15 May 2023.
20. Vertex. Vertex Announces Agreement with NHS England for Access to All Licensed Cystic Fibrosis Medicines. 2019. Available from: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-agreement-nhs-england-access-all-licensed. Date accessed: June 2023.
21. Vertex. Data on File. REF-9272. 2021.
22. Cystic Fibrosis Trust. Cystic fibrosis complications and symptoms. Available from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/cystic-fibrosis-complications. Date accessed: 17 May 2023.
23. Stalvey MS, Clines GA. Cystic fibrosis-related bone disease: insights into a growing problem. *Curr Opin Endocrinol Diabetes Obes* 2013; **20**: 547-52.
24. Kobelska-Dubiel N, Klincewicz B, Cichy W. Liver disease in cystic fibrosis. *Prz Gastroenterol* 2014; **9**: 136-41.
25. Cystic Fibrosis Trust. Fertility and cystic fibrosis. Available from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/symptoms-of-cystic-fibrosis/fertility. Date accessed: December 2022.
26. Kazmerski TM, West NE, Jain R, Uluer A, Georgiopoulos AM, Aitken ML, et al. Family-building and parenting considerations for people with cystic fibrosis. *Pediatr Pulmonol* 2022; **57 Suppl 1**: S75-S88.
27. Cystic Fibrosis Trust. Cystic Fibrosis Insight Survey – Report on the 2017 and 2018 Surveys. 2019.

28. National Institute for Health and Care Excellence. ID3834 Professional organisation submission. ACPCF. Catherine Brown. 2023.
29. National Institute for Health and Care Excellence. ID3834. Professional organisation submission. Cystic Fibrosis Trust. Ellie Davies. 2023.
30. National Institute for Health and Care Excellence. ID3834. Professional organisation submission. CF Voices. Christina Walker. 2023.
31. National Institute for Health and Care Excellence. ID3834. Professional organistaion submission. CFDigicare. Dr Martin Wildman. 2023.
32. National Institute for Health and Care Excellence. ID3834 Professional organisation submission. British Paediatric Respiratory Society. Dr Manjith Narayanan. 2023.
33. National Institute for Health and Care Excellence. ID3834. Professional organisation submission. UK Psychosocial Professionals in Cystic Fibrosis. Dr Thomas Clarke. 2023.
34. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Nicod E, Serrano-Aguilar P, 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 Serv Res* 2015; **15**: 428.
35. Daly C, Ruane P, O'Reilly K, Longworth L, Vega-Hernandez G. Caregiver burden in cystic fibrosis: a systematic literature review. *Ther Adv Respir Dis* 2022; **16**: 17534666221086416.
36. Mowforth OD, Davies BM, Kotter MR. Quality of Life Among Informal Caregivers of Patients With Degenerative Cervical Myelopathy: Cross-Sectional Questionnaire Study. *Interact J Med Res* 2019; **8**: e12381.
37. Cystic Fibrosis Trust. The cost of cystic fibrosis 2022.
38. Cystic Fibrosis Trust. Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK. 2011.
39. Habib AR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. *Ann Am Thorac Soc* 2015; **12**: 420-8.
40. Ancel J, Launois C, Perotin JM, Ravoninjatovo B, Mulette P, Hagenburg J, et al. Health-Related Quality of Life in Adults with Cystic Fibrosis: Familial, Occupational, Social, and Mental Health Predictors. *Healthcare (Basel)* 2022; **10**.
41. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002; **121**: 64-72.
42. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine* 2015; **373**: 220-31.
43. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: A systematic review and cost-effectiveness analysis. *Health Technology Assessment* 2014; **18**: 1-106.
44. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. *Health and Quality of Life Outcomes* 2016; **14**: 63.
45. Kind P HG, Macran S. . UK Population norms for EQ-5D. Discussion Paper 172. *Centre for Health Economics, University of York* 1999.
46. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res* 2003; **12**: 63-76.
47. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005; **128**: 2347-54.

48. Flume PA, Suthoff ED, Kosinski M, Marigowda G, Quittner AL. Measuring recovery in health-related quality of life during and after pulmonary exacerbations in patients with cystic fibrosis. *J Cyst Fibros* 2019; **18**: 737-42.
49. Perrem L, Stanojevic S, Shaw M, Davis S, Retsch-Bogart G, Ratjen F. Changes in the parent cystic fibrosis questionnaire-revised (CFQ-R) with respiratory symptoms in preschool children with cystic fibrosis. *J Cyst Fibros* 2020; **19**: 492-8.
50. Jaudszus A, Zeman E, Jans T, Pfeifer E, Tabori H, Arnold C, et al. Validity and Reliability of a Novel Multimodal Questionnaire for the Assessment of Abdominal Symptoms in People with Cystic Fibrosis (CFAbd-Score). *Patient* 2019; **12**: 419-28.
51. Evans J, Davies S, Cross K. The Financial Costs of Cystic Fibrosis. University of Bristol, 2023.
52. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Nicod E, Serrano-Aguilar P. 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.
53. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; **127**: 725-34.
54. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159**: 179-87.
55. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**: 75-88.
56. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008; **177**: 253-60.
57. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**: 1324-43.
58. Ejiofor LCK, Mathiesen IHM, Jensen-Fangel S, Olesen HV, Skov M, Philipsen LKD, et al. Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment. *Pediatric Pulmonology* 2020; **55**: 3364-70.
59. Foong RE, Harper AJ, Skoric B, King L, Turkovic L, Davis M, et al. The clinical utility of lung clearance index in early cystic fibrosis lung disease is not impacted by the number of multiple-breath washout trials. *ERJ Open Res* 2018; **4**.
60. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, et al. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2011; **183**: 752-8.
61. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine* 2019; **381**: 1809-19.
62. Keogh RH, Cosgriff R, Andrinopoulou ER, Brownlee KG, Carr SB, Diaz-Ordaz K, et al. Projecting the impact of triple CFTR modulator therapy on intravenous antibiotic requirements in cystic fibrosis using patient registry data combined with treatment effects from randomised trials. *Thorax* 2022; **77**: 873-81.
63. Scoffone VC, Chiarelli LR, Trespidi G, Mentasti M, Riccardi G, Buroni S. Burkholderia cenocepacia Infections in Cystic Fibrosis Patients: Drug Resistance and Therapeutic Approaches. *Front Microbiol* 2017; **8**: 1592.
64. National Institue for Health and Care Excellence. TA266 Mannitol dry powder for inhalation for treating cystic fibrosis, 2012. Available from: https://www.nice.org.uk/guidance/ta266. Date accessed: December 2022.
65. National Institute for Health and Care Excellence. TA276 Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis, 2013. Available from: https://www.nice.org.uk/guidance/ta276. Date accessed: December 2022.

66. Cystic Fibrosis Trust. UK Cystic Fibrosis Service Resourcing 2019 to 2021. 2022.
67. NHS England Specialist Respiratory Transform Clinical Reference Group. National Programmes of Care and Clinical Reference Groups Service Specification: A01 Cystic Fibrosis (Children).
68. NHS England Specialist Respiratory Transform Clinical Reference Group. National Programmes of Care and Clinical Reference Groups Service Specification: A01 Cystic Fibrosis (Adult).
69. Cystic Fibrosis Trust. Pharmacy standards in cystic fibrosis care in the UK (2022). 2022.
70. Cystic Fibrosis Trust. Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. 2020.
71. Cystic Fibrosis Trust. Nutritional Management of Cystic Fibrosis. 2016.
72. Cystic Fibrosis Trust. Mycobacterium abscessus: Recommendations for infection prevention and control. 2017.
73. Cystic Fibrosis Trust. Pharmacy Standards of Care. 2011.
74. Cystic Fibrosis Trust. Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. 2022.
75. Cystic Fibrosis Trust. Antibiotic Treatment for cystic fibrosis. 2009.
76. Cystic Fibrosis Trust. Methicillin-resistant Staphylococcus aureus (MRSA). 2008.
77. Cystic Fibrosis Trust. Pseudomonas aeruginosa infection in people with cystic fibrosis. Suggestions for Prevention and Infection Control. 2004.
78. Cystic Fibrosis Trust. The Burkholderia cepacia complex. Suggestions for Prevention and Infection Control. 2004.
79. Cystic Fibrosis Trust. Management of Cystic Fibrosis Diabetes. 2022.
80. Cystic Fibrosis Trust. National Consensus Standards for the Nursing Management of cystic fibrosis. 2001.
81. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018; **17**: 153-78.
82. Sermet-Gaudelus I, Bianchi ML, Garabedian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. *J Cyst Fibros* 2011; **10 Suppl 2**: S16-23.
83. Castellani C, Conway S, Smyth AR, Stern M, Elborn JS. Standards of Care for Cystic Fibrosis ten years later. *J Cyst Fibros* 2014; **13 Suppl 1**: S1-2.
84. Conway S, Balfour-Lynn IM, De Rijcke K, Drevinek P, Foweraker J, Havermans T, et al. European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre. *J Cyst Fibros* 2014; **13 Suppl 1**: S3-22.
85. Stern M, Bertrand DP, Bignamini E, Corey M, Dembski B, Goss CH, et al. European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis. *J Cyst Fibros* 2014; **13 Suppl 1**: S43-59.
86. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clin Nutr* 2016; **35**: 557-77.
87. Electronic Medicines Compendium. Kalydeco 25 mg granules in sachet. Available from: https://www.medicines.org.uk/emc/product/10982/smpc.
88. Electronic Medicines Compendium. Kalydeco 150 mg Film-coated Tablets. Available from: https://www.medicines.org.uk/emc/product/3040/smpc.
89. Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, et al. VX-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. *Mol Biol Cell* 2013; **24**: 3016-24.
90. Okiyoneda T, Veit G, Dekkers JF, Bagdany M, Soya N, Xu H, et al. Mechanism-based corrector combination restores DeltaF508-CFTR folding and function. *Nat Chem Biol* 2013; **9**: 444-54.

91. Veit G, Roldan A, Hancock MA, Da Fonte DF, Xu H, Hussein M, et al. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor-tezacaftor-ivacaftor (Trikafta) combination. *JCI Insight* 2020; **5**.
92. Veit G, Vaccarin C, Lukacs GL. Elexacaftor co-potentiates the activity of F508del and gating mutants of CFTR. *J Cyst Fibros* 2021; **20**: 895-8.
93. Fiedorczuk K, Chen J. Mechanism of CFTR correction by type I folding correctors. *Cell* 2022; **185**: 158-68 e11.
94. Electronic Medicines Compendium. Orkambi 100 mg/125 mg film coated tablets. Available from: https://www.medicines.org.uk/emc/product/8952/smpc. Date accessed: January 2023.
95. Electronic Medicines Compendium. Orkambi 100 mg/125 mg granules in sachet. Available from: https://www.medicines.org.uk/emc/product/9845/smpc. Date accessed: January 2023.
96. National Institue for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation, 2016. Available from: https://www.nice.org.uk/guidance/ta398. Date accessed: December 2022.
97. Electronic Medicines Compendium. Symkevi 100 mg/150 mg tablets PLGB 22352/0003. Available from: https://www.medicines.org.uk/emc/product/9634/smpc. Date accessed: January 2023.
98. Electronic Medicines Compendium. Kaftrio 75 mg 50 mg 100 mg film-coated tablets. Available from: https://www.medicines.org.uk/emc/product/11724/smpc. Date accessed: January 2023.
99. ClinicalTrials.gov. Evaluation of Long-term Safety and Efficacy of ELX/TEZ/IVA in Cystic Fibrosis (CF) Participants 2 Years and Older. Available from: https://clinicaltrials.gov/ct2/show/NCT05153317.
100. National Institue for Health and Care Excellence. Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]: Final Scope, 2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11187/documents. Date accessed: February 2023.
101. NHS England. Updated Commissioning Statement: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations. 2022.
102. UK CF Registry. Data Request Report – 469. 2023.
103. Hoo ZH, Campbell MJ, Curley R, Walters SJ, Wildman MJ. Do cystic fibrosis centres with the lowest FEV(1) still use the least amount of intravenous antibiotics? A registry-based comparison of intravenous antibiotic use among adult CF centres in the UK. *J Cyst Fibros* 2018; **17**: 360-7.
104. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest* 2009; **135**: 1610-8.
105. Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, et al. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax* 2012; **67**: 860-6.
106. European Medicines Agency. Report of the workshop on endpoints for cystic fibrosis clinical trials. 2012.
107. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.
108. Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev* 2020; **12**: CD010966.

109. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria2022.
110. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
111. Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta). *Canadian Journal of Health Technologies* 2022; **2**.
112. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Sheffield (UK): Decision Support Unit, ScHARR, University of Sheffield, 2016.
113. van Valkenhoef G KJ. gemtc: Network meta-analysis using Bayesian methods.: R Package version 1.0-1. 2021.; 2021.
114. Guide CUs. 18 stansummary: MCMC Output Analysis. Available from: https://mc-stan.org/docs/cmdstan-guide/index.html. Date accessed: May 2023.
115. Chopra R, Paul L, Manickam R, Aronow WS, Maguire GP. Efficacy and adverse effects of drugs used to treat adult cystic fibrosis. *Expert Opinion on Drug Safety* 2015; **14**: 401-11.
116. Naureckas ET, Morgan RL, Oermann CM, Resnick HE, Brady C, Campbell A, et al. CFTR modulator guidelines. *Pediatric Pulmonology* 2017; **52**: 121-2.
117. Habib A, Kajbafzadeh M, Yang CL, Skolnik K, Quon B. Clinical efficacy and safety of CFTR-directed therapies in cystic fibrosis: A systematic review and meta-analysis. *American Journal of Respiratory and Critical Care Medicine* 2018; **197**.
118. Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2018; **2018**: CD010966.
119. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, et al. Cystic fibrosis foundation pulmonary guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Annals of the American Thoracic Society* 2018; **15**: 271-80.
120. Takyar J, Thapa K, Jain A, Sharma A. PRO8 EFFICACY OF CFTR MODULATORS AGAINST PULMONARY EXACERBATION IN CYSTIC FIBROSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS. *Value in Health* 2019; **22**: S842.
121. Tronzon CJ, Fenn N. Non-respiratory effects of CFTR modulators in pediatric patients with cystic fibrosis: A systematic review. *Journal of Pediatric Pharmacology and Therapeutics* 2021; **26**: 529-30.
122. Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, et al. Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *Journal of the Academy of Nutrition and Dietetics* 2021; **121**: 1364-78.
123. Southern KW, Murphy J, Sinha IP, Nevitt SJ. A systematic cochrane review of corrector therapies (with or without potentiators) for people with cystic fibrosis with class II gene variants (most commonly F508DEL) [1]. *Paediatric Respiratory Reviews* 2021; **38**: 33-6.
124. Koutsovasili A, Gogas K, Souliotis K, Kani C, Markantonis S. POSA273 Systematic Review, Meta-Analysis of Per OS Administered Drugs in Cystic Fibrosis. *Value in Health* 2022; **25**: S173.
125. Yousif Hamdan AH, Zakaria F, Lourdes Pormento MK, Lawal OS, Opiegbe A, Zahid S, et al. Cystic Fibrosis Transmembrane Conductance Regulator Protein Modulators in Children and Adolescents with different CF Genotypes - Systematic Review and Meta-Analysis. *Current reviews in clinical and experimental pharmacology* 2023.
126. Dawood SN, Rabih AM, Niaj A, Raman A, Uprety M, Calero MJ, et al. Newly Discovered Cutting-Edge Triple Combination Cystic Fibrosis Therapy: A Systematic Review. *Cureus* 2022; **14**: e29359.

127. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2015; **2015**: CD009841.
128. Southern KW, Patel S, Sinha IP, Nevitt SJ. A systematic Cochrane Review of correctors (specific therapies for class II CFTR mutations) for cystic fibrosis [1]. *Paediatric Respiratory Reviews* 2019; **30**: 25-6.
129. Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From ivacaftor to triple combination: A systematic review of efficacy and safety of cftr modulators in people with cystic fibrosis. *International journal of molecular sciences* 2020; **21**: 1-23.
130. BMJ-TAG. Final Protocol. Elexacaftor–tezacaftor–ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor for treating cystic fibrosis [ID3834]. 2023. Date accessed: Februrary 2023.
131. Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. *The Lancet Respiratory Medicine* 2022; **10**: 267-77.
132. Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes. *The New England journal of medicine* 2021; **385**: 815-25.
133. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; **394**: 1940-8.
134. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation A Phase 3b, Randomized, Placebo-controlled Study. *American Journal of Respiratory and Critical Care Medicine* 2022; **206**: 1361-9.
135. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A Phase 3 Open-Label Study of ELX/TEZ/IVA in Children 6 Through 11 Years of Age With CF and at Least One F508del Allele. *American journal of respiratory and critical care medicine* 2021.
136. ClinicalTrials.gov. Evaluation of ELX/TEZ/IVA in Cystic Fibrosis (CF) Subjects 2 Through 5 Years. 2020.
137. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England journal of medicine* 2017; **377**: 2013-23.
138. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England journal of medicine* 2017; **377**: 2024-35.
139. Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *Journal of cystic fibrosis* 2021; **20**: 68-77.
140. Wilson J, You X, Ellis M, Urquhart DS, Jha L, Duncan M, et al. VO2max as an exercise tolerance endpoint in people with cystic fibrosis: lessons from a lumacaftor/ivacaftor trial. *Journal of cystic fibrosis* 2021; **20**: 499-505.
141. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet respiratory medicine* 2017; **5**: 557-67.

142. Stahl M, Roehmel J, Eichinger M, Doellinger F, Naehrlich L, Kopp MV, et al. An exploratory study to determine the impact of lumacaftor/ivacaftor (LUM/IVA) on disease progression in children 2 through 5 years of age with cystic fibrosis homozygous for F508del-CFTR (F/F). *Journal of cystic fibrosis* 2021; **20 Suppl 1**: S22.
143. Rayment JH, Asfour F, Rosenfeld M, Higgins M, Liu L, Mascia M, et al. A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age with Cystic Fibrosis Homozygous for F508del-CFTR. *American Journal of Respiratory and Critical Care Medicine* 2022; **206**: 1239-47.
144. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *New England Journal of Medicine* 2011; **365**: 1663-72.
145. De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *Journal of Cystic Fibrosis* 2014; **13**: 674-80.
146. Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, et al. Efficacy and safety of ivacaftor treatment: randomized trial in subjects with cystic fibrosis who have an R117H-CFTR mutation. *The Lancet Respiratory Medicine* 2015; **3**: 524-33.
147. Griese M, Tullis E, Chilvers M, Fabrizzi B, Jain R, Legg J, et al. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one F508del allele: 144-week interim results from an open-label extension study. *Journal of Cystic Fibrosis* 2022; **21**: S99-S100.
148. Ratjen F, Escobar H, Gaffin J, McColley S, Roesch E, Ruiz F, et al. Elexacaftor/tezacaftor/ivacaftor in children aged 6 and older with cystic fibrosis and at least 1 F508del allele: Interim results from a Phase 3 open-label extension study. *Journal of Cystic Fibrosis* 2021; **20**: S265.
149. ClinicalTrials.gov. NCT04058366: Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy. 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT04058366 accessed 08 July 2022]. Date accessed: 08 July 2022.
150. Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. *The Lancet Respiratory medicine* 2021.
151. Sawicki GS, Chilvers M, McNamara J, Naehrlich L, Saunders C, Sermet-Gaudelus I, et al. A Phase 3, open-label, 96-week trial to study the safety, tolerability, and efficacy of tezacaftor/ivacaftor in children >= 6 years of age homozygous for F508del or heterozygous for F508del and a residual function CFTR variant. *Journal of Cystic Fibrosis* 2022; **21**: 675-83.
152. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *The Lancet Respiratory Medicine* 2017; **5**: 107-18.
153. Chilvers MA, Davies JC, Milla C, Tian S, Han Z, Cornell AG, et al. Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study. *The Lancet Respiratory Medicine* 2021; **9**: 721-32.
154. ClinicalTrials.gov. A Study to Evaluate Efficacy and Safety of TEZ/IVA in Subjects Aged 6 Through 11 Years With Cystic Fibrosis. 2018. Available from: https://clinicaltrials.gov/show/NCT03559062.
155. Vertex. Clinical Study Report: Protocol VX14-809-109: A Phase 3, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination

With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, homozygous for the F508del-CFTR Mutation. Version 1.0. 18 January 2017. 2017.
156. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ Open* 2019; **9**: e024537.
157. Doumit M, Chuang S, Middleton P, Selvadurai H, Sivam S, Ruseckaite R, et al. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic. *J Cyst Fibros* 2023; **22**: 581-6.
158. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravitlles M, et al. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLoS One* 2021; **16**: e0255659.
159. Vertex. Clinical Study Report. Protocol VX20-445-111. A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age. 2022.
160. McNamara J, McColley SA, Owen CA, Liu F, Tian S, Waltz D, et al. A 2-part, phase 3 single-arm study to evaluate the safety and pharmacokinetics (PK) of lumacaftor/ivacaftor (LUM/IVA) combination therapy in patients (pts) aged 2 to 5 years with cystic fibrosis (CF) homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis* 2018; **17**: S2-S3.
161. NICE. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [TA398]. 2016. Available from: https://www.nice.org.uk/guidance/ta398.
162. Granger E, Davies G, Keogh RH. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? *J Cyst Fibros* 2022; **21**: 316-22.
163. Taylor-Cousar JL, Jain M, Barto TL, Haddad T, Atkinson J, Tian S, et al. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. *J Cyst Fibros* 2018; **17**: 228-35.
164. Vertex. 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. 2023.
165. O'Sullivan BP, Baker D, Leung KG, Reed G, Baker SS, Borowitz D. Evolution of pancreatic function during the first year in infants with cystic fibrosis. *The Journal of pediatrics* 2013; **162**: 808-12 e1.
166. Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. *J Pathol* 2016; **238**: 311-20.
167. Bijvelds MJC, Roos FJM, Meijsen KF, Roest HP, Verstegen MMA, Janssens HM, et al. Rescue of chloride and bicarbonate transport by elexacaftor-ivacaftor-tezacaftor in organoid-derived CF intestinal and cholangiocyte monolayers. *J Cyst Fibros* 2022; **21**: 537-43.
168. National Institue for Health and Care Excellence. ID3834. Professional organisation submission. UK Psychosocial Professionals in Cystic Fibrosis. Dr Thomas Clarke. 2023.
169. Wagener JS, Millar SJ, Mayer-Hamblett N, Sawicki GS, McKone EF, Goss CH, et al. Lung function decline is delayed but not decreased in patients with cystic fibrosis and the R117H gene mutation. *J Cyst Fibros* 2018; **17**: 503-10.
170. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020; **17**: e1003082.
171. Keogh RH, Seaman SR, Barrett JK, Taylor-Robinson D, Szczesniak R. Dynamic Prediction of Survival in Cystic Fibrosis: A Landmarking Analysis Using UK Patient Registry Data. *Epidemiology* 2019; **30**: 29-37.
172. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001; **153**: 345-52.
173. Trust CF. UK Cystic Fribrosis Registry: 2020 Annual Data Report. 2021.

174. Curley R, Campbell MJ, Walters SJ, Hoo ZH, Wildman MJ. Regarding the articles on home spirometry. *J Cyst Fibros* 2022; **21**: e212-e4.
175. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. *Pediatr Pulmonol* 2021; **56**: 1271-3.
176. Lawless M, Burgess M, Bourke S. Impact of COVID-19 on Hospital Admissions for COPD Exacerbation: Lessons for Future Care. *Medicina (Kaunas)* 2022; **58**.
177. Vertex. AURORA F/RF F/G OLE (Study 110): Clinical Study Report - Part A: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 1.0, Protocol Number: VX18-445-110. 31 August 2022. 2022.
178. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Using Negative Control Outcomes and Difference-in-Differences Analysis to Estimate Treatment Effects in an Entirely Treated Cohort: The Effect of Ivacaftor in Cystic Fibrosis. *Am J Epidemiol* 2022; **191**: 505-15.
179. Lee T, Sawicki GS, Altenburg J, Millar SJ, Geiger JM, Jennings MT, et al. Effect of Elexacaftor/Tezacaftor/Ivacaftor on Annual Rate of Lung Function Decline in People with Cystic Fibrosis. *J Cyst Fibros* 2023; **22**: 402-6.
180. Polineni D., Daines C.L., Tullis E., Costa S., Linnemann R. W., Mall M. A., et al. Long term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People With Cystic Fibrosis (CF) and At Least One F508del Allele: An Open Label, 192 Week Extension Study. *46th European Cystic Fibrosis Conference* 2023.
181. Vertex. Clinical Study Report. A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation. 2023.
182. Collignon O, Schritz A, Spezia R, Senn SJ. Implementing Historical Controls in Oncology Trials. *The oncologist* 2021; **26**: e859-e62.
183. Sacks H, Chalmers TC, Smith H, Jr. Randomized versus historical controls for clinical trials. *Am J Med* 1982; **72**: 233-40.
184. Klonoff DC. The Expanding Role of Real-World Evidence Trials in Health Care Decision Making. *J Diabetes Sci Technol* 2020; **14**: 174-9.
185. McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatr Pulmonol* 2022; **57 Suppl 1**: S5-S12.
186. Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. *Lancet Respir Med* 2023; **11**: 329-40.
187. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Investigating the effects of long-term dornase alfa use on lung function using registry data. *J Cyst Fibros* 2019; **18**: 110-7.
188. Southern K. ISRCTN14081521: A randomised open-label trial to assess change in respiratory function for people with cystic fibrosis (pwCF) established on triple combination therapy (Kaftrio™) after rationalisation of nebulised mucoactive therapies (the CF STORM trial). *ISRCTN Regsitry* 2021.
189. ClinicalTrials.gov. NCT05519020: Inhaled Therapy Adherence and Outcomes to Kaftrio in Cystic Fibrosis. 2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05519020. Date accessed: July 2023.
190. Vertex. Clinical Study Report. Protocol VX16-809-122. A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del. 2022.

191. Canadian Agency for Drugs and Technologies in Health. Economic Evaluations & Models - MEDLINE. In: CADTH Search Filters Database. Available from: https://searchfilters.cadth.ca/link/16. Date accessed: February 2023.
192. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. Performance of Ovid Medline Search Filters to Identify Health State Utility Studies. *Int J Technol Assess Health Care* 2017; **33**: 472-80.
193. Tice JA, Kuntz KM, Wherry K, Seidner M, Rind DM, Pearson SD. The effectiveness and value of novel treatments for cystic fibrosis. *Journal of Managed Care and Specialty Pharmacy* 2021; **27**: 276-80.
194. Vadagam P, Kamal KM, Covvey JR, Giannetti V, Mukherjee K. Erratum: Cost-effectiveness and budget impact of lumacaftor/ ivacaftor in the treatment of cystic fibrosis (Journal of Managed Care & Specialty Pharmacy (2018) 24:10 (987-97) DOI: 10.18553/jmcp.2018.24.10.987). *Journal of Managed Care and Specialty Pharmacy* 2019; **25**: 285-6.
195. Institute for Clinical and Economic Review (ICER). Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. 2018.
196. Institute for Clinical and Economic Review (ICER). Modulator treatments for Cystic Fibrosis: Effectiveness and Value. Institute for Clinical and Economic Review 101 Merrimac St., 10th FL., Boston MA, USA 02114, Tel: (617) 724-4445 , Fax: (617) 726-9414 info@icer-review.org United States United States: Institute for Clinical and Economic Review (ICER), 2020.
197. Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the Long-Term Clinical and Economic Outcomes of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients with Homozygous phe508del Mutation. *Value in Health* 2017; **20**: 1329-35.
198. Sharma D, Xing S, Hung YT, Caskey RN, Dowell ML, Touchette DR. Cost-effectiveness analysis of lumacaftor and ivacaftor combination for the treatment of patients with cystic fibrosis in the United States. *Orphanet Journal of Rare Diseases* 2018; **13**: 172.
199. Vadagam P, Kamal KM, Covvey JR, Giannetti V, Mukherjee K. Cost-Effectiveness and Budget Impact of Lumacaftor/Ivacaftor in the Treatment of Cystic Fibrosis. *Journal of managed care & specialty pharmacy* 2018; **24**: 987-97.
200. Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi): (Vertex Pharmaceuticals (Canada) Incorporated): Indication-For the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene. 2016.
201. Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi): (Vertex Pharmaceuticals (Canada) Incorporated): Indication: For the treatment of cystic fibrosis in patients 6 years of age and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene. 2018.
202. National Institute for Health and Care Excellence (NICE). Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [TA786], 2016.
203. Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document – July 2018 PBAC Meeting. LUMACAFTOR WITH IVACAFTOR for treatment of patients with cystic fibrosis (CF) aged ≥12 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. 2018.
204. Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document - July 2018 PBAC meeting. (lumacaftor/ivacaftor) for the treatment of patients with cystic fibrosis (CF) aged 6–11 years who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene. 2018.
205. Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document - July 2019 PBAC Meeting. lumacaftor/ivacaftor granules for treatment of cystic fibrosis (CF) patients aged 2

years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene. 2019.
206. Scottish Medicines Consortium (SMC). lumacaftor 200mg, ivacaftor 125mg film-coated tablet (Orkambi®), 2016.
207. Scottish Medicines Consortium (SMC). lumacaftor and ivacaftor 200mg/125mg, 100mg/125mg film-coated tablets and 100mg/125mg,150mg/188mg granules in sachets (Orkambi®). 2019.
208. Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document - March 2019 PBAC Meeting. tezacaftor/ivacaftor for treatment of cystic fibrosis (CF) patients aged 12 years and older who have at least one residual function (RF) mutation in the CFTR gene. 2019.
209. Scottish Medicines Consortium (SMC). tezacaftor and ivacaftor 100mg/150mg film-coated tablets (Symkevi®), 2019.
210. Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta). 2021.
211. Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document – December 2021 PBAC Meeting. Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets. 2021.
212. Vertex. TRAFFIC Clinical Study Report: Protocol VX12-809-103. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. V.1. 08 September 2014. 2014.
213. Vertex. TRANSPORT: Clinical Study Report. Protocol VX12-809-104. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2014.
214. Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. *Health and Quality of Life Outcomes* 2015; **13**: 33.
215. Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *The European respiratory journal* 2013; **41**: 571-7.
216. Cameron R, Matthews J, Office D, Rowley M, Abbott J, Simmonds N, et al. Patient valuation of health-related quality of life associated with treatment burden and pulmonary exacerbation in cystic fibrosis. *Journal of Cystic Fibrosis* 2021; **20**: S158.
217. Tappenden P, Harnan S, Uttley L, Mildred M, Carroll C, Cantrell A. Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis: Systematic review and economic model. *Health Technology Assessment* 2013; **17**: a-204.
218. Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-Related Quality of Life for Adults with Cystic Fibrosis: A Regression Approach to Assessing the Impact of Recombinant Human DNase. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2000; **20**: 1167-74.
219. Acaster S, Mukuria C, Rowen D, Brazier J, Wainwright C, Quon B, et al. Development of the cystic fibrosis questionnaire-revised preference based scoring algorithm. *Pediatric Pulmonology* 2019; **54**: 443.
220. Acaster S, Mukuria C, Rowen D, Brazier JE, Wainwright CE, Quon BS, et al. Development of the Cystic Fibrosis Questionnaire-Revised-8 Dimensions: Estimating Utilities From the Cystic Fibrosis Questionnaire-Revised. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2022.

221. Bell SC, Mainz JG, MacGregor G, Madge S, MacEy J, Fridman M, et al. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: Results from a cross-sectional study. *BMC Pulmonary Medicine* 2019; **19**: 146.
222. Tappenden P, Harnan S, Uttley L, Mildred M, Walshaw M, Taylor C, et al. The cost effectiveness of dry powder antibiotics for the treatment of pseudomonas aeruginosa in patients with cystic fibrosis. *PharmacoEconomics* 2014; **32**: 159-72.
223. Tappenden P, Sadler S, Wildman M. An Early Health Economic Analysis of the Potential Cost Effectiveness of an Adherence Intervention to Improve Outcomes for Patients with Cystic Fibrosis. *PharmacoEconomics* 2017; **35**: 647-59.
224. Tappenden P, Navega Biz A, Hernandez Alava M, Sasso A, Sutton L, Ennis K, et al. A model-based economic analysis of the CFHealthHub intervention to support adherence to inhaled medications for people with cystic fibrosis in the UK. *International Journal of Technology Assessment in Health Care* 2023; **39**: e6.
225. Wildman MJ, O'Cathain A, Hind D, Maguire C, Arden MA, Hutchings M, et al. An intervention to support adherence to inhaled medication in adults with cystic fibrosis: the ACtiF research programme including RCT. 2021.
226. UK Cystic Fibrosis Registry. 2021 Annual Data Report. 2022.
227. Liou TG, Kartsonaki C, Keogh RH, Adler FR. Evaluation of a five-year predicted survival model for cystic fibrosis in later time periods. *Scientific reports* 2020; **10**: 1-11.
228. European Medicines Agency. Symkevi Publication Details. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/symkevi accessed 08 May 2022]. Date accessed: 08 May 2022.
229. European Medicines Agency. Kaftrio Publication Details. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio.
230. European Medicines Agency. Orkambi Publication Details. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi accessed 08 May 2022]. Date accessed: 08 May 2022.
231. Daines CL, Tullis E, Costa S, Linnemann RW, Mall MA, McKone EF, et al. Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One F508del Allele: 96-Week Interim Results From an Open-Label Extension Study. Poster presented at the 35th Annual North American Cystic Fibrosis Conference (virtual)2021.
232. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Process and methods [PMG36]. 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: Sept 2022.
233. European Medicines Agency. Orkambi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi#assessment-history-section. Date accessed: December 2022.
234. European Medicines Agency. Symkevi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/symkevi#assessment-history-section. Date accessed: December 2022.
235. European Medicines Agency. Kaftrio. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio#assessment-history-section. Date accessed: December 2022.
236. Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *J Cyst Fibros* 2018; **17**: 218-27.
237. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value in*

health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2012; 15: 821-7.
238. Davis S, Stevenson M, Tappenden P, Wailoo AJ. NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation. 2012.
239. NHS. National Cost Collection for the NHS. 2023. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Date accessed: January 2023.
240. UK CF Registry. 2018 Genotype Data by Nation and Age: Number of individuals eligible by genotype for CFTR modulating therapy in each nation of the UK, defined by centre attended. 2020.
241. Mitchell M, Muftakhidinov B, Winchen T. Engauge Digitizer Software. 2023. Available from: http://markummitchell.github.io/engauge-digitizer, . Date accessed: June 15 2023.
242. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. *Thorax* 2007; **62**: 360-7.
243. Adler AI, Shine BSF, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. *Diabetes care* 2008; **31**: 1789-94.
244. Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, et al. Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review. *Journal of* clinical medicine 2021; 10.
245. Newsome SK, R. Daniel, R. CF-EpiNet. IPD2.03 The effects of 3-year ivacaftor use on lung function and intravenous days seen in UK CF Registry Data. Journal of Cystic Fibrosis 2018; 17.
246. Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Stat Med 2002; 21: 1575-600.
247. Engels EA, Schmid CH, Terrin N, Olkin I, Lau J. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med* 2000; **19**: 1707-28.
248. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007; **4**: e297.
249. NHS England. ANNUAL REPORT ON CARDIOTHORACIC ORGAN TRANSPLANTATION REPORT FOR 2021/2022 2022.
250. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. Assessment of quality of life in lung transplantation using a simple generic tool. *Thorax* 2001; **56**: 218-22.
251. Raguragavan A, Jayabalan D, Saxena A. Health-related quality of life following lung transplantation for cystic fibrosis: A systematic review. *Clinics (Sao Paulo, Brazil)* 2023; **78**: 100182.
252. BNF. British National Formulary. 2021. Available from: https://bnf.nice.org.uk/.
253. Cystic Fibrosis Trust. UK Cystic Fribrosis Registry: 2018 Annual Data Report 2019.
254. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. An economic evaluation of lung transplantation. J Thorac Cardiovasc Surg 2002; 123: 411-8; discussion 8-20.
255. PSSRU. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. 2021.
256. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021.
257. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.
258. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011.

259. Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in health care, 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: May 23.
260. McNally P, Fleming A, Elnazir B, Williamson M, Cox D, Linnane B, et al. Impact of elexacaftor/tezacaftor/ivacaftor treatment on clinical outcomes in people with CF in a real-world setting-The RECOVER trial. *Journal of Cystic Fibrosis* 2021; **20**: S266.
261. McNally P, Fleming A, Elnazir B, Williamson M, Cox D, Linnane B, et al. Impact of one year of treatment with elexacaftor/tezacaftor/ivacaftor on clinical outcomes in people with cystic fibrosis in a real-world setting - the RECOVER study. *Journal of Cystic Fibrosis* 2022; **21**: S11.
262. Sagel SD, Khan U, Heltshe SL, Clancy JP, Borowitz D, Gelfond D, et al. Clinical Effectiveness of Lumacaftor/Ivacaftor in Patients with Cystic Fibrosis Homozygous for F508del-CFTR A Clinical Trial. *Annals of the American Thoracic Society* 2021; **18**: 75-83.
263. Sagel SD, Khan U, Heltshe SL, Clancy JP, Borowitz D, Gelfond D, et al. Clinical Effectiveness of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients Homozygous for F508del-CFTR. *Annals of the American Thoracic Society* 2020.
264. Williams E, Edgeworth D, Fantidis M, Finlayson F, Button BM, Clark D, et al. Patient reported adherence to ivacaftor. *Journal of Cystic Fibrosis* 2015; **14**: S46.
265. ClinicalTrials.gov. NCT03956589: Functional Respiratory Imaging and Orkambi in CF. 2020. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03956589. Date accessed: July 2023.
266. Deutsches Register Klinischer Studien. DRKS00023862: Einfluss von CFTR-Modulation mit Elexacaftor/Tezacaftor/Ivacaftor auf die körperliche Leistungsfähigkeit, das intestinale und respiratorische Mikrobiom sowie mikrobielle und inflammatorische Metaboliten bei Patienten mit zystischer Fibrose. 2023. Available from: https://drks.de/search/de/trial/DRKS00023862. Date accessed: July 2023.
267. Deutsches Register Klinischer Studien. DRKS00022267: OrkambiKIDS: Einfluss von CFTR-Modulation mit Lumacaftor/Ivacaftor auf das intestinal und respiratorische Mikrobiom und mikrobielle Metabolite bei Kindern im Alter von 2- 12 Jahren. 2022. Available from: https://drks.de/search/de/trial/DRKS00022267. Date accessed: July 2023.
268. Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *New England Journal of Medicine* 2010; **363**: 1991-2003.
269. Accurso F, Rowe SM, Durie PR, Konstan MW, Dunitz J, Hornick D. Improvement in sweat chloride concentration by the CFTR potentiator VX-770 in subjects with cystic fibrosis and the G551D-CFTR mutation [abstract. *Pediatric pulmonology* 2009; **44 Suppl 32**: 296, Abstract no: 40.
270. Accurso FJ, Rowe SM, Durie PR, Konstan MW, Dunitz J, Hornick DB. Final results of a 14-and 28-day study of VX-770 in subjects with CF. *Journal of cystic fibrosis* 2009; **8 Suppl 2**: S25, Abstract no: 97.
271. Konstan MW, Accurso FJ, Boyle MP, Clancy JP, Ordonez CL, Zha J, et al. Relationship between pulmonary outcomes, biomarkers of CF disease, and serum drug levels in subjects with the G551D-CFTR mutation treated with VX-770, an investigational oral potentiator of CFTR. *American journal of respiratory and critical care medicine* 2010; **181**.
272. Rowe SM, Accurso FJ, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Improvement in ion transport biomarkers and spirometry with the investigational CFTR potentiator VX-770 in subjects with cystic fibrosis and the G551D-CFTR mutation. *Paediatric Respiratory Reviews* 2010; **11**: S99.
273. Rowe SM, Liu B, Hill A, Hathorne H, Cohen M, Beamer JR, et al. Optimizing Nasal Potential Difference Analysis for CFTR Modulator Development: Assessment of Ivacaftor in CF Subjects with the G551D-CFTR Mutation. *PLoS ONE* 2013; **8**: e66955.

274. Accurso FJ, Van Goor F, Zha J, Stone AJ, Dong Q, Ordonez CL, et al. Sweat chloride as a biomarker of CFTR activity: Proof of concept and ivacaftor clinical trial data. *Journal of Cystic Fibrosis* 2014; **13**: 139-47.
275. Shah S. VX-770, a CFTR potentiator, may have a potential clinical benefit in a subgroup of people with cystic fibrosis. *Thorax* 2011; **66**: 984.
276. ClinicalTrials.gov. NCT00457821: Safety Study of Ivacaftor in Subjects With Cystic Fibrosis. 2012. Available from: https://www.clinicaltrials.gov/study/NCT00457821. Date accessed: July 2023.
277. EU Clinical Trials Register. A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study of VX-770 to Evaluate Safety, Pharmacokinetics, and Biomarkers of CFTR Activity in Cystic Fibrosis (CF) Subjects with Genotype G551D. 2007. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2007-002657-23. Date accessed: July 2023.
278. Boyle MP, Bell SC, Konstan MW, McColley SA, Rowe SM, Rietschel E, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: A phase 2 randomised controlled trial. *The Lancet Respiratory Medicine* 2014; **2**: 527-38.
279. Boyle M, Bell SC, Konstan M, McColley S, Flume P, Kang L. Lumacaftor, an investigational CFTR corrector, in combination with ivacaftor, a CFTR potentiator, in CF patients with the F508del-CFTR mutation: phase 2 interim analysis. *Journal of cystic fibrosis* 2013; **12 Suppl 1**: S14, Abstract no: WS7.4.
280. Boyle MP, Bell S, Konstan M, McColley SA, Kang L, Patel N. The investigational cftr corrector, VX-809 (lumacaftor) co-administered with the oral potentiator ivacaftor improved CFTR and lung function in F508DEL homozygous patients: Phase II study results. *Pediatric Pulmonology* 2012; **47**: 315.
281. Boyle MP, Bell S, Konstan MW, McColley SA, Wisseh S, Spencer-Green G. VX-809, an investigational CFTR corrector, in combination with VX-770, an investigational CFTR potentiator, in subjects with CF and homozygous for the F508del-CFTR mutation. *Pediatric Pulmonology* 2011; **46**: 287.
282. Rowe SM, McColley SA, Rietschel E, Li X, Bell SC, Konstan M, et al. Effect of 8 weeks of lumacaftor in combination with ivacaftor in patients with CF and heterozygous for the F508delCFTR mutation. *Pediatric Pulmonology* 2014; **49**: 306.
283. Rowe SM, McColley SA, Rietschel E, Li X, Bell SC, Konstan MW, et al. Lumacaftor/ivacaftor treatment of patients with cystic fibrosis heterozygous for F508del-CFTR. *Annals of the American Thoracic Society* 2017; **14**: 213-9.
284. ClinicalTrials.gov. Study of VX-809 Alone and in Combination With VX-770 in Cystic Fibrosis (CF) Patients Homozygous or Heterozygous for the F508del-CFTR Mutation. *https://clinicaltrialsgov/show/NCT01225211* 2010.
285. EU Clinical Trials Register. 2010-020413-90: A Phase 2, Multicenter, Double-Blinded, Placebo-Controlled, Multiple-Dose Study to Evaluate Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Lumacaftor Monotherapy, and Lumacaftor and Ivacaftor Combination Therapy in Subjects with Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation. 2010. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020413-90/results. Date accessed: July 2023.
286. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *American journal of respiratory and critical care medicine* 2013; **187**: 1219-25.
287. Aherns R, Rodriguez S, Yen K, Davies JC. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D-CFTR mutation. *Pediatric pulmonology* 2011; **46**: 283.
288. Davies JC, Li H, Yen K, Ahrens R. Ivacaftor in subjects 6 to 11 years of age with cystic fibrosis and the G551D-CFTR mutation. *Journal of cystic fibrosis* 2012; **11**: S13.

289. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *American Journal of Respiratory and Critical Care Medicine* 2013; **187**: 1219-25.
290. Stalvey MS, Niknian M, Higgins M, Tarn V, Heltshe SL, Rowe SM. Ivacaftor improves linear growth in children with cystic fibrosis (CF) and a G551D-CTFR mutation: Data from the ENVISION study. *Journal of Cystic Fibrosis* 2016; **15**: S101.
291. Stalvey MS, Niknian M, Higgins M, Tarn VE, Heltshe SL, Rowe SM. Ivacaftor improves linear growth in G551D cystic fibrosis children: Results of a multicenter, placebo-controlled study. *Pediatric Pulmonology* 2015; **50**: 402.
292. Stalvey MS, Pace J, Niknian M, Higgins MN, Tarn V, Davis J, et al. Growth in prepubertal children with cystic fibrosis treated with ivacaftor. *Pediatrics* 2017; **139**: e20162522.
293. ClinicalTrials.gov. NCT00909727. Study of Ivacaftor in Cystic Fibrosis Subjects Aged 6 to 11 Years With the G551D Mutation. 2012. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00909727.
294. EU Clinical Trials Register. 2008-007479-26. A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551D Mutation. 2011. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007479-26/results.
295. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/Ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR. *American Journal of Respiratory and Critical Care Medicine* 2017; **195**: 912-20.
296. Rosenfeld M, Marigowda G, Liu F, Waltz D. Effect of lumacaftor in combination with ivacaftor on fev1 and safety measures in patients aged 6-11 years with cf who are homozygous for f508del-cftr. *Pediatric Pulmonology* 2014; **49**: 287.
297. ClinicalTrials.gov. NCT01897233. Study of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2013. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01897233.
298. EU Clinical Trials Register. 2017-001078-41. A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2015. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001078-41/results.
299. Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, et al. Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American journal of respiratory and critical care medicine* 2018; **197**: 214-24. Online data supplement.
300. Donaldson S, Pilewski J, Griese M, Dong Q, Lee PS. VX-661, an investigational CFTR corrector, in combination with ivacaftor, a CFTR potentiator, in patients with CF and homozygous for the F508Del-CFTR mutation: interim analysis. *Journal of cystic fibrosis* 2013; **12 Suppl 1**: S14, Abstract no: WS7.3.
301. Donaldson SH, Pilewski JM, Cooke J, Himes-Lekstrom J. Addition of VX-661, an investigational CFTR corrector, to ivacaftor, a CFTR potentiator, in patients with CF and heterozygous for F508del/G551D-CFTR. *Pediatric pulmonology* 2014; **49**: 308-9.
302. EU Clinical Trials Register. A Phase 2, Multicenter, Double Blinded, Placebo Controlled Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of VX-661 Monotherapy and VX-661/Ivacaftor Cotherapy in Subjects with Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2011-003821-93-DE* 2011.

303. ClinicalTrials.gov. Study of VX-661 Alone and in Combination With Ivacaftor in Subjects Homozygous or Heterozygous to the F508del-Cystic Fibrosis Transmembrane Conductance Regulator(CFTR) Mutation. *https://clinicaltrialsgov/show/NCT01531673* 2012.
304. Pilewski JM, Cooke J, Lekstrom-Himes J, Donaldson S. VX-661 in combination with ivacaftor in patients with cystic fibrosis and the F508del-CFTR mutation. *Journal of cystic fibrosis* 2015; **14**: S1.
305. Pilewski JM, Donaldson SH, Cooke J, Lekstrom-Himes J. Phase 2 studies reveal additive effects of VX-661, an investigational CFTR corrector, and ivacaftor, a CFTR potentiator, in patients with CF who carry the F508Del-CFTR mutation. *Pediatric pulmonology* 2014; **49 Suppl 38**: 157-9.
306. Tierney AC, Edgeworth D, Williams E, Finlayson F, Keating D, Clark D, et al. Ivacaftor and its effects on body composition in adults with G551D related cystic fibrosis. *Journal of Cystic Fibrosis* 2015; **14**: S50.
307. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *The Lancet Respiratory Medicine* 2019; **7**: 325-35.
308. ClinicalTrials.gov. NCT02797132. Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del. 2016. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02797132.
309. EU Clinical Trials Register. 2016-001004-33. A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation. 2016. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001004-33/results.
310. Hoppe JE, Chilvers M, Ratjen F, McNamara JJ, Owen CA, Tian S, et al. Long-term safety of lumacaftor-ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. *The Lancet Respiratory medicine* 2021.
311. Hoppe J, Chilvers M, Ratjen F, McNamara JJ, Owen CA, Tian S, et al. Long-term safety of lumacaftor/ivacaftor therapy in persons with cystic fibrosis aged 2-5 years homozygous for the F508del-CFTR mutation (F/F). *Journal of Cystic Fibrosis* 2020; **19**: S31.
312. ClinicalTrials.gov. NCT03125395. A Rollover Safety Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2017. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03125395.
313. EU Clinical Trials Register. 2019-003112-31. A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. 2019. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-003112-31.
314. Schwarz C, Sutharsan S, Epaud R, Klingsberg RC, Fischer R, Rowe SM, et al. Tezacaftor/ivacaftor in people with cystic fibrosis who stopped lumacaftor/ivacaftor due to respiratory adverse events. *Journal of cystic fibrosis* 2021; **20**: 228-33.
315. EU Clinical Trials Register. Study to Evaluate Safety, Efficacy, and Tolerability of TEZ/IVA in Subjects With Cystic Fibrosis (CF) Who Have Previously Discontinued Orkambi. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-000540-18-DE* 2017.
316. ClinicalTrials.gov. A Study to Evaluate Safety, Efficacy, and Tolerability of TEZ/IVA in Orkambi® (Lumacaftor/Ivacaftor) -Experienced Subjects With Cystic Fibrosis (CF). *https://clinicaltrialsgov/show/NCT03150719* 2017.
317. Schwarz C, Sutharsan S, Epaud R, Klingsberg R, Fischer R, Rowe SM, et al. Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor in Cystic Fibrosis Patients Who Previously Discontinued Lumacaftor/Ivacaftor Due To Respiratory Adverse Events: a Randomized, Double-Blind, Placebo-Controlled Phase 3b Study. *Pneumologie (Stuttgart, Germany)* 2019; **73**.

318. Keating D, Taylor-Cousar J, Marigowda G, Burr L, Daines C, Mall M, et al. Phase 2 safety and efficacy: Cystic fibrosis transmembrane conductance regulator (CFTR) modulator regimen VX-445/tezacaftor(TEZ)/ ivacaftor(IVA). *Respirology* 2019; **24**: 67.
319. EU Clinical Trials Register. A Study of VX-445 in Healthy Subjects and Subjects with Cystic Fibrosis. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-000797-11-NL* 2017.
320. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England journal of medicine* 2018; **379**: 1612-20.
321. ClinicalTrials.gov. A Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis. *https://clinicaltrialsgov/show/NCT03227471* 2017.
322. McNally P, McKone E, Cox D, Linnane B, Williamson M, Elnazir B, et al. RECOVER - the Real World Clinical Outcomes with Novel Modulator therapy combinations in people with cystic fibrosis. *Journal of Cystic Fibrosis* 2021; **20**: S51.
323. Walker S, Flume P, McNamara J, Solomon M, Chilvers M, Chmiel J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11years with cystic fibrosis. *Journal of Cystic Fibrosis* 2019; **18**: 708-13.
324. ClinicalTrials.gov. NCT02953314. A Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/Ivacaftor in Pediatric Subjects With Cystic Fibrosis (CF). 2016. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02953314.
325. EU Clinical Trials Register. A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation. 2017. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001164-38/3rd.
326. ClinicalTrials.gov. A Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation. *https://clinicaltrialsgov/show/NCT02730208* 2016.
327. EU Clinical Trials Register. A phase 2, randomized, placebo-controlled, double-blind study to evaluate the effect of VX-661 in combination with ivacaftor on chest imaging endpoints in subjects aged 12 years and older with cystic fibrosis, homozygous for the f508del-cftr mutation. *https://wwwclinicaltrialsregistereu/ctr-search/trial/2019-002189-11/results* 2019.
328. ClinicalTrials.gov. A Phase 2 Study to Evaluate Effects of VX-661/Ivacaftor on Lung and Extrapulmonary Systems in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. *https://clinicaltrialsgov/show/NCT02508207* 2015.
329. ClinicalTrials.gov. Study to Evaluate Safety and Efficacy of VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation With an Open-Label Expansion. *https://clinicaltrialsgov/show/NCT02070744* 2014.
330. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: A randomised controlled trial. *The Lancet Respiratory Medicine* 2013; **1**: 630-8.
331. Anonymous. Corrections: Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial (The Lancet Respiratory Medicine (2013) 1(8) (630-638) (S2213260013701826) (10.1016/S2213-2600(13)70182-6)). *The Lancet Respiratory Medicine* 2017; **5**: e26.
332. Button BM, Edgeworth D, Finlayson F, Fantidis M, Wilson L, Talbot A, et al. Effect of ivacaftor on wellness, quality of life and cognitive function in adults with cystic fibrosis and G551D mutation. *Journal of Cystic Fibrosis* 2015; **14**: S18.

333. Button BM, Edgeworth D, Wilson LM, Sayer J, Tierney A, Finlayson F, et al. Ivacaftor improves wellness, quality of life and cognitive function in G551D cystic fibrosis. *Pediatric Pulmonology* 2015; **50**: 437.
334. ClinicalTrials.gov. NCT01262352. Study of the Effect of Ivacaftor on Lung Clearance Index in Subjects With Cystic Fibrosis and the G551D Mutation. 2010. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01262352.
335. Davies JC, Sheridan H, Lee P, Song T, Stone A, Ratjen F. Lung clearance index to evaluate the effect of ivacaftor on lung function in subjects with cf who have the G551D-CFTR mutation and mild lung disease. *Pediatric Pulmonology* 2012; **47**: 311.
336. Davies JC, Sheridan H, Lee PS, Song T, Stone A, Ratjen F. Effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease: A comparison of lung clearance index (LCI) vs. spirometry. *Journal of Cystic Fibrosis* 2012; **11**: S15.
337. EU Clinical Trials Register. 2010-020546-96. A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of VX-770 on Lung Clearance Index in Subjects with Cystic Fibrosis, the G551D Mutation, and FEV1 >90%. 2010.
338. Ratjen F, Sheridan H, Lee P, Song T, Stone A, Davies JC. Lung clearance index as an outcome measure in cystic fibrosis clinical trials. *Pediatric Pulmonology* 2011; **46**: 282-3.
339. Ratjen F, Sheridan H, Lee PS, Song T, Stone A, Davies J. Effect of ivacaftor on lung clearance index and FEV1 in subjects with CF who have the G551DCFTR mutation and mild lung disease. *European Respiratory Journal* 2012; **40**.
340. Ratjen FA, Sheridan H, Lee PS, Song T, Stone A, Davies J. Lung clearance index as an endpoint in a multicenter randomized control trial of ivacaftor in subjects with cystic fibrosis who have mild lung disease. *American Journal of Respiratory and Critical Care Medicine* 2012; **185**.
341. Davies JC, Sheridan H, Lee P, Song T, Stone A, Ratjen F. Lung clearance index to evaluate the effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease. *Pediatric pulmonology* 2012; **47**: 311, Abstract no: 249.
342. Edgeworth D, Keating D, Ellis M, Button B, Williams E, Clark D, et al. Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: A double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. *Clinical Science* 2017; **131**: 2037-45.
343. Edgeworth D, Keating D, Williams E, Clark D, Button B, Tierney A, et al. Exercise improvements in ivacaftor treated G551D cystic fibrosis patients are not solely related to FEV1 and sweat changes. *European Respiratory Journal* 2015; **46**.
344. Edgeworth D, Keating D, Williams E, Clark D, Button BM, Tierney AC, et al. Ivacaftor improves exercise capacity in patients with G551D CF gene mutations. *Journal of Cystic Fibrosis* 2015; **14**: S27.
345. Keating D, Edgeworth D, Heretier S, Denise C, Tierney A, Kotsimbos T, et al. Sweat chloride response does not reliably correlate with clinical parameters: A placebo controlled crossover trial of ivacaftor in G551D CF patients. *Journal of Cystic Fibrosis* 2017; **16**: S75.
346. King SJ, Tierney AC, Edgeworth D, Keating D, Williams E, Kotsimbos T, et al. Body composition and weight changes after ivacaftor treatment in adults with cystic fibrosis carrying the G551 D cystic fibrosis transmembrane conductance regulator mutation: A double-blind, placebo-controlled, randomized, crossover study with open-label extension. *Nutrition (Burbank, Los Angeles County, Calif)* 2021; **85**: 111124.
347. Peleg AY, Choo JM, Langan KM, Edgeworth D, Keating D, Wilson J, et al. Antibiotic exposure and interpersonal variance mask the effect of ivacaftor on respiratory microbiota composition. *Journal of Cystic Fibrosis* 2018; **17**: 50-6.
348. Wilson J, Allen-Graham J, Talbot A, Finlayson F, Clark D, Keating D, et al. Treatment with ivacaftor in CF patients with the G551D mutation is associated with improvement in cognition. *Journal of Cystic Fibrosis* 2018; **17**: S57.

349. Wilson J, Keating D, Clark D, Edgeworth D, Allen-Graham J, Finlayson F, et al. The effect of ivacaftor CFTR gene-potentiating therapy on cytokine levels in CF patients with the G551D mutation. *Journal of Cystic Fibrosis* 2017; **16**: S83.
350. Wilson JW, Keating D, Clark D, Edgeworth D, Allen-Graham J, Finlayson F, et al. Ivacaftor CFTR gene-potentiating therapy reduces inflammatory cytokine levels in CF patients with G551D mutation. *Pediatric Pulmonology* 2017; **52**: 236-7.
351. Keating D, Wilson L, Williams E, Kotsimbos T, Wilson J. Ivacaftor withdrawal syndrome during a randomised placebo-controlled cross-over study. *Journal of Cystic Fibrosis* 2019; **18**: S130.
352. ClinicalTrials.gov. CPET in CF Patients With One G551D Mutation Taking VX770. 2013. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01937325.
353. Ng C, Dellschaft N, Hoad C, Marciani L, Mainz J, Hill T, et al. Effects of tezacaftor/ivacaftor on gut function and transit in cystic fibrosis: A randomized, double-blind, placebo-controlled, crossover trial. *Journal of Cystic Fibrosis* 2021; **20**: S102.
354. ClinicalTrials.gov. Gut Imaging for Function & Transit in Cystic Fibrosis Study 2 (GIFT-CF2). 2019. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04006873.
355. ClinicalTrials.gov. A Study to Evaluate Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified CFTR Gating Mutation. 2016. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02742519.
356. ClinicalTrials.gov. A Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor in Participants With Cystic Fibrosis (CF). 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT05111145.
357. ClinicalTrials.gov. Evaluation of Long-term Safety and Efficacy of ELX/TEZ/IVA in Cystic Fibrosis (CF) Participants 2 Years and Older. 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT05153317.
358. ClinicalTrials.gov. A Study to Evaluate ELX/TEZ/IVA on Cough and Physical Activity in Subjects With Cystic Fibrosis (CF). 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT04969224.
359. ClinicalTrials.gov. A Study to Assess the Effect of ELX/TEZ/IVA on Glucose Tolerance in Participants With Cystic Fibrosis (CF). 2020. Available from: https://classic.clinicaltrials.gov/ct2/show/study/NCT04599465.
360. ClinicalTrials.gov. A Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis (CF) Subjects 6 Years and Older and F/MF Genotypes. 2020.
361. ClinicalTrials.gov. Long-term Safety of Lumacaftor/Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for F508del and 12 to <24 Months of Age at Treatment Initiation. 2020.
362. Clancy JP, Rowe SM, Accurso FJ, Aitken ML, Amin RS, Ashlock MA, et al. Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation. *Thorax* 2012; **67**: 12-8.
363. Clancy JP, Rowe SM, Accurso FJ, Ballmann M, Boyle MP, DeBoeck C, et al. A phase II, randomized, placebo-controlled, clinical trial of four doses of VX-809 in CF patients homozygous for the F508del CFTR mutation. *Pediatric Pulmonology* 2010; **45**: 298.
364. Clancy JP, Rowe SM, Durie PR, Konstan MW, Dunitz J, Hornick DB, et al. Comparison of NPD parameters in a phase iia study to optimize detection of CFTR modulator bioactivity in clinical trials. *Pediatric Pulmonology* 2010; **45**: 301.
365. Clancy JP, Spencer-Green G. Clinical evaluation of VX-809, a novel investigational oral F508del-CFTR corrector, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis* 2010; **9**: S20.

366. Clancy JP, Rowe SM, Liu B, Hathorne H, Dong Q, Wisseh S, et al. Variability of nasal potential difference measurements in clinical testing of CFTR modulators. *Pediatric Pulmonology* 2011; **46**: 283.
367. Lu H, Cui Y, Wang D, Vernillet L. Pharmacokinetic and pharmacodynamic analysis of VX-809 in cystic fibrosis subjects homozygous for the F508DEL mutation. *Clinical pharmacology and therapeutics* 2011; **89**: S25-S6.
368. ClinicalTrials.gov. Study of VX-809 in Cystic Fibrosis Subjects With the ΔF508-CFTR Gene Mutation. *https://clinicaltrialsgov/show/NCT00865904* 2009.
369. EU Clinical Trials Register. A randomized, double-blind, placebo-controlled, multiple dose study of VX-809 to evaluate safety, pharmacokinetics, and pharmacodynamics of VX-809 in cystic fibrosis subjects homozygous for the deltaF508-CFTR gene mutation - Study VX08-809-101. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2008-006446-25-NL* 2009.
370. Davies JC, Moskowitz S, Brown CD, Horsley AR, Mall MA, McKone EF, et al. Phase 2 safety and efficacy of the triple combination CFTR modulator regimen VX-659/ TEZ/IVA in CF. *Pediatric Pulmonology* 2018; **53**: 228-9.
371. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordonez CL, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* 2012; **142**: 718-24.
372. Flume PA, Borowitz D, Liou T, Li H, Yen K, Ordonez C, et al. VX-770 in subjects with CF and homozygous for the F508del-CFTR mutation. *Pediatric Pulmonology* 2011; **46**: 284-5.
373. Flume PA, Borowitz DS, Liou TG, Li H, Yen K, Ordonez CL, et al. VX-770 in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis* 2011; **10**: S16.
374. Kerem E, Cohen-Cymberknoh M, Tsabari R, Wilschanski M, Reiter J, Shoseyov D, et al. Ivacaftor in People with Cystic Fibrosis and a 3849110kb C->T or D1152H Residual Function Mutation. *Annals of the American Thoracic Society* 2021; **18**: 433-41.
375. Kerem E, Cohen-Cymberknoh M, Tsabari R, Wilschanski M, Reiter J, Shoseyov D, et al. Ivacaftor in People With Cystic Fibrosis and a 3849+10kb C ->T or D1152H Residual Function Mutation. *Annals of the American Thoracic Society* 2020.
376. McKone EF, DiMango EA, Sutharsan S, Barto TL, Campbell D, Ahluwalia N, et al. A phase 3, randomized, double-blind, parallel-group study to evaluate tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2021; **20**: 234-42.
377. ClinicalTrials.gov. A Phase 3 Study of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Who Have One F508del-CFTR Mutation and a Second Mutation That Has Been Demonstrated to be Clinically Responsive to Ivacaftor. *https://clinicaltrialsgov/show/NCT02412111* 2015.
378. EU Clinical Trials Register. A study in people with Cystic Fibrosis (a rare hereditary lung disease) to assess the efficacy and safety of a combination of two experimental drugs. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2014-004838-25-IT* 2015.
379. Munck A, Kerem E, Ellemunter H, Campbell D, Wang LT, Ahluwalia N, et al. Tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for minimal function CFTR mutations. *Journal of Cystic Fibrosis* 2020; **19**: 962-8.
380. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation. *https://clinicaltrialsgov/show/NCT02516410* 2015.
381. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of VX-661 in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, heterozygous for the f508del-cftr mutation and with a second CFTR mutation that is not likely to respond to VX-661 and/or ivacaftor therapy (f508del/nr). *https://wwwclinicaltrialsregistereu/ctr-search/trial/2014-004787-37/results* 2017.

382. Euctr DE. A study in people with Cystic Fibrosis (a rare hereditary lung disease) to assess the efficacy and safety of a combination of two experimental drugs. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2014-004787-37-DE* 2015.
383. Berkers G, van der Meer R, Heijerman H, Beekman JM, Boj SF, Vries RGJ, et al. Lumacaftor/ivacaftor in people with cystic fibrosis with an A455E-CFTR mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2021; **20**: 761-7.
384. EU Clinical Trials Register. Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2016-001585-29-NL* 2016.
385. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: A phase 3, open-label extension study (PERSIST). *The Lancet Respiratory Medicine* 2014; **2**: 902-10.
386. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright CE, et al. Long-term safety and efficacy of investigational CFTR potentiator, VX-770, in subjects with CF. *Pediatric Pulmonology* 2011; **46**: 284.
387. McKone E, Li H, Yen K, Davies JC. Long-term safety and efficacy of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR Mutation. *Journal of Cystic Fibrosis* 2012; **11**: S13.
388. McKone E, Li H, Gilmartin G, Davies JC. Long-term safety and efficacy of ivacaftor in persons with cystic fibrosis who have the G551D-CFTR mutation. *Pediatric Pulmonology* 2012; **47**: 296-7.
389. McKone E, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the G551D-CFTR mutation: Response through 144 weeks of treatment (96 weeks of persist). *Pediatric Pulmonology* 2013; **48**: 287.
390. Altes TA, Johnson M, Fidler M, Botfield M, Tustison NJ, Leiva-Salinas C, et al. Use of hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with cystic fibrosis. *Journal of Cystic Fibrosis* 2017; **16**: 267-74.
391. Altes T, Johnson M, Mugler IJ, Miller GW, Flors L, Mata J, et al. The effect of ivacaftor, an investigational CFTR potentiator, on hyperpolarized noble gas magnetic resonance imaging in subjects with cystic fibrosis who have the G551D-CFTR mutation. *American Journal of Respiratory and Critical Care Medicine* 2012; **185**.
392. Altes T, Johnson MA, Miller GW, Mugler JP, Flors L, Mata J, et al. Hyperpolarized Gas MRI of ivacaftor therapy in subjects with cystic fibrosis who have the G551D-CFTR mutation. *Journal of Cystic Fibrosis* 2012; **11**: S67.
393. Altes T, Johnson MA, Miller GW, Mugler JP, Flors L, Mata J, et al. Hyperpolarized gas MRI of ivacaftor therapy in persons with cystic fibrosis and the G551D-CFTR mutation. *Pediatric Pulmonology* 2012; **47**: 291.
394. Altes T, Johnson M, Higgins M, Fidler M, Botfield M, Mugler IJP, et al. The effect of ivacaftor treatment on lung ventilation defects as measured by hyperpolarized helium-3 MRI, on patients with cystic fibrosis and a G551D-CFTR mutation. *Journal of Cystic Fibrosis* 2014; **13**: S6.
395. Sawicki GS, McKone EF, Millar SJ, Pasta DJ, Konstan MW, Lubarsky B, et al. Patients with cystic fibrosis and a G551D or homozygous F508del mutation: Similar lung function decline. *American Journal of Respiratory and Critical Care Medicine* 2017; **195**: 1673-6.
396. Gilmartin GS, Cotton C, Singh M, Bialek PE, Lee P, Wilson S, et al. Baseline cystic fibrosis transmembrane conductance regulator protein expression predicts subject response to lumacaftor-ivacaftor treatment. *American Journal of Respiratory and Critical Care Medicine* 2018; **197**.
397. Nick JA, St. Clair C, Jones MC, Lan L, Higgins M. Ivacaftor in cystic fibrosis with residual function: Lung function results from an N-of-1 study. *Journal of Cystic Fibrosis* 2020; **19**: 91-8.

398. Nick JA, Rodman D, St Clair C, Jones MC, Li H, Higgins M. Utilization of an "n-of-1" study design to test the effect of ivacaftor in CF patients with residual CFTR function and FEV1 >=40% of predicted. *Pediatric Pulmonology* 2014; **49**: 188-9.
399. Nick JA, Rodman D, St Clair C, Jones MC, Li H, Higgins M, et al. Effect of ivacaftor in patients with cystic fibrosis, residual cftr function, and fev1 >=40% of predicted, n-of-1 study. *Pediatric Pulmonology* 2014; **49**: 285.
400. McGarry ME, Finkbeiner WE, Illek B, Fischer H, Zlock LT, Olshansky S, et al. Ivacaftor response is not predicted by signs of residual CFTR function. *Pediatric Pulmonology* 2015; **50**: 292.
401. Suthoff ED, Bonafede M, Limone B, O'Callaghan L, Sawicki GS, Wagener JS. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. *Journal of medical economics* 2016; **19**: 845-51.

9 Appendices

9.1 Literature search strategies

9.1.1 EAG database searches

Table 90. EAG search strategy for MEDLINE via Ovid.

#	Searches	Results 16/02/2023
1	exp Cystic Fibrosis/	39400
2	cystic fibrosis.tw.	49120
3	(fibrocystic adj10 disease adj10 pancreas).tw.	215
4	mucoviscidos$.tw.	1471
5	(cystic$ adj10 fibros$).tw.	49965
6	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10555
7	(f508del or deltaF508 or CFTR).mp.	13058
8	or/1-7	58105
9	(ivacaftor or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).ti,ab.	13226
10	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).ti,ab.	5236
11	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).ti,ab.	4596
12	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).ti,ab.	4747
13	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).ti,ab.	57
14	(Symkevi or Symdeko or "1969264 35 4" or "D11042").ti,ab.	5
15	(Trikafta or Kaftrio or "2398469 65 1").ti,ab.	54
16	or/9-15	14066
17	8 and 16	1184
18	exp animals/ not humans.sh.	5093682
19	17 not 18	1155

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to February 15, 2023

Table 91. EAG search strategy for Embase via Ovid.

#	Searches	Results 16/02/2023
1	exp Cystic Fibrosis/	80914
2	cystic fibrosis.tw.	75534
3	(fibrocystic adj10 disease adj10 pancreas).tw.	17
4	mucoviscidos$.tw.	1029
5	(cystic$ adj10 fibros$).tw.	76676
6	exp Cystic Fibrosis Transmembrane Conductance Regulator/	9595
7	(f508del or deltaF508 or CFTR).mp.	22111
8	or/1-7	99216
9	exp ivacaftor/	3005
10	(ivacaftor or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).ti,ab.	22396
11	exp lumacaftor/	1275
12	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).ti,ab.	8607
13	exp elexacaftor/	260
14	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).ti,ab.	7388
15	exp tezacaftor/	495
16	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).ti,ab.	7538
17	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).ti,ab.	231
18	(Symkevi or Symdeko or "1969264 35 4" or "D11042").ti,ab.	65
19	(Trikafta or Kaftrio or "2398469 65 1").ti,ab.	164
20	or/9-19	24893
21	8 and 20	4288
22	21 not ((exp animal/ or nonhuman/) not exp human/)	4086
Database(s): Embase 1974 to February 15, 2023		

9.1.2 *Cystic Fibrosis Trials Register*

The Cystic Fibrosis Trials Register is maintained by the Cochrane Cystic Fibrosis and Genetic Disorders Group, and is compiled from database searches of MEDLINE (weekly searches from 1966 to present), Embase (searched 1974 to August 1995) and CENTRAL (searched on each new issue of

the Cochrane library), and also includes records hand-searched from the Journal of Cystic Fibrosis, Pediatric Pulmonology and conference abstracts. Full details of the current search strategies used to compile the Cystic Fibrosis Trials Register are given in Table 92 and Table 93. Records identified from the searches used to generate the Cystic Fibrosis Trials Register are manually screened by an information specialist, and only references that are RCTs or possible RCTs are included in the register. The EAG considers the Cystic Fibrosis Trials Register to provide an up-to-date, comprehensive and systematic search of randomised control trials relating to cystic fibrosis, which includes all interventions and comparators relevant to the current MTA.

Table 92. Cochrane Cystic Fibrosis and Genetic Disorders Group CENTRAL search strategy used to compile the Cystic Fibrosis Trial Register

ID	Search Term
1	(cystic next fibros*)
2	CYSTIC FIBROSIS
3	CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR
4	Cftr
5	(fibrocystic and pancrea*)
6	mucoviscido*
7	(#1 or #2 or #3 or #4 or #5 or #6)
8	(#7 and (not sr-cf))

Searches are performed on each new issue of the Cochrane Library, which is published monthly. Search terms shown in capitals are MeSH terms.

Table 93. Cochrane Cystic Fibrosis and Genetic Disorders Group MEDLINE search strategy used to compile the Cystic Fibrosis Trial Register

ID	Search Term
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.

6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp animals/ not humans.sh
11	9 not 10
12	exp Cystic Fibrosis/
13	cystic fibrosis.tw.
14	fibrocystic adj10 disease adj10 pancreas.tw.
15	mucoviscidos$.tw.
16	(cystic$ adj10 fibros$).tw.
17	or/12-16
18	11 and 17

The current search strategy for Ovid MEDLINE is provided. Other strategies have been used previously and searched on SilverPlatter CD-ROM, from 1966 to 2002 and monthly on Ovid from 2003 to the present.

Table 94. EAG search strategy of CENTRAL to identify records for inclusion in the systematic literature review, using the Cystic Fibrosis Trial Register (SR-CF filter)

ID	Search	Hits (16/02/2023)
1	SR-CF	8506
2	(ivacaftor* OR Kalydeco OR VX*770 OR "VX 770" OR "873054 44 5" OR IVA)	1820
3	(lumacaftor OR VX*809 OR "VX 809" OR VRT826809 OR "VRT 826809" OR "936727 05 8" OR "EGP8L81APK" OR LUM)	604
4	(elexacaftor OR VX*445 OR "VX 445" OR "2216712 66 0" OR RRN67GMB0V OR "WHO 11180" OR WHO11180 OR ELX)	96
5	(tezacaftor OR VX*661 OR "VX 661" OR "1152311 62 0" OR 8RW88Y506K OR TEZ)	439
6	(Orkambi OR "1815566 23 4" OR S900006790 OR SCHEMBL19410545)	27

7	(Symkevi OR Symdeko OR "1969264 35 4" OR "D11042")	8
8	(Trikafta OR Kaftrio OR "2398469 65 1")	8
9	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2577
10	#1 AND #9	333

9.1.3 Economic evaluation and HRQoL SLR search strategies

Table 95. Economic evaluations search strategy for Medline via Ovid

#	Searches	Results
1	Economics/	27490
2	exp "Costs and Cost Analysis"/	262655
3	Economics, Nursing/	4013
4	Economics, Medical/	9241
5	Economics, Pharmaceutical/	3094
6	exp Economics, Hospital/	25676
7	Economics, Dental/	1920
8	exp "Fees and Charges"/	31300
9	exp Budgets/	14076
10	budget*.ti,ab,kf.	35119
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	274125
12	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	368356
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	202778
14	(value adj2 (money or monetary)).ti,ab,kf.	2956

15	exp models, economic/	16182
16	economic model*.ab,kf.	4081
17	markov chains/	15902
18	markov.ti,ab,kf.	28195
19	monte carlo method/	31936
20	monte carlo.ti,ab,kf.	58695
21	exp Decision Theory/	13002
22	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	35610
23	or/1-22	874458
24	exp Cystic Fibrosis/	39400
25	cystic fibrosis.tw.	49120
26	(fibrocystic adj10 disease adj10 pancreas).tw.	215
27	mucoviscidos$.tw.	1471
28	(cystic$ adj10 fibros$).tw.	49965
29	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10555
30	(f508del or deltaF508 or CFTR).mp.	13058
31	or/24-30	58105
32	(ivacaftor* or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).mp.	13722
33	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).mp.	5749
34	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).mp.	4750
35	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).mp.	4945
36	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).mp.	70

37	(Symkevi or Symdeko or "1969264 35 4" or "D11042").mp.	8
38	(Trikafta or Kaftrio or "2398469 65 1").mp.	75
39	or/32-38	14877
40	23 and 31 and 39	54

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to February 15, 2023

Economic evaluations search strategy for EMBASE via Ovid

#	Searches	Results
1	Economics/	243981
2	Cost/	61673
3	exp Health Economics/	998288
4	Budget/	33171
5	budget*.ti,ab,kf.	46602
6	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	339209
7	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	514938
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	283536
9	(value adj2 (money or monetary)).ti,ab,kf.	3990
10	Statistical Model/	171317
11	economic model*.ab,kf.	6111
12	Probability/	143435
13	markov.ti,ab,kf.	37060
14	monte carlo method/	48812
15	monte carlo.ti,ab,kf.	61584
16	Decision Theory/	1812
17	Decision Tree/	20062
18	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	48933
19	or/1-18	1950324
20	exp Cystic Fibrosis/	80914

21	cystic fibrosis.tw.	75534
22	(fibrocystic adj10 disease adj10 pancreas).tw.	17
23	mucoviscidos$.tw.	1029
24	(cystic$ adj10 fibros$).tw.	76676
25	exp Cystic Fibrosis Transmembrane Conductance Regulator/	9595
26	(f508del or deltaF508 or CFTR).mp.	22111
27	or/20-26	99216
28	exp ivacaftor/	3005
29	(ivacaftor or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).mp.	26419
30	exp lumacaftor/	1275
31	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).mp.	11904
32	exp elexacaftor/	260
33	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).mp.	10369
34	exp tezacaftor/	495
35	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).mp.	10550
36	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).mp.	388
37	(Symkevi or Symdeko or "1969264 35 4" or "D11042").mp.	132
38	(Trikafta or Kaftrio or "2398469 65 1").mp.	242
39	or/28-38	28117
40	19 and 27 and 39	463
Database(s): Embase 1974 to 2023 February 15		

Table 96. EAG HRQoL search strategy for Medline via Ovid

#	Searches	Results
1	exp Cystic Fibrosis/	39464
2	cystic fibrosis.tw.	49219
3	(fibrocystic adj10 disease adj10 pancreas).tw.	215
4	mucoviscidos$.tw.	1471
5	(cystic$ adj10 fibros$).tw.	50067
6	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10582
7	(f508del or deltaF508 or CFTR).mp.	13096
8	or/1-7	58214
9	Quality-Adjusted Life Years/	15456
10	Value of Life/	5802
11	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	14154

12	(quality adjusted or adjusted life year$).ti,ab,kf.	22571
13	disability adjusted life.ti,ab,kf.	5052
14	daly$1.ti,ab,kf.	4443
15	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1141
16	(multiattribute$ or multi attribute$).ti,ab,kf.	1274
17	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.	42606
18	utility.ab. /freq=2	22810
19	utilities.ti,ab,kf.	9139
20	disutili$.ti,ab,kf.	606
21	(HSUV or HSUVs).ti,ab,kf.	106
22	health$1 year$1 equivalent$1.ti,ab,kf.	40
23	(hye or hyes).ti,ab,kf.	76
24	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1922
25	(illness state$1 or health state$1).ti,ab,kf.	8156
26	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf.	15912
27	(eq-sdq or eqsdq).ti,ab,kf.	1
28	(short form$ or shortform$).ti,ab,kf.	42853
29	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	26091
30	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.	3909
31	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.	6110
32	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.	33
33	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.	356
34	(15D or 15-D or 15 dimension).ti,ab,kf.	6025
35	(standard gamble$ or sg).ti,ab,kf.	13810
36	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2317
37	or/9-36	184339
38	8 and 37	313

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to March 03, 2023

EAG HRQoL search strategy for EMBASE via Ovid

#	Searches	Results
1	quality adjusted life year/	34672
2	socioeconomics/	158360
3	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	26833
4	(quality adjusted or adjusted life year$).ti,ab,kf.	33831
5	disability adjusted life.ti,ab,kf.	6248
6	daly$1.ti,ab,kf.	5949
7	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1765
8	(multiattribute$ or multi attribute$).ti,ab,kf.	1540
9	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.	66783
10	utility.ab. /freq=2	36168
11	utilities.ti,ab,kf.	14985
12	disutili$.ti,ab,kf.	1230
13	(HSUV or HSUVs).ti,ab,kf.	192
14	health$1 year$1 equivalent$1.ti,ab,kf.	44
15	(hye or hyes).ti,ab,kf.	169
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	3036
17	(illness state$1 or health state$1).ti,ab,kf.	14463
18	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf.	29452
19	(eq-sdq or eqsdq).ti,ab,kf.	1
20	(short form$ or shortform$).ti,ab,kf.	59365
21	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	45361
22	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.	5403
23	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.	10513
24	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.	62
25	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.	376
26	(15D or 15-D or 15 dimension).ti,ab,kf.	7623
27	(standard gamble$ or sg).ti,ab,kf.	20815
28	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	3483
29	or/1-28	434414
30	exp Cystic Fibrosis/	81861

31	cystic fibrosis.tw.	76309
32	(fibrocystic adj10 disease adj10 pancreas).tw.	17
33	mucoviscidos$.tw.	1031
34	(cystic$ adj10 fibros$).tw.	77461
35	exp Cystic Fibrosis Transmembrane Conductance Regulator/	9863
36	(f508del or deltaF508 or CFTR).tw.	21328
37	or/30-36	100166
38	29 and 37	1021
Database(s): Ovid Embase 1974 to 2023 March 03		

9.1.4 *Critique of Company's SLR*

The Company conducted a SLR to identify evidence on the safety and efficacy of CFTR modulators and treatments that comprise ECM for people with CF. Two SLRs were performed, one to identify relevant clinical trials (performed 10 May 2022) and one to identify relevant observational studies (performed 12 May 2022). Compared to the EAG's SLR, the Company's SLRs were broader in scope as it also retrieved studies on non-CFTR modulator therapies for the treatment of CF. A comparison of the EAG's and Company's SLR for clinical trials is presented in Table 97.

Table 97. Summary of EAG's critique of the methods implemented by the Company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Data sources	B.2.1 and Appendix D.1	**The EAG considers the sources searched to be appropriate, but is concerned that the date of the search may have missed recent evidence. This concern was alleviated by the provision of recent clinical study reports and unpublished data from the Company, along with a list-of ongoing studies.** Databases searched: MEDLINE®, Embase®, CENTRAL, CDSR and MEDLINE® In-Process. Additional sources: Hand-searching of conference proceedings (published in 2015 to 2022) and searching of key websites. Latest search update: 12 May 2022.
Search strategies	Appendix D.1.3	**The EAG is satisfied that the searches have identified all evidence relevant to the decision problem.** Search strategies for the literature review combined comprehensive terms for the population and interventions, using free-text and medical subject headings.
Inclusion criteria	Appendix D.1.4	**The EAG considers it likely that no relevant evidence was excluded.**

Screening and data extraction	Appendix D.1	**The EAG considers the methods for screening and data extraction to be robust.** Records for the clinical SLR were screened by two independent reviewers with any discrepancies resolved by a third reviewer. Results of the literature screening processes were summarised in PRISMA diagrams. Data extraction was carried out by two independent reviewers, and any discrepancies were resolved by a third reviewer.
Tool for quality assessment of included study or studies	D.3.1	**The EAG considers the Company's choice of quality assessment tool to be reasonable, although notes that quality was only assessed at the level of the study.** The Company used minimum criteria for assessment of risk of bias in RCTs from the Centre for Reviews and Dissemination guidance for undertaking reviews in health care.[259] The EAG notes that it is plausible that the risk-of-bias may have differed for different outcomes within the clinical trials, and as such an outcome specific risk-of-bias assessment for criteria that might differ between outcome (e.g., missing data) would have been preferable. Nevertheless, the EAG notes the Company provided transparent justification for each risk of bias decision, and that the Company's assessment of risk of bias was in-line with the EAG's.

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CS: Company submission; EAG: External Assessment Group; HTA: health technology assessment; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; SLR: systematic literature review.

Table 98. A comparison between the Company's and EAG's SLRs for clinical trials

Feature of SLR	EAG approach	Company approach
Date of database search	16 February 2023	10 May 2022
Databases searched	Embase, MEDLINE In-Process, CENTRAL, CDSR and DARE, HTA database	Embase, MEDLINE In-Process, CENTRAL, CDSR and DARE, HTA database
Other sources	Conference abstracts 2010-2022 • European Cystic Fibrosis Conference • Annual North American Cystic Fibrosis Conference Trial registries	Conference abstracts 2015-2022 • International Congress on Pediatric Pulmonology • Thoracic Society • International Society for

	• US National Institutes of Health Database (ClinicalTrials.gov) • World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) • European Medicines Agency (EMA) (www.clinicaltrialsregister.eu/ctrsearch/search) HTA bodies • NICE; • Pharmaceutical Benefits Advisory Committee (PBAC); • Scottish Medicines Consortium (SMC); • Canadian Agency for Drugs and Technologies in Health (CADTH). Company submission	Pharmacoeconomics and Outcomes Research Trial registries • Clinicaltrials.gov Websites • Cystic Fibrosis Foundation • Cystic Fibrosis Europe • National Institute for Health and Clinical Excellence • American Lung Association • Cystic Fibrosis Network • European Lung Foundation • Cystic Fibrosis Trust
Review approach	Separate title/abstract appraisal and full text appraisal by two reviewers. Data extraction performed by a single reviewer and validated by another.	Separate title/abstract appraisal and full text appraisal by two reviewers. Data extraction performed by a single reviewer and validated by another.
Interventions and comparators	CFTR modulators only	CFTR modulators and established clinical medicine therapies
Age inclusion criteria	• CF patients aged ≥1 year for studies of LUM/IVA • CF patients aged ≥2 years for studies of ELX/TEZ/IVA • CF patients aged ≥6 years for studies of TEZ/IVA or IVA monotherapy	• CF patients aged ≥2 years with two CFTR *F508del* mutations • CF patients aged ≥6 years with at least one *F508del* mutation ((F/F, F/MF, F/RF & F/Gating)

Limitations	No date limit, non-English studies included but not extracted	Date limited to 2007 and English language studies
Quality assessment	Completed at the study level and at the outcome level.	Completed at the study level only.

Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane regulator; CS: Company submission; DARE: Database of Abstracts of Reviews of Effects; EAG: External Assessment Group; ELX: elexacaftor; HTA: health technology assessment; IVA: ivacaftor; LUM: lumacaftor; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; SMC: Scottish Medicines Consortium; SLR: systematic literature review; TEZ: tezacaftor; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

The Company's SLR for clinical trials retrieved 4,083 deduplicated records for title and abstract appraisal, of which 555 were included for full text appraisal. In total, 272 records were included following full text appraisal, and an additional 87 records were added from the grey literature searches, providing a total of 359 records from 184 unique studies included in the SLR, of which 39 were studies of CFTR modulator combination therapies and 7 were studies of ivacaftor monotherapy. In addition, the Company's SLR for observational retrieved 6,146 deduplicated records for title and abstract appraisal, of which 745 were included for full text appraisal. In total, 292 records were included following full text appraisal, and an additional 92 records were added from the grey literature searches, providing a total of 384 potentially relevant records.

In Tables 10, 11 and 12 of the Company submission, the Company further outlined the trials comprising the clinical trial programmes for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA. Both the EAG's SLR and the Company SLR included all studies that comprise the CFTR modulator clinical trial programme, and the EAG considers the Company SLRs to have appropriately identified all clinical trials relevant to the NICE Final Scope. The EAG notes that the Company was able to provide all clinical study reports and unpublished posters from the CFTR modulator clinical trial programme that were requested by the EAG.

Finally, the EAG notes that a small number of trials included but not prioritised in the EAG's clinical literature review were not Vertex sponsored trials, either being non-randomised Phase 4 trials,[260-263] a randomised phase 2 RCT of IVA without reporting *F508del* subgroup data with unclear sponsor details,[264] or trials of ambiguous status for which no results were available.[265-267] Hence, the EAG is satisfied that the Company SLRs appropriately identified all evidence of clear relevance to the decision problem, and considers the results of the EAG and Company SLRs to be consistent.

9.2 Quality assessment

9.2.1 Study-level quality assessment

Table 99. Risk of bias assessment conducted at the study level by the EAG for RCTs included in the EAG SLR.

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Sutharsan 2022	Low Interactive web response system was used to assign randomisation and concealment.	Low Interactive web response system was used to assign randomisation and concealment.	Low Double-blind	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low Few missing outcome data	Low Analysis followed statistical analysis protocol	Low
Barry 2021	Low An interactive web response system was used to assign patients to treatment and to monitor enrolment of the specified subgroups	Low An interactive web response system was used to assign patients to treatment and to monitor enrolment of the specified subgroups	Low Double-blind, placebo controlled with triple masking (Participant, Care Provider, Investigator). All subjects, site personnel and members of the study team were blinded to the treatment codes)	Low Active controlled trial, reducing the risk of guessing treatment assignment	Low The number of people who did not complete treatment/the study was low in both groups (4/126 in the combined active control group and 1/132 in the intervention group). The efficacy and safety sets included all randomised participants.	Low Outcomes analysed in-line with openly available statistical analysis plan	Low

Middleton 2019	Low Randomisation was performed in permuted blocks, with stratification according to percentage of predicted FEV1 at screening (<70% vs. ≥70%), age at screening (<18 years vs. ≥18 years), and sex. An IWRS was used to assign subjects to treatment.	Low An IWRS was used to assign subjects to treatment.	Low Double-blind, placebo-controlled with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor).	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low Modified ITT used for FEV_1 analysis which included 200/201 in the intervention group and 203/204 in the placebo group.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
Heijerman 2019	Low An IWRS was used to assign subjects to treatment.	Low An IWRS was used to assign subjects to treatment.	Low [redacted]	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low mITT analysis of patients who received the study drug. MMRM with appropriate covariate structure used. Unclear how missing data were handled in the models if a patient had no Day 15 or Week 4 measure.	Low All extracted outcomes were prespecified in the statistical analysis protocol	Low
Mall 2022	Low An IWRS was used to assign subjects to treatment. Some	Low An IWRS was used to assign subjects to treatment.	Low Double-blind, placebo-controlled with quadruple	Medium Due to the effects of the intervention, effective unblinding	Low One child in the intervention group stopped treatment	Low Outcome analysed in accordance	Low

	imbalances in patient baseline characteristics noted, e.g. height- and weight-for-age z-scores, ppFEV1 and LCI2.5, but likely to reflect random variation due to sample size rather than a problem with randomisation.		masking (Participant, Care Provider, Investigator, Outcomes Assessor).	upon outcome assessment is plausible	due to an adverse event - no other mention of dropout or missing data. The full analysis set included all randomized participants.	with the study protocol	
Taylor-Cousar 2017	Low Randomisation was stratified according to age (<18 years vs ≥18 years), sex, and the percentage of the predicted forced expiratory volume in 1 second (FEV1) (<70% vs ≥70%) at screening. Method of sequence generation and allocation: An interactive web response system	Low Method of sequence generation and allocation: An interactive web response system	Low Double-blind, placebo-controlled trial with triple blinding (Participant, Care Provider, Investigator).	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low Small amount of missing data. Three randomized patients in each group were not included in the set. Clinicaltrials.gov details that 245/251 and 256/259 in the intervention and placebo groups, respectively, were included in the analysis (differing slightly from the numbers reported in the paper).	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov. Multiple timepoints measured but 24 weeks clearly specified as the primary endpoint.	Low
Rowe 2017	Low An IWRS was used to assign subjects to	Low An IWRS was used to assign subjects to	Low Double-blind, placebo controlled with triple	Medium Due to the effects of the intervention,	Low One patient assigned to placebo and 1	Low SAP available via	Low

	treatment sequence and to ensure enrollment of at least 25% of subject with Class II to IV residual function mutations. The IWRS used a list of randomization codes generated by a designated vendor	treatment sequence and to ensure enrollment of at least 25% of subject with Class II to IV residual function mutations. The IWRS used a list of randomization codes generated by a designated vendor	masking (Participant, Care Provider, Investigator).	effective unblinding upon outcome assessment is plausible	patient assigned to ivacaftor alone in period 1 were later deemed to be ineligible and did not receive the intervention. Of the remaining 246 patients, 234 (95%) completed both intervention periods, resulting in 481 periods that could be evaluated	clinicaltrials.gov fully defined outcome, measurement schedule and analysis. Crossover analysis fully described to control for period effects and within-subject covariance.	
Davies 2021	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low Double-blind trial with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor).	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Medium 54/55 TEZ/IVA, 3/3 IVA and 8/11 Placebo (for LCI, 9/11 for ppFEV1) were included in the analyses, representing a higher percentage of missing data in the placebo group (as per clinicaltrials.gov data tables). Reasons for missing data not provided to assess whether missingness	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Some concerns

					depended on the outcome's true value.		
TRAFFIC	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low Double-blinded	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low For ppFEV1, 14 (4.5%) people with missing data for this outcome. No reported missing data for adverse events or PEx.	Low Outcomes of relevance to the MTA were key primary (FEV1), secondary (PEx) or safety outcomes	Low
TRANSPORT	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low IWRS interactive web response system was used to assign randomisation and concealment.	Low Double-blinded	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low For ppFEV1, 11 (3%) people with missing data for this outcome, and 1 person (<1%) missing data for PEx. No reported missing data for adverse events.	Low Outcomes of relevance to the MTA were key primary (FEV1), secondary (PEx) or safety outcomes	Low
Wilson 2021	Low IWRS used to assign randomisation and concealment.	Low IWRS used to assign randomisation and concealment.	Low Subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Medium For ppFEV1, 8 (11%) of participants did not provide data.	Low Statistical analyses followed SAP	Low
Ratjen 2017	Low	Low	Low	Medium	Low	Low	Low

	Random assignment was determined using an IWRS	Random assignment was determined using an IWRS	[redacted]	Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible.	Low rates of missing data for key outcomes (n=6 missing for ppFEV1 endpoint, n=1 individual lost to follow-up)	Outcome of relevance to the MTA was pre-specified as a secondary outcome (FEV1). Primary outcome was LCI2.5.	
Stahl 2021	Low An interactive web or voice response system was used to assign randomisation and concealment. Limited baseline characteristics reported, although reasonably well balanced in terms of $LCI_{2.5}$	Low An interactive web or voice response system was used to assign randomisation and concealment.	Low Double blinded	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Low Few missing outcome data	Low Analysed as stated in the statistical analysis plan	Low
Ramsey 2011 (F/Gating subgroup)	Medium A blinded statistician developed the randomisation code to be provided to the Interactive Voice Response System (IVRS)/IWRS. The study was not	Low IWRS used to assign randomisation and concealment.	Low Double blinded study	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Medium It was unclear if there was missing data as it was unclear how many people comprised the subgroup of interest.	Medium This was a post-hoc analysis. It is unclear how the analysis was developed and if multiple	Some concerns

	stratified by the subgroup reported. No large differences between the subgroups were observed but limited data on each group was available.					analyses were performed. The alignment between this analysis and the pre-specified analyses from Barry 2021 reduces the risk of bias.	
De Boeck 2014 (F/Gating 12+ subgroup)	Medium IWRS was used for blinding and allocation concealment. The randomisation was not stratified by the subgroup used in this analysis. The data provided indicated similar treatment groups but limited details were provided.	Low IWRS used to assign randomisation and concealment.	Low Double blinded study	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Medium It was unclear if there was missing data as it was unclear how many people comprised the subgroup of interest.	Medium This was a post-hoc analysis. It is unclear how the analysis was developed and if multiple analyses were performed. The alignment between this analysis and the pre-specified analyses from Barry 2021 reduces the risk of bias.	Some concerns

Moss 2015 (F/Gating 12+ subgroup)	Medium The masked study biostatistician created the randomisation specification and dummy randomisation code. The intervention group had a much higher CFQ-R RD and ppFEV1 at baseline, whereas the PBO group had more severe CF at baseline	Low IWRS used to assign randomisation and concealment.	Low Double blinded study	Medium Due to the effects of the intervention, effective unblinding upon outcome assessment is plausible	Medium It was unclear if there was missing data as it was unclear how many people comprised the subgroup of interest.	Medium This was a post-hoc analysis. It is unclear how the analysis was developed and if multiple analyses were performed. The alignment between this analysis and the pre-specified analyses from Barry 2021 reduces the risk of bias.	Some concerns

Abbreviations: EAG: external assessment group; CFQR: Cystic Fibrosis Questionnaire-Revised; IVRS: interactive voice response system; IWRS: interactive web response system: $LCI_{2.5}$: lung clearance index 2.5; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; RD: respiratory domain; SLR: systematic literature review.

9.2.2 *Outcome-level risk of bias assessment for $ppFEV_1$ and $LCI_{2.5}$*

Table 100. EAG risk of bias assessment for $ppFEV_1$ (adult and adolescent) or $LCI_{2.5}$ outcomes (children) reported in RCTs prioritised in the EAG SLR.

Study ID	Comparison	Outcome	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Barry 2021	ELX/TEZ/IVA versus IVA	Absolute change in $ppFEV_1$ 8 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo controlled with triple masking. All subjects who received at least one dose of a study drug were included in the analyses.	Low The proportion of people who did not complete treatment or the study was low in both arms.	Low Specifics of how $ppFEV_1$ was measured were not provided.	Low SAP available via clinicaltrials.gov fully defined outcome, measurement schedule and analysis.	Low
Davies 2021	TEZ/IVA versus placebo or IVA	Absolute change in $LCI_{2.5}$ / $ppFEV_1$ at 8 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances in baseline characteristics between treatment groups were noted but randomisation was 4:1 meaning there were small	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Some concerns A higher proportion of missing data in the placebo group Reasons for missing data were not provided to assess whether missingness depended on the outcome's true value.	Low Specifics of how $ppFEV_1$ and $LCI_{2.5}$ were measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov. Multiple timepoints measured but 24 weeks clearly specified as the primary endpoint.	Some concerns due to missing data in the placebo group.

			numbers in the comparator groups.					
Heijerman 2019	ELX/TEZ/IVA versus TEZ/IVA	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm	Low Outcome well defined as absolute change from baseline at week 24. Specifics of how $ppFEV_1$ was measured are not provided, but robust measurements expected given the size and oversight of the trial.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
KONDUCT (Moss (2015)	IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Some concerns IWRS was used to assign patients to treatment and to ensure allocation concealment. There were differences in baseline characteristics between the treatment arms. The intervention group had a much higher CFQ-R RD and ppFEV1 at baseline.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Some concerns Missing data unclear in the subgroup of interest.	Low Specifics of how $ppFEV_1$ was measured were not provided.	Low No access to the pre-specified planned analysis.	Some concerns due to randomisation and missing data.

KONNECTION (De Boeck 2014)	IVA versus placebo	Absolute change in $ppFEV_1$ at 8 weeks	High No details provided of the method used to assign patients to treatment and to ensure allocation concealment. Randomisation was not stratified by the subgroup used in this analysis. Limited baseline characteristics provided indicated similar treatment arms.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Some concerns Missing data unclear in the subgroup of interest. The primary analysis was based on a mixed-effects model for repeated measures.	Low Specifics of how $ppFEV_1$ was measured were not provided.	Low No access to the pre-specified planned analysis.	High risk of bias due to randomisation and missing data.
Mall 2022	ELX/TEZ/IVA versus placebo	Absolute change in LCI Absolute change in $_{2.5}$ / $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances noted, e.g. height- and weight-for-age z-scores, ppFEV1 and LCI 2.5, but likely to reflect random variation due to sample size.	Low Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed treatment assignment from side-effects.	Low Low proportion of missing data in each treatment arm	Low Measurement of $LCI_{2.5}$ and $ppFEV_1$ not described, but robust methods are reported for blinding including outcome assessors.	Low $LCI_{2.5}$ was the primary outcome, but $ppFEV_1$ is not reported on clinicaltrials.gov as an outcome and was not mentioned in the SAP.	Low

Middleton 2019	ELX/TEZ/IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed assignment from side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Outcome well defined. Specifics of how $ppFEV_1$ was measured are not provided, but robust measurements expected given the size and oversight of the trial.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
NCT03625466 (Stahl 2021)	LUM/IVA versus placebo	Absolute change in $LCI_{2.5}$ at 48 weeks	Some concerns IWRS was used to assign patients to treatment and to ensure allocation concealment. Some concerns as to whether the treatment arms were adequately similar for potentially confounding factors	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low No missing data.	Low Specifics of how $LCI_{2.5}$ was measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
Ratjen 2017	LUM/IVA versus placebo	Absolute change in $LCI_{2.5}$ / $ppFEV_1$	Low IWRS was used to assign patients to treatment and to	Low Double-blind trial. ITT analysis.	Low Low proportion of missing data in each treatment arm.	Low Specifics of how $ppFEV_1$ and $LCI_{2.5}$ was measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low

		at 24 weeks	ensure allocation concealment.					
Rowe 2017	TEZ-IVA versus placebo	Absolute change in $ppFEV_1$ at 8 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo controlled with triple masking. Crossover analysis fully described to control for period effects and within-subject covariance.	Low Low proportion of missing data in each treatment arm.	Low Standards for calculating predicted FEV_1 stated in SAP.	Low SAP available via clinicaltrials.gov fully defined outcome, measurement schedule and analysis.	Low
STRIVE (Ramsey 2011)	IVA versus placebo	Absolute change in $ppFEV_1$ at 8 weeks	Some concerns IWRS was used to assign patients to treatment and to ensure allocation concealment. Randomisation study was not stratified by the subgroup used in this analysis. No differences in baseline characteristics were noted in the limited data provided.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Some concerns Missing data unclear in the subgroup of interest.	Low Specifics of how $ppFEV_1$ was measured were not provided.	Low No access to the pre-specified planned analysis.	Some concerns due to randomisation and missing data.
Suthars an 2022	ELX/TEZ/IVA versus placebo	Absolute change in $ppFEV_1$	Low IWRS was used to assign patients to treatment and to	Low Double-blind trial. All subjects who received at least	Low No missing data.	Low Specifics of how ppFEV1 was	Low Outcome analysed in accordance with	Low

		at 24 weeks	ensure allocation concealment.	one dose of a study drug were included in the analyses."		measured were not provided.	the study protocol and analysis plan.	
Taylor-Cousar 2017	TEZ-IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled trial with triple blinding. Possible that participants and investigators could have guessed assignment. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Specifics of how $ppFEV_1$ was measured are not provided, but robust measurements expected given the size and oversight of the trial.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov. Multiple timepoints measured but 24 weeks clearly specified as the primary endpoint.	Low
TRAFFIC (Wainwright 2015)	LUM/IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Specifics of how ppFEV1 was measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
TRANSPORT (Wainwright 2015)	LUM/IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Specifics of how ppFEV1 was measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low

Wilson 2021	LUM/IVA versus placebo	Absolute change in $ppFEV_1$ at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Some concerns 11% of participants did not provide data for this outcome. However, similar numbers were missing from each treatment group.	Low Specifics of how $ppFEV_1$ was measured were not provided.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Some concerns due to missing data

Abbreviations: EAG: external assessment group; IWRS: interactive web response system: $LCI_{2.5}$: lung clearance index 2.5; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SAP: statistical analysis protocol; SLR: systematic literature review.

9.2.3 Outcome-level risk of bias assessment for pulmonary exacerbations

Table 101. EAG risk of bias assessment for pulmonary exacerbations reported in RCTs prioritised in the EAG SLR.

Study ID	Comparison	Outcome	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Risk of Bias
Barry 2021	ELX/TEZ/IVA versus IVA	Pulmonary exacerbations (as AE) at 12 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo controlled with triple masking. All subjects who received at least one dose of a study drug were included in the analyses.	Low The proportion of people who did not complete treatment or the study was low in both arms.	Some concerns Pulmonary exacerbations only reported as an adverse event with no definition presented.	Low SAP available via clinicaltrials.gov fully defined outcome, measurement schedule and analysis.	Some concerns because no definition of PE used in the trial was provided.

Davies 2021	TEZ/IVA versus placebo or IVA	Pulmonary exacerbations (as AE) at 12 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances in baseline characteristics between treatment groups were noted but randomisation was 4:1 meaning there were small numbers in the comparator groups.	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low The proportion of people who did not complete treatment or the study was low in all arms.	Some concerns Pulmonary exacerbations only reported as an adverse event with no definition presented.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Some concerns because no definition of PE used in the trial was provided.
Heijerman 2019	ELX/TEZ/IVA versus TEZ/IVA	Pulmonary exacerbations (as AE) at 8 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm	Some concerns Pulmonary exacerbations only reported as an adverse event with no definition presented.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Some concerns because no definition of PE used in the trial was provided.
Mall 2022	ELX/TEZ/IVA	Pulmonary	Low	Low	Low	Some concerns	Low	Some concerns because no

	versus placebo	exacerbations (as AE) at 28 weeks	IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances noted, e.g. height- and weight-for-age z-scores, ppFEV1 and LCI 2.5, but likely to reflect random variation due to sample size.	Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed treatment assignment from side-effects.	Low proportion of missing data in each treatment arm "	Pulmonary exacerbations only reported as an adverse event with no definition presented. "	Safety outcomes presented in accordance with statistical analysis plan provided on clinicaltrials.gov.	definition of PE used in the trial was provided.
Middleton 2019	ELX/TEZ/IVA versus placebo	PE leading to hospitalisations at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed assignment from side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Clear definition provided.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
NCT03625466 (Stahl 2021)	LUM/IVA versus placebo	Pulmonary exacerbations	Some concerns IWRS was used to assign patients to treatment and to	Low Double-blind trial. All subjects who received at least	Low No missing data.	Some concerns Pulmonary exacerbations only reported as an	Low Outcome analysed in accordance with	Some concerns due to randomisation and because no definition of PE

		(as AE) at 48 weeks	ensure allocation concealment. Some concerns as to whether the treatment arms were adequately similar for potentially confounding factors	one dose of a study drug were included in the analyses.		adverse event with no definition presented.	the study protocol and analysis plan.	used in the trial was provided.
Ratjen 2017	LUM/IVA versus placebo	Pulmonary exacerbations (as AE) at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. ITT analysis.	Low Low proportion of missing data in each treatment arm.	Low Pulmonary exacerbations clearly defined.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
Rowe 2017	TEZ-IVA versus placebo	Pulmonary exacerbations (as AE) at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo controlled with triple masking. Crossover analysis fully described to control for period effects and within-subject covariance.	Low Low proportion of missing data in each treatment arm.	Some concerns No definition given for pulmonary exacerbations, or information about how the assessments were made. Numbers differ from pulmonary exacerbations reported as adverse events and serious adverse events.	Some concerns Pulmonary exacerbation frequencies and estimated annual rates are not described as an endpoint in the protocol/ statistical analysis plan, and sections of the endpoint sections are redacted. Described as an exploratory endpoint in the paper.	Some concerns because no definition of PE used in the trial was provided and the selection of the reported result.

Suthars an 2022	ELX/TEZ/IVA versus placebo	Pulmonary exacerbations (as AE) at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low No missing data.	Some concerns Pulmonary exacerbations only reported as an adverse event with no definition presented.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Some concerns because no definition of PE used in the trial was provided.
Taylor-Cousar 2017	TEZ-IVA versus placebo	Pulmonary exacerbations at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled trial with triple blinding. Possible that participants and investigators could have guessed assignment. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Outcome clearly defined.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
TRAFFIC (Wainwright 2015)	LUM/IVA versus placebo	PE leading to hospitalisations at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Outcome clearly defined.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low

TRANSPORT (Wainwright 2015)	LUM/IVA versus placebo	PE leading to hospitalisations at 24 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Outcome clearly defined.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
Wilson 2021	LUM/IVA versus placebo	Pulmonary exacerbations (as AE) at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low No missing data.	Some concerns Pulmonary exacerbations only reported as an adverse event with no definition presented.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Some concerns because no definition of PE used in the trial was provided.

Abbreviations: AE: adverse event; EAG: external assessment group; IWRS: interactive web response system: $LCI_{2.5}$: lung clearance index 2.5; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SAP: statistical analysis protocol; SLR: systematic literature review.

9.2.4 Outcome-level risk of bias assessment for serious adverse events

Table 102. EAG risk of bias assessment for serious adverse events reported in RCTs prioritised in the EAG SLR.

Study ID	Comparison	Outcome	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Risk of Bias
Barry 2021	ELX/TEZ/IVA	Any serious adverse	Low IWRS was used to assign patients to	Low Double-blind, placebo controlled	Low The proportion of people who did not	Low Standard MedDRA coding used for all	Low SAP available via clinicaltrials.gov fully	Low

	versus IVA	event at 12 weeks	treatment and to ensure allocation concealment.	with triple masking. All subjects who received at least one dose of a study drug were included in the analyses.	complete treatment or the study was low in both arms.	safety data (MedDRA 23.0) and safety overseen by independent monitoring committee	defined outcome, measurement schedule and analysis.	
Davies 2021	TEZ/IVA versus placebo or IVA	Any serious adverse event at 12 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances in baseline characteristics between treatment groups were noted but randomisation was 4:1 meaning there were small numbers in the comparator groups.	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Standard MedDRA coding used for adverse events and safety was monitored by an independent data monitoring committee.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
Heijerman 2019	ELX/TEZ/IVA versus TEZ/IVA	Any serious adverse event at 8 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial with quadruple masking. Participants and investigators could have guessed assignment from drug side-effects. All subjects who	Low Low proportion of missing data in each treatment arm	Low Standard MedDRA coding used for adverse events and safety was monitored by an independent data monitoring committee.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low

				received at least one dose of a study drug were included in the analyses.				
Mall 2022	ELX/TEZ/IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment. Some imbalances noted, e.g. height- and weight-for-age z-scores, ppFEV1 and LCI 2.5, but likely to reflect random variation due to sample size.	Low Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed treatment assignment from side-effects.	Low Low proportion of missing data in each treatment arm	Low Standard MedDRA coding used for adverse events and safety was monitored by an independent data monitoring committee.	Low Presented in accordance with statistical analysis plan provided on clinicaltrials.gov.	Low
Middleton 2019	ELX/TEZ/IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled with quadruple masking. Possible that participants and investigators could have guessed assignment from side-effects. All subjects who received at least one dose of a study	Low Low proportion of missing data in each treatment arm.	Low Standard MedDRA coding used for adverse events and safety was monitored by an independent data monitoring committee.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low

				drug were included in the analyses.				
NCT03625466 (Stahl 2021)	LUM/IVA versus placebo	Any serious adverse event at 48 weeks	Some concerns IWRS was used to assign patients to treatment and to ensure allocation concealment. Some concerns as to whether the treatment arms were adequately similar for potentially confounding factors	Low Double-blind trial. The Safety Set included all patients who receive at least 1 dose of study drug.	Low No missing data.	Low Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA).	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
Ratjen 2017	LUM/IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. ITT analysis.	Low Low proportion of missing data in each treatment arm.	Low Serious adverse events definition available via clinicaltrials.gov.	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
Rowe 2017	TEZ-IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo controlled with triple masking. Crossover analysis fully described to control for period effects and within-subject covariance.	Low Low proportion of missing data in each treatment arm.	Low All safety data collected and reported using standard MedDRA terminology and overseen by a safety monitoring committee.	Low SAP available via clinicaltrials.gov fully defined outcome, measurement schedule and analysis.	Low
Sutharsan 2022	ELX/TEZ/IVA	Any serious	Low	Low	Low No missing data.	Low	Low	Low

	versus placebo	adverse event at 28 weeks	IWRS was used to assign patients to treatment and to ensure allocation concealment.	Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses."		Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA).	Outcome analysed in accordance with the study protocol and analysis plan.	
Taylor-Cousar 2017	TEZ-IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind, placebo-controlled trial with triple blinding. Possible that participants and investigators could have guessed assignment. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Standard MedDRA coding used for adverse events and safety was monitored by an independent data monitoring committee.	Low Outcome analysed in accordance with the study protocol and analysis plan available via clinicaltrials.gov.	Low
TRAFFIC)	LUM/IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low No missing data.	Low Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA).	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low
TRANSPORT	LUM/IVA versus placebo	Any serious adverse event at	Low IWRS was used to assign patients to treatment and to	Low Double-blind trial. All subjects who received at least one dose of a study	Low No missing data.	Low Adverse events were coded with the Medical Dictionary for Regulatory	Low Outcome analysed in accordance with	Low

		28 weeks	ensure allocation concealment.	drug were included in the analyses.		Activities (MedDRA).	the study protocol and analysis plan.	
Wilson 2021	LUM/IVA versus placebo	Any serious adverse event at 28 weeks	Low IWRS was used to assign patients to treatment and to ensure allocation concealment.	Low Double-blind trial. All subjects who received at least one dose of a study drug were included in the analyses.	Low Low proportion of missing data in each treatment arm.	Low Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA).	Low Outcome analysed in accordance with the study protocol and analysis plan.	Low

Abbreviations: AE: adverse event; EAG: external assessment group; IWRS: interactive web response system: $LCI_{2.5}$: lung clearance index 2.5; PBO: placebo; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SAP: statistical analysis protocol; SLR: systematic literature review.

9.2.5 Economic evaluations studies quality assessment- Drummond checklist

	Multiple CFTR modulators		Elexacaftor/Tezacafor/Ivacaftor (ELX/TEZ/IVA)			Lumacaftor/Ivacaftor (LUM/IVA)										Tezacaftor/Ivacaftor (TEZ/IVA)	
Study	ICER 2018	ICER 2020	PBAC 2021	CADTH 2021	CADTH 2022	NICE 2016	Dilokthornsakul 2017	Sharma 2018	Vadagam 2018	SMC, 2016	SMC, 2019a	PBAC 2018a	PBAC 2019b	PBAC 2018b	CADTH 2016	CADTH 2018	SMC, 2019b	PBAC 2019a
Study design																		
1. The research question is stated.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2. The economic importance of the research	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

question is stated.																		
3. The viewpoint(s) of the analysis are clearly stated and justified.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4. The rationale for choosing alternative programmes or interventions compared is stated.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
5. The alternatives being compared are clearly described.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
6. The form of economic	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes

evaluation used is stated.																		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	no	no	not applicable	yes	yes	yes	no	yes	no	not applicable	not applicable	not applicable	not applicable	not applicable	yes	yes	not applicable	not applicable
Data collection																		
8. The source(s) of effectiveness estimates used are stated.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
9. Details of the design and results of effectiveness	yes	yes	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes	no	yes	yes

study are given (if based on a single study).																		
10. Details of the methods of synthesis or meta-analysis of estimates are given	no	no	partly	redacted	redacted	not applicable	not applicable	not applicable	not applicable	yes	yes	not applicable	not applicable	not applicable	no	no	yes	not applicable
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
12. Methods to value benefits are stated.	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no	yes	yes	no	yes	yes
13. Details of the	no	no	no	no	no	yes	no	no	not applicable	no	no	no	no	no	no	no	no	no

subjects from whom valuations were obtained were given.																		
14. Productivity changes (if included) are reported separately.	yes	yes	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
15. The relevance of productivity changes to the study question is discussed.	yes	yes	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
16. Quantities of resource use are reported separatel	yes	yes	no	no	no	yes	yes	no	yes	no	no	no	no	no	no	no	no	no

y from their unit costs.																		
17. Methods for the estimation of quantities and unit costs are described.	yes	yes	no	yes	yes	yes	no	yes	yes	partly	no	no	no	no	no	no	yes	no
18. Currency and price data are recorded.	yes	yes	no	no	no	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no
19. Details of currency of price adjustments for inflation or currency conversion are given.	no	no	no	no	no	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no
20. Details of any model	yes	yes	yes	yes	yes	yes	yes	yes	partly	yes	yes	yes	yes	yes	yes	yes	yes	yes

used are given.																		
21. The choice of model used and the key parameters on which it is based are justified.	yes	yes	no	yes	yes	yes	no	yes	partly	yes	yes	no	no	no	yes	yes	yes	no
Analysis and interpretation of results																		
22. Time horizon of costs and benefits is stated.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
23. The discount rate(s) is stated.	yes	yes	yes	yes	yes	yes	yes	yes	not applicable	no	no	no	no	no	yes	yes	no	no
24. The choice of discount rate(s) is justified.	yes	yes	no	yes	yes	yes	yes	yes	not applicable	no	no	no	no	no	yes	yes	no	no
25. An explanation is given if	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable

costs and benefits are not discounted.																		
26. Details of statistical tests and confidence intervals are given for stochastic data.	yes	yes	no	yes	yes	yes	no	no	no	no	no	no	no	no	no	no	no	no
27. The approach to sensitivity analysis is given.	yes	yes	no	yes	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	no
28. The choice of variables for sensitivity analysis is justified.	yes	yes	no	yes	yes	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no
29. The ranges over which the variables are	no	no	no	no	no	yes	no	no	no	no	no	no	no	no	no	no	no	no

varied are justified.																		
30. Relevant alternatives are compared.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
31. Incremental analysis is reported.	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
32. Major outcomes are presented in a disaggregated as well as aggregated form.	yes	yes	partly	yes	yes	yes	yes	yes	yes	no	yes	partly	partly	partly	yes	yes	yes	partly
33. The answer to the study question is given.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
34. Conclusions follow from the	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

data reported.																		
35. Conclusions are accompanied by the appropriate caveats.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

9.3 Clinical data extraction tables

9.3.1 Baseline characteristics

9.3.1.1 Studies recruiting children up to age 12

Table 103. Baseline characteristics of CFTR modulator trials of children with CF aged 1 to 12 prioritised in the EAG's SLR

Study	Rayment 2022: Part B	Stahl 2021		EudraCT Number 202000225138 Part B	Ratjen 2017		Davies 2021			Zemanick 2021	Mall 2022	
Intervention	LUM/IVA	LUM/IVA	Placebo	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA	IVA	Placebo	ELX/TEZ/IVA	ELX/TEZ/IVA	Placebo
N	46	35	16	75	103	101	55	3	11	66	60	61
Genotype	F/F	F/F	F/F	F/F; F/MF	F/F	F/F	F/F; F/RF	F/RF	F/F	F/F; F/MF	F/MF	F/MF
Age, years (SD)	1.51 (0.29)	4.20 (1.00)	4.20 (1.00)	4.10 (1.10)	8.70 (1.60)	8.90 (1.60)	8.50 (1.70)	9.00 (1.70)	9.00 (1.70)	9.30 (1.90)	9.10 (1.80)	9.20 (1.70)
Sex, %												
Male	47.8	68.6	56.3	45.3	39	43	46.3	33.3	40	40.9	41.7	42.6
Female	52.2	31.4	43.8	54.7	61	57	53.7	66.7	60	59.1	58.3	57.4
Region, %												
North America	NR	NR	NR	NR	57	59	NR	NR	NR	71.2	NR	NR
Europe	NR	NR	NR	NR	27	29	NR	NR	NR	NR	71.7	80.3
Other	NR	NR	NR	US 49; Australia 11; Canada 11;	Australia 16 (16%)	Australia 12 (12%)	NR	NR	NR	Europe and Australia	Australia, Canada and Israel 17 (28.3%)	Australia, Canada and Israel 12 (19.7%)

				UK 5; Germany 7						19 (28.8%)		
Race, %												
White	78.3	100	100	NR	NR	NR	94.4	100	100	87.9	75	68.9
Black or African American	2.2	0	0	NR	NR	NR	1.9	0	0	0	1.7	0
Asian	2.2	0	0	NR	NR	NR	0	0	0	1.5	1.7	0
Weight, kg (SD)	11.20 (1.30)	NR	NR	NR	NR	NR	28.90 (6.70)	NR	NR	30.00 (7.70)	29.10 (7.60)	29.80 (8.60)
Weight-for-age z-score	0.46 (0.79)	[redacted]	[redacted]	NR	-0.20 (0.80)	-0.20 (0.80)	-0.28 (0.72)	NR	NR	-0.22 (0.76)	-0.27 (0.99)	-0.29 (0.96)
BMI (SD)	17.17 (1.22)	NR	NR	NR	16.40 (1.70)	16.60 (2.00)	16.13 (1.66)	NR	NR	16.39 (1.69)	16.33 (1.84)	16.11 (2.32)
BMI-for-age z-score	0.86 (0.77)	[redacted]	[redacted]	NR	NA (0.80)	NA (0.90)	-0.25 (0.85)	NR	NR	-0.16 (0.74)	-0.17 (0.85)	-0.39 (0.92)
$ppFEV_1$ (SD)	NR	NR	NR	NR	88.80 (13.70)	90.70 (10.80)	86.50 (12.90)	NR	NR	88.80 (17.70)	91.40 (13.80)	87.20 (15.80)
$LCI_{2.5}$ (SD)	NR	[redacted]	[redacted]	NR	10.30 (2.40)	10.30 (2.20)	9.56 (2.06)	8.60 (1.40)	9.67 (1.65)	9.77 (2.68)	10.26 (2.22)	9.75 (1.95)
Sweat chloride, mmol/L (SD)	104.20 (7.70)	[redacted]	[redacted]	NR	102.60 (10.30)	103.40 (9.80)	99.20 (19.50)	NR	NR	102.20 (9.10)	102.80 (10.00)	102.60 (8.60)
EQ-5D-3L utility score (SD)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

CFQ-R RD Score (SD)	NR	NR	NR	NR	NR	NR	84.60 (11.40)	NR	NR	80.30 (15.20)	85.70 (11.70)	82.70 (14.10)
Pancreatic sufficient, %	0	NR	NR	NR	99	99	NR	NR	NR	NR	NR	NR
CF related diabetes, %	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pseudomonas aeruginosa-positive, %	NR	NR	NR	NR	43	43	NR	NR	NR	39.4	NR	NR

Continuous data are presented as mean (SD) unless stated.

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review; TEZ: tezacaftor.

9.3.1.1 Studies recruiting people with CF aged 12+ years, LUM/IVA and TEZ/IVA trials

Table 104. Baseline characteristics of LUM/IVA and TEZ/IVA trials of people with CF aged 12+ prioritised in the EAG's SLR.

Study	TRAFFIC		TRANSPORT		Wilson 2021		Taylor-Cousar 2017		Rowe 2017	
Intervention	LUM/IVA	Placebo	LUM/IVA	Placebo	LUM/IVA	Placebo	TEZ/IVA	Placebo	TEZ/IVA	Placebo
N	182	184	187	187	34	36	248	256	83	80
Genotype	F/F	F/F	F/F	F/F	F/F	F/F	F/F	F/F	F/RF	F/RF
Age, years (SD)	25.50 [redacted]	25.00 [redacted]	25.00 [redacted]	25.70 [redacted]	24.90 (10.17)	26.10 (10.58)	26.90 (11.20)	25.70 (9.50)	35.60 (13.50)	32.60 (13.90)
Sex, %										
Male	54	54	47.6	48.1	61.8	50	51.20968	51.17188	42	42

Female	46.2	45.7	52.4	51.9	38.2	50	48.8	48.8	58	58
Region, %										
North America	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	23.8	26.6	54	49
Europe	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	76.2	73.4	46	51
Other	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NA	NA
Race, %	[redacted]	[redacted]	[redacted]	[redacted]						
White	[redacted]	[redacted]	[redacted]	[redacted]	100	100	98.8	99.2	NR	NR
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	0.4	0	NR	NR
Asian	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	0	0.8	NR	NR
Weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR (NR)	NR (NR)	NR (NR)	[redacted]	[redacted]
BMI (SD)	[redacted]	[redacted]	[redacted]	[redacted]	21.10 (2.95)	21.30 (3.05)	20.96 (2.95)	21.12 (2.88)	23.60 (4.60)	24.60 (5.00)
ppFEV1 (SD)	60.50 (NR)	60.50 (NR)	60.60 (NR)	60.40 (NR)	65.60 (15.00)	67.50 (19.33)	59.60 (14.70)	60.40 (15.70)	61.80 (14.90)	62.10 (14.00)
Sweat chloride, mmol/L (SD)	NR	NR	NR	NR	NR (NR)	NR (NR)	101.30 (10.90)	100.50 (10.20)	64.10 (28.90)	70.70 (24.00)
EQ-5D-3L utility score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
CFQR-RD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	69.90 (16.78)	66.00 (19.39)	70.10 (16.80)	69.90 (16.60)	66.50 (17.90)	67.80 (17.50)
Pancreatic sufficient, %	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	13	14
CF related diabetes, %	28.6	29.3	33.2	27.3	NR	NR	NR	NR	NR	NR
Pseudomonas aeruginosa-positive, %	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	74.6	71.1	63	60

Continuous data are presented as mean (SD) unless stated.

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; SD: standard deviation; SLR: systematic literature review; TEZ: tezacaftor.

9.3.1.2 *Studies recruiting people with CF aged 12+ years, ELX/TEZ/IVA trials*

Table 105. Baseline characteristics of ELX/TEZ/IVA trials of people with CF aged 12+ prioritised in the EAG's SLR.

Study	Heijerman 2019		Sutharsan 2022		Middleton 2019		Barry 2021		Barry 2021	
Intervention	TEZ/IVA	ELX/TEZ/IVA	TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	Placebo	TEZ/IVA	ELX/TEZ/IVA	IVA monotherapy	ELX/TEZ/IVA
N	52	55	88	87	202	203	81	82	45	50
Genotype	F/F	F/F	F/F	F/F	F/MF	F/MF	F/RF	F/RF	F/GM	F/GM
Age, years (SD)	27.90 (10.80)	28.80 (11.50)	27.80 (11.00)	27.90 (11.80)	25.60 (9.70)	26.80 (11.30)	41.50 (14.40)	40.20 (14.70)	30.80 (11.20)	33.50 (13.80)
Sex, %										
Male	46	44	49	51	52	51.7	45.7	45.1	62.2	56
Female	54	56	51	49	48	48.3	54.3	54.9	37.8	44
Region, %										
North America	63	62	NR	NR	59	59.1	34.6	36.6	44.4	38
Europe	37	38	NR	NR	NR	NR	65.4	63.4	55.6	62
Other	NR	NR	NR	NR	Europe/Australia combined 82 (41%)	Europe/Australia combined 83 (40.9%)	Europe including Australia	Europe including Australia	Europe including Australia	Europe including Australia
Race, %										
White	100	98.2	100	98	92.5	89.7	NR	NR	NR	NR
Black or African American	0	0	0	0	1.5	0.5	NR	NR	NR	NR
Asian	0	0	0	0	NR	NR	NR	NR	NR	NR

Weight, kg (SD)	[redacted]	[redacted]	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
BMI (SD)	21.88 (4.12)	21.75 (3.19)	NA (NA)	NA (NA)	21.49 (3.07)	21.31 (3.14)	24.68 (5.22)	24.29 (5.23)	22.91 (3.39)	23.71 (3.76)
ppFEV1 (SD)	60.20 (14.40)	61.60 (15.40)	64.20 (15.10)	63.00 (16.70)	61.60 (15.00)	61.30 (15.50)	68.10 (16.40)	67.80 (16.30)	68.10 (16.60)	66.00 (14.80)
Sweat chloride, mmol/L (SD)	90.00 (12.30)	91.40 (11.00)	89.80 (11.70)	89.00 (12.20)	102.30 (11.90)	102.90 (9.80)	61.40 (27.30)	64.70 (27.90)	47.60 (19.10)	50.90 (23.30)
EQ-5D-3L utility score (SD)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CFQ-R Respiratory Domain Score (SD)	72.60 (17.90)	70.60 (16.20)	73.10 (17.60)	71.20 (19.60)	68.30 (16.90)	70.00 (17.80)	78.10 (14.70)	76.70 (16.90)	75.80 (17.60)	76.30 (16.40)
Pancreatic sufficient, %	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
CF related diabetes, %	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Pseudomonas aeruginosa-positive, %	60	71	NR	NR	75	70	58.7: Reported as combined active control only	59.8	NR	NR

Continuous data are presented as mean (SD) unless stated.

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; LUM: lumacaftor; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review; TEZ: tezacaftor.

9.3.1.3 *Studies recruiting people with CF aged 12+ years, IVA trials, F/Gating 12+ subgroup data*

Table 106. Baseline characteristics of IVA trials of people with CF aged 12+ prioritised in the EAG's SLR.

Study	Ramsay 2011		De Boeck 2014		Moss 2015	
Intervention	IVA monotherapy	Placebo	IVA monotherapy	Placebo	IVA monotherapy	Placebo
N	64	58	17	17	20	19
Genotype	F/Gating	F/Gating	F/Gating	F/Gating	F/Gating	F/Gating
Age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, %						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, %						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$ppFEV_1$ (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sweat chloride, mmol/L (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFQR-R Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic sufficient, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF related diabetes, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pseudomonas aeruginosa-positive, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review.

9.3.2 *Participant disposition*

Table 107. Participant disposition in studies prioritised in the EAG SLR

Study	Intervention	N	N mITT	N SAS	Completed treatment	Discontinued due to AEs	Lost to follow-up	Withdrew consent	Pregnancy	Other
Heijerman 2019	TEZ/IVA	52	52	52	52	0	0	0	0	0
Heijerman 2019	ELZ/TEZ/IVA	55	55	55	55	0	0	0	0	0
EudraCT Number 202000225138 Part B	ELZ/TEZ/IVA	75	NR	75	74	1	0	0	0	0
Middleton 2019	ELX/TEZ/IVA	201	200	202	197	2	0	0	1	0
Middleton 2019	Placebo	204	203	201	203	0	0	0	0	0
Taylor-Cousar 2017	TEZ-IVA	251	248	251	235	7	0	5	0	4
Taylor-Cousar 2017	Placebo	259	256	258	240	8	0	5	0	5

Davies 2021	TEZ/IVA	55	54	54	53	0	0	0	0	2
Davies 2021	IVA monotherapy	3	3	3	3	0	0	0	0	0
Davies 2021	Placebo	11	10	10	10	0	0	0	0	1
Zemanick 2021 Part B	ELX/TEZ/IVA	69	66	66	64	1	0	1	0	0
Mall 2022	ELX-TEZ-IVA	60	60	60	59	1	0	0	0	0
Mall 2022	Placebo	61	61	61	61	0	0	0	0	0
Rowe 2017	TEZ/IVA	84	83	83	80	1	0	0	1	1
Rowe 2017	Placebo	82	80	81	75	2	1	2	0	2
Barry 2021 F/Gating	IVA monotherapy	45	45	45	NR	NR	NR	NR	NR	NR
Barry 2021 F/Gating	ELX/TEZ/IVA	50	50	50	NR	NR	NR	NR	NR	NR
Barry 2021 F/RF	TEZ/IVA	81	81	81	NR	NR	NR	NR	NR	NR
Barry 2021 F/RF	ELX/TEZ/IVA	82	82	82	NR	NR	NR	NR	NR	NR
Ratjen 2017	LUM/IVA	104	103	103	97	3	1	1	0	1
Ratjen 2017	Placebo	102	101	101	96	2	0	2	0	1
Wilson 2021	LUM/IVA	34	NR	34	31	2	0	0	0	1
Wilson 2021	Placebo	36	NR	36	36	0	0	0	0	0
Stahl 2021	LUM/IVA	35	35	35	33	1	0	1	0	0
Stahl 2021	Placebo	16	16	16	16	0	0	0	0	0

Sutharsan 2022	ELX/TEZ/IVA	88	87	87	86	1	0	0	0	0
Sutharsan 2022	TEZ/IVA	88	88	88	86	2	0	0	0	0
TRAFFIC	LUM/IVA	187	182	182	172	6	0	1	0	3
TRAFFIC	Placebo	187	184	184	180	4	0	0	0	0
TRANSPORT	LUM/IVA	187	187	187	172	11	0	1	0	3
TRANSPORT	Placebo	187	187	187	182	2	0	0	0	3

Abbreviations: EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; mITT: modified intention-to-treat; NR: not reported; SAS: safety analysis set; SLR: systematic literature review; TEZ: tezacaftor.

9.3.3 Prior and concomitant medication

Table 108. Prior and concomitant medications reported in studies prioritised in the EAG SLR

Study	Intervention	Any CTFRm %	IVA %	LUM IVA %	TEZ IVA %	ELX TEZ IVA %	Azithromycin %	Bronchodilators %	Dornase alfa %	Inhaled hypertonic saline %	Inhaled corticosteroids %	Mannitol %	Inhaled antibiotic %
Heijerman 2019	TEZ/IVA	65	[redacted]	[redacted]	[redacted]	[redacted]	48	90	92	79	54	[redacted]	54
Heijerman 2019	ELX/TEZ/IVA	58	[redacted]	[redacted]	[redacted]	[redacted]	60	98	93	69	65	[redacted]	64
EudraCT Number 202000225138	ELX/TEZ/IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Middleton 2019	ELX/TEZ/IVA	NR	NR	NR	NR	NR	55	93.5	81	73.5	60	NR	59
Middleton 2019	Placebo	NR	NR	NR	NR	NR	56.2	94.1	80.8	62.6	58.6	NR	65
Taylor-Cousar 2017	TEZ-IVA	NR	NR	NR	NR	NR	54.4	89.1	66.5	50.8	56	NR	54.8
Taylor-Cousar 2017	Placebo	NR	NR	NR	NR	NR	55.1	91.4	72.3	52	63.3	NR	62.5

Davies 2021	TEZ/IVA	0.037	0	0.037	NR	NR	NR	NR	NR	NR	NR	NR	NR
Davies 2021	IVA	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Davies 2021	Placebo	0.1	0	0.1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zemanick 2021	ELX/TEZ/IVA	21.2	NR	NR	NR	NR	28.8	92.4	81.8	78.8	NR	NR	12.1
Mall 2022	ELX/TEZ/IVA	NR	NR	NR	NR	NR	18.3	63.3	70	76.7	25	NR	25
Mall 2022	Placebo	NR	NR	NR	NR	NR	14.8	75.4	67.2	75.4	29.5	NR	13.1
Rowe 2017	TEZ/IVA	NR	NR	NR	NR	NR	39	89	57	52	60	NR	31
Rowe 2017	Placebo	NR	NR	NR	NR	NR	48	89	68	49	56	NR	29
Barry 2021 F/Gating	IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barry 2021 F/Gating	ELX/TEZ/IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barry 2021 F/RF	TEZ/IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barry 2021 F/RF	ELX/TEZ/IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ratjen 2017	LUM/IVA	NR	NR	NR	NR	NR	NR	83	85	65	37	NR	19
Ratjen 2017	Placebo	NR	NR	NR	NR	NR	NR	81	87	53	47	NR	30
Wilson 2021	LUM/IVA	0	0	0	0	0	NR	NR	NR	NR	NR	NR	NR
Wilson 2021	Placebo	0	0	0	0	0	NR	NR	NR	NR	NR	NR	NR
Stahl 2021	LUM/IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stahl 2021	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ramsey 2011	IVA	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR
Ramsey 2011	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR
De Boeck 2014	IVA	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR
De Boeck 2014	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR
Moss 2015	IVA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moss 2015	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sutharsan 2022	ELX/TEZ/IVA	45	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sutharsan 2022	TEZ/IVA	44	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

TRAFFIC	LUM/IVA	NR	NR	NR	NR	NR	52.2	95.1	67.6	61.5	59.9	NR	62.1
TRAFFIC	Placebo	NR	NR	NR	NR	NR	59.2	93.5	73.4	54.3	61.4	NR	66.3
TRANSPORT	LUM/IVA	NR	NR	NR	NR	NR	64.2	91.4	80.2	61.5	55.1	NR	59.9
TRANSPORT	Placebo	NR	NR	NR	NR	NR	66.3	90.9	78.1	64.2	57.2	NR	72.7

Abbreviations: CFTRm: cystic fibrosis transmembrane conductance regulator modulator; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; NR: not reported; SLR: systematic literature review; TEZ: tezacaftor.

9.3.4 Clinical outcomes

Table 109. Clinical efficacy outcomes of studies recruiting people under 12 years prioritised in the EAG SLR.

Study	Rayment 2022: Part B	Stahl 2021		EudraCT Number 2020002251 38 Part B	Ratjen 2017		Davies 2021			Zemanick 2021		Mall 2022	
Ages	1 to 2	2 to 5		2 to 5	6 to 11		6 to 11			6 to 11		6 to 11	
Genotype	F/F	F/F		F/F, F/MF	F/F		F/F, F/RF	F/RF	F/F	F/F	F/MF	F/MF	
Intervention	LUM/IVA	LUM/IVA	Placebo	ELZ/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA	IVA	PBO	ELX/TEZ/IVA		ELX/TEZ/IVA	PBO
N	46	35	16	75	103	101	54	3	10	29	37	60	61
Timepoint, weeks	24	48	48	28	24	24	8	8	8	24	24	24	24
N deaths	0	0	0	0	0	0	0	0	0	0	0	0	0
CFB in sweat chloride at timepoint, mmol/L (95% CI)	–29.1 (–34.8 to –23.4)	–25.4 (NR)	1 (NR)	[redacted]	–21.6 (NR)	3.2 (NR)	–12.3 (–15.3 to –9.3)	–1 (NR)	–1 (NR)	–70.4 (–75.6 to –65.3)	–55.1 (–59 to –51.2)	–52.1 (–55 to –49.2)	–0.9 (–3.8 to 2)

Difference from reference (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	–51.2 (–55.3 to –47.1)	
CFB in ppFEV$_1$ at timepoint (95% CI)	NR	NR	NR	NR	1.1 (–0.4 to 2.6)	–1.3 (–2.8 to 0.2)	2.8 (1 to 4.6)	–0.4 (NR)	–3.7 (NR)	11.2 (7.2 to 15.2)	9.1 (6.3 to 11.9)	9.5 (6.6 to 12.4)	–1.5 (–4.4 to 1.4)
Difference from reference (95% CI)	NR	NR	NR	NR	2.4 (0.4 to 4.4)		NR	NR	NR	NR	NR	11 (6.9 to 15.1)	
CFB in LCI$_{2.5}$ at timepoint (95% CI)	NR	–0.37 (–0.85 to 0.1)	0.32 (–0.2 to 0.84)	[redacted]	–1.01 (–1.3 to –0.8)	0.08 (–0.2 to 0.3)	–0.51 (–0.74 to –0.29)	–0.61 (NR)	0.1 (NR)	–1.64 (–2.34 to –0.94)	–1.72 (–2.11 to –1.33)	–2.29 (–2.6 to –1.97)	–0.02 (–0.34 to 0.29)
Difference from reference (95% CI)	NR	NR	NR	NR	–1.09 (–1.43 to –0.75)		NR	NR	NR	NR	NR	–2.26 (–2.71 to –1.81)	
Pulmonary exacerbations reported	As AE only	As AE only	As AE only	Yes	Yes	Yes	As AE only	As AE only	As AE only	NR	NR	As AE only	As AE only
N exacerbations	9	26	19	[redacted]	[redacted]	[redacted]	3	0	2	NR	NR	1	16
Annualised event rate	0.6	0.75	1.17	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
Difference from reference, rate ratio (95% CI)	NR	NR	NR	NR	[redacted]		NR	NR	NR	NR	NR	NR	NR
CFB in BMI at timepoint (95% CI)	–0.2 (–0.47 to 0.08)	NR	NR	NR	0.38 (0.3 to 0.5)	0.27 (0.1 to 0.4)	–0.04 (NR)	0.11 (NR)	0.02 (NR)	NR	NR	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	0.1 (–0.1 to 0.3)		NR	NR	NR	NR	NR	NR	NR

CFB in BMI-for-age z-score at timepoint (95% CI)	0.04 (–0.14 to 0.22)	0.2 (–0.02 to 0.41)	–0.24 (–0.55 to 0.07)	NR	0.08 (0 to 0.2)	0.05 (0 to 0.1)	–0.08 (NR)	0.08 (NR)	–0.05 (NR)	NR	NR	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	0 (–0.1 to 0.1)		NR	NR	NR	NR	NR	NR	NR
CFB in weight at timepoint, kg (95% CI)	1.3 (1.1 to 1.5)	NR	NR	NR	2 (NR)	1.7 (NR)	0.3 (NR)	0.5 (NR)	0.6 (NR)	NR	NR	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CFB in weight-for-age z score at timepoint (95% CI)	0.06 (–0.05 to 0.17)	0.13 (–0.01 to 0.27)	–0.07 (–0.24 to 0.11)	[redacted]	0.06 (NR)	0.02 (NR)	–0.04 (NR)	0.03 (NR)	–0.02 (NR)	0.28 (0.18 to 0.39)	NR	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	[redacted]		NR	NR	NR	NR	NR	NR	NR
CFB in CFQ-R Respiratory Domain score at timepoint (95% CI)	NR	NR	NR	NR	5.5 (3.4 to 7.6)	3 (1 to 5)	2.3 (–0.1 to 4.6)	2.8 (NR)	9.2 (NR)	7 (3.9 to 10.1)	6.9 (3.2 to 10.6)	5.9 (2.8 to 9.1)	0.5 (–2.7 to 3.6)
Difference from reference (95% CI)	NR	NR	NR	NR	2.5 (–0.1 to 5.1)		NR	NR	NR	NR	NR	5.5 (1 to 10)	

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review.

Table 110. Clinical efficacy outcomes of studies of LUM/IVA or TEZ/IVA recruiting people 12+ years prioritised in the EAG SLR.

Study	TRAFFIC		TRANSPORT		Wilson 2021		Taylor-Cousar 2017		Rowe 2017	
Intervention	LUM/IVA	Placebo	LUM/IVA	Placebo	LUM/IVA	Placebo	TEZ/IVA	Placebo	TEZ/IVA	Placebo
Genotype	F/F	F/F	F/F	F/F	F/F	F/F	F/F	F/F	F/RF	F/RF
N	182	184	187	187	34	36	248	256	161	161
Timepoint, weeks	24	24	24	24	24	24	24	24	8	8
N deaths	0	0	0	0	0	0	0	0	0	0
CFB in sweat chloride at timepoint, mmol/L (95% CI)	NR	NR	NR	NR	NR	NR	–9.9 (–10.9 to –8.9)	0.2 (–0.8 to 1.2)	–9.9 (– 11.8 to –8)	–0.4 (–2.3 to 1.5)
Difference from reference (95% CI)	NR	NR	NR	NR	NR	NR	–10.1 (–11.4 to –8.8)		–9.5 (–11.7 to –7.3)	
CFB in ppFEV$_1$ at timepoint (95% CI)	2.16 (NR)	–0.44 (NR)	2.85 (NR)	–0.15 (NR)	–0.6 (–4 to 2.9)	–4 (–7.3 to –0.7)	3.4 (2.7 to 4)	–0.6 (–1.3 to 0)	6.5 (5.6 to 7.3)	–0.3 (–1.2 to 0.6)
Difference from reference (95% CI)	2.6 (1.18 to 4.01)		3 (1.56 to 4.44)		3.4 (–1.2 to 8.1)		4 (3.1 to 4.8)		6.8 (5.7 to 7.8)	
Pulmonary exacerbations reported	Yes	Yes	Yes	Yes	As AE only (28 weeks)	As AE only (28 weeks)	Yes	Yes	Yes	Yes
N exacerbations	73	112	79	139	8	6	78	122	11	20
Annualised event rate	0.71	1.07	0.67	1.18	NR	NR	0.64	0.99	0.34	0.63
Difference from reference, rate ratio (95% CI)	0.66 (0.47 to 0.93)		0.57 (0.42 to 0.76)		NR		0.65 (0.48 to 0.88)		0.54 (0.26 to 1.13)	
CFB in BMI at timepoint (95% CI)	0.32 (NR)	0.19 (NR)	0.43 (NR)	0.07 (NR)	0.5 (0.1 to 0.8)	0.3 (0 to 0.6)	0.18 (0.08 to 0.28)	0.12 (0.03 to 0.22)	0.34 (NR)	0.18 (NR)
Difference from reference (95% CI)	0.13 (–0.07 to 0.32)		0.36 (0.17 to 0.54)		0.2 (–0.3 to 0.6)		0.06 (–0.08 to 0.19)		NR	
CFB in BMI-for-age z-score at timepoint (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]

Difference from reference (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CFB in weight at timepoint, kg (95% CI)	1.23 (NR)	0.93 (NR)	1.38 (NR)	0.44 (NR)	NR	NR	0.7 (0.4 to 1)	0.6 (3 to 0.8)	[redacted]	[redacted]
Difference from reference (95% CI)	0.3 (–0.26 to 0.86)		0.95 (0.43 to 1.46)		NR		NR		NR	
CFB in weight-for-age z score at timepoint (95% CI)	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	NR	NR	[redacted]		[redacted]	
CFB in CFQ-R Respiratory Domain score at timepoint (95% CI)	2.6 (NR)	1.1 (NR)	5.66 (NR)	2.81 (NR)	0.1 (–5.9 to 6.1)	-6.1 (-11.7 to -0.5)	5 (3.5 to 6.5)	-0.1 (-1.6 to 1.4)	10.1 (8.2 to 12.1)	-1 (-2.9 to 1)
Difference from reference (95% CI)	1.5 (–1.69 to 4.69)		2.85 (–0.27 to 5.98)		6.2 (–1.8 to 14.1)		5.1 (3.2 to 7)		11.1 (8.7 to 13.6)	

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; IVA: ivacaftor; kg: kilograms; $LCI_{2.5}$: lung clearance index 2.5; NR: not reported; $ppFEV_1$: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review.

Table 111. Clinical efficacy outcomes of studies of ELX/TEZ/IVA studies recruiting people 12+ years prioritised in the EAG SLR.

Study	Heijerman 2019		Sutharsan 2022		Middleton 2019		Barry 2021		Barry 2021	
Intervention	TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	TEZ/IVA	ELX/TEZ/IVA	Placebo	ELX/TEZ/IVA	IVA monotherapy	ELX/TEZ/IVA	TEZ/IVA
Genotype	F/F	F/F	F/F	F/F	F/MF	F/MF	F/Gating	F/Gating	F/RF	F/RF
N	52	55	87	88	200	203	50	45	82	81
Timepoint, weeks	4	4	24	24	24	24	8	8	8	8
N deaths	0	0	0	0	0	0	0	0	0	0

CFB in sweat chloride at timepoint, mmol/L (95% CI)	1.7 (–1.9 to 5.3)	–43.4 (–46.9 to –40)	–46.2 (–48.7 to –43.7)	–3.4 (–5.8 to –1)	–42.2 (–44 to –40.4)	-0.4 (-2.2 to 1.4)	-21.8 (-25.7 to -17.8)	-1.8 (-5.7 to 2.2)	-23.1 (-25.6 to -20.6)	1.7 (-0.9 to 4.3)
Difference from reference (95% CI)	–45.1 (–50.1 to –40.1)		–42.8 (–46.2 to –39.3)		–41.8 (–44.4 to –39.3)		–20 (–25.4 to –14.6)		–24.8 (–28.4 to –21.2)	
CFB in ppFEV$_1$ at timepoint (95% CI)	0.4 (–1.4 to 2.3)	10.4 (8.6 to 12.2)	11.2 (9.8 to 12.6)	1 (–0.4 to 2.4)	13.9 (12.8 to 15)	–0.4 (–1.5 to 0.7)	5.8 (4.2 to 7.4)	0.1 (–1.6 to 1.7)	2.5 (1.4 to 3.5)	0.5 (–0.5 to 1.5)
Difference from reference (95% CI)	10 (7.4 to 12.6)		10.2 (8.2 to 12.1)		14.3 (12.7 to 15.8)		5.8 (3.5 to 8)		2 (0.5 to 3.4)	
Pulmonary exacerbations reported	As adverse event	As adverse event	As adverse event	As adverse event	Efficacy outcome	Efficacy outcome	As adverse event	As adverse event	As adverse event	As adverse event
N exacerbations	6	1	10	36	41	113	NR	NR	NR	NR
Annualised event rate	NR	NR	NR	NR	0.37	0.98	NR	NR	NR	NR
Difference from reference, rate ratio (95% CI)	NR	NR	NR	NR	0.37		NR	NR	NR	NR
CFB in BMI at timepoint (95% CI)	[redacted]	[redacted]	NR	NR	1.13 (0.99 to 1.26)	0.09 (-0.05 to 0.22)	NR	NR	NR	NR
Difference from reference (95% CI)	[redacted]		NR		1.04 (0.85 to 1.23)		[redacted]		[redacted]	
CFB in BMI-for-age z-score at timepoint (95% CI)	NR	NR	NR	NR	0.34 (0.25 to 0.44)	0.04 (-0.05 to 0.14)	NR	NR	NR	NR
Difference from reference (95% CI)	NR	NR	NR	NR	0.3 (0.17 to 0.43)		NR	NR	NR	NR
CFB in weight at timepoint, kg (95% CI)	[redacted]	[redacted]	NR	NR	3.4 (3 to 3.8)	0.5 (0.2 to 0.9)	NR	NR	NR	NR
Difference from reference (95% CI)	[redacted]		NR		2.9 (2.3 to 3.4)		NR		NR	
CFB in weight-for-age z score at timepoint (95% CI)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Difference from reference (95% CI)	NR		[redacted]		[redacted]		[redacted]		[redacted]	
CFB in CFQ-R Respiratory Domain score at timepoint (95% CI)	–1.4 (–5.4 to 2.6)	16 (12.1 to 19.9)	17.1 (14.1 to 20.1)	1.2 (–1.7 to 4.2)	17.5 (15.6 to 19.5)	-2.7 (-4.6 to -0.8)	10.2 (6.6 to 13.8)	1.3 (–2.5 to 5.2)	10.4 (7.2 to 13.7)	1.9 (-1.4 to 5.1)
Difference from reference (95% CI)	17.4 (11.8 to 23)		15.9 (11.7 to 20.1)		20.2 (17.5 to 23)		8.9 (3.8 to 14)		8.5 (4 to 13.1)	

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; IVA: ivacaftor; kg: kilograms; LCI2.5: lung clearance index 2.5; NR: not reported; ppFEV1: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review.

Table 112. Clinical efficacy outcomes of studies of IVA monotherapy studies, post hoc analyses provided by the Company for people 12+ years with F/Gating mutations.

Study	Ramsey 2011		De Boeck 2014		Moss 2015	
Age	12+		12+		12+	
Genotype	F/Gating		F/Gating		F/Gating	
Intervention	IVA monotherapy	Placebo	IVA monotherapy	Placebo	IVA monotherapy	Placebo
N	64	58	17	17	20	19
Timepoint, weeks	8	8	8	8	8	8
N deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB sweat chloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]		[redacted]		[redacted]	
CFB ppFEV1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]		[redacted]		[redacted]	
Pulmonary exacerbations reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annualised event rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB BMI-z-score	[redacted]		[redacted]		[redacted]	
Difference from reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB Weight-z-score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB CFQ-R Respiratory Domain	[redacted]		[redacted]		[redacted]	

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; EAG: external assessment group; IVA: ivacaftor; kg: kilograms; LCI2.5: lung clearance index 2.5; NR: not reported; ppFEV1: percent-predicted forced expiratory volume in one second; RD: respiratory domain; SD: standard deviation; SLR: systematic literature review.

9.3.5 Adverse events

Table 113. Summary of adverse events extracted by the EAG from ELX/TEZ/IVA clinical trials

Trial programme	ELX/TEZ/IVA						
Study	**VX20-445-111**	**Zemanick 2019**	**Mall 2022**	**Barry 2021**	**Heijerman 2019**	**Middleton 2019**	**Sutharsan 2022**
Genotype	F/F or F/MF	F/F or F/MF	F/MF	F/RF or F/Gating	F/F	F/MF	F/F

Age group	2 to 5	6 to 11	6 to 11		12+		12+		12+		12+	
Safety Period up to Week X	28	28	28	28	12	12	8	8	28	28	28	28
Arm	ELX/TEZ/IVA	ELX/TEZ/IVA	ELX/TEZ/IVA	Placebo	ELX/TEZ/IVA	TEZ/IVA	ELX/TEZ/IVA	TEZ/IVA	ELX/TEZ/IVA	Placebo	ELX/TEZ/IVA	TEZ/IVA
N SAS	[redacted]	66	60	61	132	126	55	52	202	201	87	88
Participants with AEs	[redacted]	65	48	57	88	83	33	32	188	193	77	81
Participants with serious AEs	[redacted]	1	4	9	5	11	2	1	28	42	5	14
Alanine aminotransferase increased	[redacted]	7	3	5	8	0	[redacted]	[redacted]	20	7	6	1
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	8	0	[redacted]	[redacted]	19	4	5	0
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased bilirubin	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]	NR	NR	10	2	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	NR	NR	NR	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Cataracts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lens opacities	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: where inconsistencies occurred between the study CSR, full text and other trial records, AE data were preferentially included from the study CSRs.

Abbreviations: AE: adverse event; CSR: clinical study report; EAG: external assessment group; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor.

Table 114. Summary of adverse events extracted by the EAG from TEZ/IVA and LUM/IVA clinical trials

Trial programme	TEZ/IVA								LUM/IVA											
Study	**Davies 2021**			**Taylor-Cousar 2017**		**Rowe 2017**			**Rayment 2022**	**Stahl 2021**		**Ratjen 2017**		**Wilson 2021**		**TRAFFIC**		**TRANSPORT**	
Genotype	F/F or F/RF			F/F		F/RF			F/F	F/F		F/F		F/F		F/F		F/F	
Age group	6 to 11			12+		12+			1 to 2	2 to 5		6 to 11		12+		12+		12+	
Safety Period up to Week X	12			28		28*			26	48		28		28		28		28	
Arm	TEZ/IVA	PBO	IVA	TEZ/IVA	PBO	TEZ/IVA	PBO	IVA	LUM/IVA	LUM/IVA	PBO	LUM/IVA	PBO	LUM/IVA	PBO	LUM/IVA	PBO	LUM/IVA	PBO
N SAS	54	10	3	251	258	162	162	157	46	35	16	103	101	34	36	182	184	187	186
Subjects with AEs	41	8	2	227	245	117	126	114	44	35	17	98	98	30	35	174	174	175	181
Subjects with serious AEs	0	0	0	31	47	8	14	10	5	7	2	13	11	15	9	33	49	31	57
Alanine aminotransferase increased	1	1	0	13	8	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3	5	4	4
Aspartate aminotransferase increased	0	1	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3	3	5	5
Gamma-glutamyltransferase increased	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	NR	NR	1	0	1	1
Increased bilirubin	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR

Hepatic enzyme increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	NR	NR	2	0	2	0
Rash events	[redacted]	[redacted]	[redacted]	4	13	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	0	2	6	2	18	5
Hypertension	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	[redacted]	[redacted]	2	0	0	0
Cataracts	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Lens opacities	NR	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR

Note: where inconsistencies occurred between the study CSR, full text and other trial records, AE data were preferentially included from the study CSRs.

Abbreviations: AE: adverse event; CSR: clinical study report; EAG: external assessment group; IVA: ivacaftor; LUM: lumacaftor; TEZ: tezacaftor.

9.4 Linked references of prioritised studies

Table 115. Linked references of studies prioritised in the EAG's clinical systematic literature review

Title	Journal, Year	Authors	DOI/URL
Sutharsan 2022			
Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial	The Lancet Respiratory Medicine, 2022	Sutharsan, S., McKone, E. F., Downey, D. G., Duckers, J., MacGregor, G., Tullis, E., Van Braeckel, E., Wainwright, C. E., Watson, D., Ahluwalia, N., Bruinsma, B. G., Harris, C., Lam, A. P., Lou, Y., Moskowitz, S. M., Tian, S., Yuan, J., Waltz, D., Mall, M. A., Aurora, P., Verhulst, S., Lorenz, M., Roehmel, J., Gleiber, W., Naehrig, S., Stehling, F., van Koningsbruggen-Rietschel, S., Fischer, R., Downey, D., Haworth, C., Legg, J., Barry, P., Thursfield, R., Doe, S. J., Hilliard, T., Nash, E. F., Withers, N. J., Peckham, D., Barr, H.	10.1016/S2213-2600%2821%2900454-9

		L., Lee, T., Gray, R., Vermeulen, F., Vanderhelst, E., Robinson, P. J., Smith, D. J., Mulrennan, S. A., Clements, B. S., Wark, P.	
A study to evaluate the safety and efficacy of VX-445 / Tezacaftor / Ivacaftor in patients suffering from Cystic Fibrosis	2019	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-001735-31-GB, 2019
A Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del	2019	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT04105972, 2019
Barry 2021			
Triple therapy for cystic fibrosis Phe508del-gating and -residual function genotypes	New England Journal of Medicine, 2021	Barry, P. J., Mall, M. A., Alvarez, A., Colombo, C., de Winter-De Groot, K. M., Fajac, I., McBennett, K. A., McKone, E. F., Ramsey, B. W., Sutharsan, S., Taylor-Cousar, J. L., Tullis, E., Ahluwalia, N., Jun, L. S., Moskowitz, S. M., Prieto-Centurion, V., Tian, S., Waltz, D., Xuan, F., Zhang, Y., Rowe, S. M., Polineni, D.	10.1056/NEJMoa2100665
A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)	2019	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT04058353
Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating or residual function mutation	Journal of Cystic Fibrosis, 2022	Chmiel, J., Barry, P. J., Colombo, C., De Wachter, E., Fajac, I., Mall, M., McBennett, K., McKone, E., Mondejar-Lopez, P., Quon, B., Ramsey, B., Robinson, P., Sutharsan, S., Ahluwalia, N., Lu, M., Moskowitz, S., Prieto-Centurion, V., Tian, S., Waltz, D., Weinstock, T., Xuan, F., Zelazoski, L., Zhang, Y., Polineni, D.	10.1016/S1569-1993%2822%2900875-X
A phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of VX-445 combination therapy in subjects with cystic fibrosis WHO are heterozygous for the f508del mutation and a gating or residual function mutation (F/G and F/RF genotypes)	2021	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002835-76/results

A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)	2019	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-002835-76-IE
Middleton 2019			
Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele	New England Journal of Medicine, 2019	Middleton, P. G., Mall, M. A., Drevinek, P., Lands, L. C., McKone, E. F., Polineni, D., Ramsey, B. W., Taylor-Cousar, J. L., Tullis, E., Vermeulen, F., Marigowda, G., McKee, C. M., Moskowitz, S. M., Nair, N., Savage, J., Simard, C., Tian, S., Waltz, D., Xuan, F., Rowe, S. M., Jain, R.	10.1056/NEJMoa1908639
Phase 3 efficacy and safety of the ELX/TEZ/IVA triple combination in people with CF and F508del/minimal function genotypes	Pediatric Pulmonology, 2019	Jain, R., Mall, M., Drevinek, P., Lands, L., McKone, E., Polineni, D., Ramsey, B., Taylor-Cousar, J., Tullis, E., Vermeulen, F., Marigowda, G., McKee, C., Moskowitz, S., Nair, N., Savage, J., Simard, C., Tian, S., Waltz, D., Xuan, F., Rowe, S., Middleton, P.	10.1002/ppul.22495
Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508del and a minimal function mutation: Results from a phase 3 clinical study	Pediatric Pulmonology, 2020	Fajac, I., Van Brunt, K., Daines, C., Durieu, I., Goralski, J. L., Heijerman, H., Knoop, C., Majoor, C. J., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A. L.	10.1136/thorax-2020-BTSabstracts.70
Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508del and a minimal function mutation (F/MF): Results from a phase 3 clinical study	Thorax, 2021	Fajac, I., Van Brunt, K., Daines, C., Durieu, I., Goralski, J., Heijerman, H., Knoop, C., Majoor, C., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A.	10.1136/thorax-2020-BTSabstracts.70
Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis heterozygous for F508del and a minimal function mutation: results from a Phase 3 clinical study	Journal of Cystic Fibrosis, 2020	Fajac, I., Van Brunt, K., Daines, C., Durieu, I., Goralski, J., Heijerman, H., Knoop, C., Majoor, C., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A.	10.1016/S1569-1993%2820%2930555-5

A Phase 3 Study of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT03525444
A Phase 3 Study of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)	2018	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-000183-28-SE
PRS77 Application of the CFQ-R-8D to Estimate Utility Benefit of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People with Cystic Fibrosis (CF)	Value in Health, 2020	McGarry, L., Lopez, A., Booth, J., Yuan, J., Morlando Geiger, J., Lou, Y., Moskowitz, S. M.	10.1016/j.jval.2020.08.1957
Heijerman 2019			
Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial	The Lancet, 2019	Heijerman, H. G. M., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., Mall, M. A., Welter, J. J., Ramsey, B. W., McKee, C. M., Marigowda, G., Moskowitz, S. M., Waltz, D., Sosnay, P. R., Simard, C., Ahluwalia, N., Xuan, F., Zhang, Y., McCoy, K. S., McCoy, K., Donaldson, S., Walker, S., Chmiel, J., Rubenstein, R., Froh, D. K., Neuringer, I., Jain, M., Moffett, K., Taylor-Cousar, J. L., Barnett, B., Mueller, G., Flume, P., Livingston, F., Mehdi, N., Teneback, C., Welter, J., Jain, R., Kissner, D., Patel, K., Calimano, F. J., Johannes, J., Daines, C., Keens, T., Scher, H., Chittivelu, S., Reddivalam, S., Klingsberg, R. C., Johnson, L. G., Verhulst, S., Macedo, P., Connett, G., Nash, E., Withers, N., Lee, T., Bakker, M., Heijerman, H., Vermeulen, F., Knoop, C., De Wachter, E., van der Meer, R., Merkus, P., Majoor, C.	10.1016/S0140-6736%2819%2932597-8
Phase 3 efficacy and safety of the ELX/TEZ/IVA triple combination in people with CF homozygous for the F508del mutation	Pediatric Pulmonology, 2019	Heijerman, H., McKone, E., Downey, D. G., Mall, M., Ramsey, B., Rowe, S., Tullis, E., Van Braeckel, E., Welter, J., Ahluwalia, N., Marigowda, G., McKee, C., Moskowitz, S., Simard, C., Sosnay, P., Waltz, D., Xuan, F., Zhang, Y., Taylor-Cousar, J., McCoy, K.	10.1002/ppul.22495

Impact of elexacaftor/tezacaftor/ ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis homozygous for F508del: Results from a phase 3 clinical study	Pediatric Pulmonology, 2020	Majoor, C. J., Van Brunt, K., Daines, C., Durieu, I., Fajac, I., Goralski, J. L., Heijerman, H., Knoop, C., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A. L.	10.1136/thorax-2020-BTSabstracts.71
Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis homozygous for F508DEL (F/F): Results from a phase 3 clinical study	Thorax, 2021	Majoor, C., Van Brunt, K., Daines, C., Durieu, I., Fajac, I., Goralski, J., Heijerman, H., Knoop, C., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A.	10.1136/thorax-2020-BTSabstracts.71
Impact of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) triple combination therapy on health-related quality of life (HRQoL) in people with cystic fibrosis (pwCF) homozygous for F508del (F/F): results from a Phase 3 clinical study	Journal of Cystic Fibrosis, 2020	Majoor, C., Van Brunt, K., Daines, C., Durieu, I., Fajac, I., Goralski, J., Heijerman, H., Knoop, C., Booth, J., Moskowitz, S. M., Savage, J., Wang, C., Quittner, A.	10.1016/S1569-1993%2820%2930268-X
A Study of VX-445 Combination Therapy in CF Subjects Homozygous for F508del (F/F)	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT03525548
A Phase 3 Study of VX-445 Combination Therapy in CF Subjects Homozygous for F508del (F/F)	2018	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-000184-89-BE
Erratum: Department of Error (The Lancet (2019) 394(10212) (1940-1948), (S0140673619325978), (10.1016/S0140-6736(19)32597-8))	The Lancet, 2020	Anonymous	10.1016/S0140-6736%2820%2931021-7
Mall 2022			
Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation A Phase 3b, Randomized, Placebo-controlled Study	American Journal of Respiratory and Critical Care Medicine, 2022	Mall, M. A., Brugha, R., Gartner, S., Legg, J., Moeller, A., Mondejar-Lopez, P., Prais, D., Pressler, T., Ratjen, F., Reix, P., Robinson, P. D., Selvadurai, H., Stehling, F., Ahluwalia, N., Arteaga-Solis, E., Bruinsma, B. G., Jennings, M., Moskowitz, S. M., Noel, S., Tian, S., Weinstock, T. G., Wu, P., Wainwright, C. E., Davies, J. C.	10.1164/rccm.202202-0392OC

A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis and F/MF Genotypes	2020	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT04353817
A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 through 11 Years Old With Cystic Fibrosis and F/MF genotypes	2020	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-003554-86-GB
Zemanick 2021			
A phase 3 open-label study of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis and at least one F508del allele	American Journal of Respiratory and Critical Care Medicine, 2021	Zemanick, E. T., Taylor-Cousar, J. L., Davies, J., Gibson, R. L., Mall, M. A., McKone, E. F., McNally, P., Ramsey, B. W., Rayment, J. H., Rowe, S. M., Tullis, E., Ahluwalia, N., Chu, C., Ho, T., Moskowitz, S. M., Noel, S., Tian, S., Waltz, D., Weinstock, T. G., Xuan, F., Wainwright, C. E., McColley, S. A.	10.1164/rccm.202102-0509OC
Evaluation of VX 445/TEZ/IVA in Cystic Fibrosis Subjects 6 Through 11 Years of Age	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT03691779
A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age	2018	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001695-38/results
NCT04537793			
Evaluation of ELX/TEZ/IVA in Cystic Fibrosis (CF) Subjects 2 Through 5 Years	2020	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT04537793
A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age	2020	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002251-38/DE
Taylor-Cousar 2017			

Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients with cystic fibrosis homozygous for F508DEL-CFTR: Patient-reported outcomes in a phase 3 randomized, controlled trial (EVOLVE)	Thorax, 2018	Yang, Y., Rizio, A. A., Chuang, C. C., Loop, B., You, X., Kosinski, M., Rendas-Baum, R., Lekstrom-Himes, J., Taylor-Cousar, J., Sole, A., Elborn, J. S.	10.1136/thorax-2018-212555.74
Effects of tezacaftor/ivacaftor treatment in patients with cystic fibrosis and F508DEL/ F508DEL-CFTR: Patient-reported outcomes in a phase 3 randomized, controlled trial	Pediatric Pulmonology, 2018	Yang, Y., Rizio, A., Chuang, C., Loop, B., You, X., Kosinski, M., Rendas-Baum, R., Lekstrom-Himes, J., Taylor-Cousar, J. L., Sole, A., Elborn, J.	10.1002/ppul.24152
Advances in treating patients homozygous for F508del	Pediatric Pulmonology, 2017	Taylor-Cousar, J. L., Elborn, S.	10.1002/ppul.23839
Efficacy and safety of tezacaftor/ ivacaftor in patients aged >=12 years with cf homozygous for f508del-cftr: A randomized placebo-controlled phase 3 trial	Pediatric Pulmonology, 2017	Taylor-Cousar, J. L., Lekstrom-Himes, J., Wang, L., Lu, Y., Elborn, S.	10.1002/ppul.23840
Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del	New England Journal of Medicine, 2017	Taylor-Cousar, J. L., Munck, A., McKone, E. F., Van Der Ent, C. K., Moeller, A., Simard, C., Wang, L. T., Ingenito, E. P., McKee, C., Lu, Y., Lekstrom-Himes, J., Elborn, J. S.	10.1056/NEJMoa1709846
Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients with cystic fibrosis and F508del/F508del-CFTR: Patient-reported outcomes in a Phase 3, randomised, controlled trial (EVOLVE)	Pneumologie, 2019	Sommerburg, O., Yang, Y., Rizio, A. A., Loop, B., You, X., Kosinski, M., Rendas-Baum, R., Lekstrom-Himes, J., Elborn, J. S.	10.1055/s-0039-1678165
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor	2015	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT02347657
Efficacy and safety of tezacaftor/ivacaftor in patients aged >= 12 years with CF homozygous for F508del-CFTR: A randomized placebo (PBO)-controlled phase 3 trial	Pneumologie, 2018	Sutharsan, S., Taylor-Cousar, J., Lekstrom-Himes, J., Wang, L., Lu, Y., Elborn, J. S.	10.1055/s-0037-1619211

A study in people with Cystic Fibrosis (a rare hereditary lung disease) to assess the efficacy and safety of a combination of two experimental drugs	2015	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-004837-13-SE
Rowe 2017			
Efficacy and safety of tezacaftor/ ivacaftor and ivacaftor in patients aged >=12 years with CF heterozygous for f508del and a residual function mutation: A randomized, double-blind, placebo-controlled, crossover phase 3 study	Pediatric Pulmonology, 2017	Rowe, S. M., Davies, J. C., Nair, N., Han, L., Lekstrom-Himes, J.	10.1002/ppul.23840
CFTR modulation with tezacaftor/ivacaftor in patients heterozygous for F508del and a residual function mutation	Pediatric Pulmonology, 2017	Rowe, S. M., Davies, J.	10.1002/ppul.23839
Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis	New England Journal of Medicine, 2017	Rowe, S. M., Daines, C., Ringshausen, F. C., Kerem, E., Wilson, J., Tullis, E., Nair, N., Simard, C., Han, L., Ingenito, E. P., McKee, C., Lekstrom-Himes, J., Davies, J. C.	10.1056/NEJMoa1709847
Efficacy and safety of tezacaftor/ivacaftor in patients (Pts) aged >= 12 years with CF heterozygous for F508del and a residual function mutation: A randomized, double-blind, placebo-controlled, crossover phase 3 study	Pneumologie, 2018	Fischer, R., Rowe, S. M., Davies, J. C., Nair, N., Han, L., Lekstrom-Himes, J.	10.1055/s-0037-1619210
Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients heterozygous for F508DEL-CFTR and a residual function mutation: patient-reported outcomes in a phase 3 randomized, controlled trial (expand)	Thorax, 2018	Chuang, C. C., Rizio, A. A., Loop, B., Lekstrom-Himes, J., You, X., Kosinski, M., Rendas-Baum, R., Davies, J. C., Rowe, S. M., Yang, Y.	10.1136/thorax-2018-212555.73
Effects of tezacaftor/ivacaftor treatment in patients heterozygous for F508DEL-CFTR and a residual function mutation: Patientreported outcomes in a phase 3 randomized, controlled trial	Pediatric Pulmonology, 2018	Chuang, C., Rizio, A., Loop, B., Lekstrom-Himes, J., You, X., Kosinski, M., Rendas-Baum, R., Davies, J. C., Rowe, S. M., Yang, Y.	10.1002/ppul.24152

Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients heterozygous for F508del-CFTR and a residual function mutation: Patient-reported outcomes in a Phase 3, randomised, controlled trial (EXPAND)	Pneumologie, 2019	Fischer, R., Rizio, A. A., Loop, B., Lekstrom-Himes, J., You, X., Kosinski, M., Rendas-Baum, R., Davies, J., Rowe, S. M., Yang, Y.	10.1055/s-0039-1678161
A Phase 3 Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutation	2015	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT02392234
A study in people with cystic fibrosis (a rare hereditary lung disease) to assess the efficacy and safety of two experimental drugs: ivacaftor and VX-661 in combination with ivacaftor	2015	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-004788-18-NL
Davies 2021			
A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation	Journal of Cystic Fibrosis, 2021	Davies, J. C., Sermet-Gaudelus, I., Naehrlich, L., Harris, R. S., Campbell, D., Ahluwalia, N., Short, C., Haseltine, E., Panorchan, P., Saunders, C., Owen, C. A., Wainwright, C. E.	10.1016/j.jcf.2020.07.023
A Study to Evaluate Efficacy and Safety of TEZ/IVA in Subjects Aged 6 Through 11 Years With Cystic Fibrosis	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT03559062
A Study to Evaluate Efficacy and Safety of TEZ/IVA in Subjects Aged 6 through 11 Years With Cystic Fibrosis	2018	WHO International Clinical Trials Registry Platform Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-004479-35-PL

A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous or heterozygous for the F508del-CFTR mutation	2018	EU Clinical Trials Register Record	www.clinicaltrialsregister.eu/ctr-search/trial/2016-004479-35
Wainwright 2015, TRAFFIC/TRANSPORT			
Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis	The Lancet Respiratory Medicine, 2016	Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., Waltz, D., Wainwright, C. E.	10.1016/S2213-2600%2816%2930121-7
Effect of lumacaftor in combination with ivacaftor in patients with CF who are homozygous for DELTAF508-CFTR: Phase 3 TRAFFIC and TRANSPORT studies	Pediatric Pulmonology, 2014	Wainwright, C. E., Elborn, J. S., Ramsey, B., Huang, X., Marigowda, G., Waltz, D., Boyle, M. P.	10.1002/ppul.23107
Combination lumacaftor/ivacaftor therapy improves inflammatory biomarkers in patients with CF homozygous for the F508DEL-CFTR mutation	Pediatric Pulmonology, 2016	Sullivan, J. C., Accurso, F. J., Marigowda, G., Beusmans, J., Geho, D., Zhang, E., Moss, R., Waltz, D.	10.1002/ppul.23576
Association between changes in percent predicted FEV1 and incidence of pulmonary exacerbations, including those requiring hospitalization and/or iv antibiotics, in patients with CF treated with lumacaftor in combination with ivacaftor	Pediatric Pulmonology, 2015	McColley, S. A., Konstan, M. W., Ramsey, B. W., Elborn, J., Boyle, M. P., Wainwright, C. E., Waltz, D., Vera-Llonch, M., Jiang, J., Rubin, J.	10.1002/ppul.23297
Efficacy and safety of lumacaftor+ivacaftor combination therapy in patients with CF homozygous for F508DEL-CFTR by FEV1 subgroups	Pediatric Pulmonology, 2015	De Boeck, K., Elborn, J., Ramsey, B., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., Waltz, D., Wainwright, C. E.	10.1002/ppul.23297
Improvement in inflammatory biomarkers in patients (pts) with cystic fibrosis (CF) homozygous for the F508del-CFTR mutation treated with lumacaftor (LUM) and ivacaftor (IVA)	Journal of Cystic Fibrosis, 2016	Sullivan, J. C., Accurso, F. J., Marigowda, G., Beusmans, J., Geho, D., Zhang, E., Moss, R. B., Waltz, D.	10.1016/S1569-1993(16)30079-0

Effect of lumacaftor in combination with ivacaftor in patients with CF who are homozygous for F508-CFTR: phase 3 TRAFFIC and TRANSPORT studies	Pediatric pulmonology, 2014	Wainwright, C. E., Elborn, J. S., Ramsey, B., Huang, X., Marigowda, G., Waltz, D.	2014;49 Suppl 38:156. [ABSTRACT NO.: S10.3]
Improvement in inflammatory biomarkers in patients (pts) with cystic fibrosis (CF) homozygous for the f508del-cftr mutation treated with lumacaftor (LUM) and ivacaftor (IVA)	Journal of Cystic Fibrosis, 2016	Sullivan, J. C., Accurso, F. J., Marigowda, G., Beusmans, J., Geho, D., Zhang, E., Moss, R. B., Waltz, D.	10.1016/S1569-1993(16)30079-0
Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1	Journal of Cystic Fibrosis, 2019	McColley, S. A., Konstan, M. W., Ramsey, B. W., Stuart Elborn, J., Boyle, M. P., Wainwright, C. E., Waltz, D., Vera-Llonch, M., Marigowda, G., Jiang, J. G., Rubin, J. L.	10.1016/j.jcf.2018.07.011
Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for the F508del-CFTR mutation	Journal of Cystic Fibrosis, 2015	Elborn, J. S., Ramsey, B., Boyle, M. P., Wainwright, C., Konstan, M., Huang, X., Marigowda, G., Waltz, D.	10.1016/S1569-1993(15)30003-5
Lumacaftor/ivacaftor combination therapy in CF patients homozygous for F508del-CFTR with severe lung dysfunction	Journal of Cystic Fibrosis, 2015	Elborn, J. S., Ramsey, B., Boyle, M. P., Wainwright, C., Konstan, M., Huang, X., Marigowda, G., Waltz, D.	10.1016/S1569-1993(15)30320-9
Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR	The New England journal of medicine, 2015	Wainwright, Claire E., Elborn, J. Stuart, Ramsey, Bonnie W.	10.1056/NEJMc1510466
Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del CFTR	New England Journal of Medicine, 2015	Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., Colombo, C., Davies, J. C., De Boeck, K., Flume, P. A., Konstan, M. W., McColley, S. A., McCoy, K., McKone, E. F., Munck, A., Ratjen, F., Rowe, S. M., Waltz, D., Boyle, M. P.	10.1056/NEJMoa1409547
Pulmonary exacerbations, lung dysfunction, and EQ-5D measures in adolescents and adults with cystic fibrosis and homozygous for the F508del-CFTR mutation	Value in Health, 2016	Solem, C. T., Vera-Llonch, M., Tai, M., O'Callaghan, L.	10.1016/j.jval.2016.03.461

Measuring recovery in health-related quality of life during and after pulmonary exacerbations in patients with cystic fibrosis	Journal of Cystic Fibrosis, 2019	Flume, P. A., Suthoff, E. D., Kosinski, M., Marigowda, G., Quittner, A. L.	10.1016/j.jcf.2018.12.004
Impact of pulmonary exacerbations (PEx) on health-related quality of life (HRQoL) assessed by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) in TRAFFIC and TRANSPORT	Journal of Cystic Fibrosis, 2018	Suthoff, E. D., Kosinski, M., Sikirica, S., Quittner, A. L.	10.1016/S1569-1993(16)30376-9
Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for F508del-CFTR: Transport study	Pediatric Pulmonology, 2014	Ramsey, B., Boyle, M. P., Elborn, J., Huang, X., Marigowda, G., Waltz, D., Wainwright, C. E.	10.1002/ppul.23108
A Study of Lumacaftor in Combination With Ivacaftor in Cystic Fibrosis Subjects Aged 12 Years and Older Who Are Homozygous for the F508del-CFTR Mutation	2013	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT01807949
A study in people with Cystic Fibrosis (a rare hereditary pulmonary disease) to assess the efficacy and safety of a combination of two experimental drugs	2013	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2012-003990-24-DK
Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for F508del-CFTR: The TRAFFIC study	Pediatric Pulmonology, 2014	Elborn, J., Wainwright, C. E., Ramsey, B., Huang, X., Marigowda, G., Waltz, D., Boyle, M. P.	10.1002/ppul.23108
Prevalence of cataracts in a population of cystic fibrosis patients homozygous for the F508del mutation*	Journal of Cystic Fibrosis, 2015	Seliger, V., Bai, Y., Volkova, N., Tian, S., Waltz, D.	10.1016/S1569-1993(15)30373-8
A Study of Lumacaftor in Combination With Ivacaftor in Cystic Fibrosis Subjects Aged 12 Years and Older Who Are Homozygous for the F508del-CFTR Mutation	2013	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT01807923
A study in people with Cystic Fibrosis (a rare hereditary pulmonary disease) to assess the efficacy and safety of a combination of two experimental drugs	2013	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2012-003989-40-IE
Wilson 2021			

VO_2 max as an exercise tolerance endpoint in people with cystic fibrosis: Lessons from a lumacaftor/ivacaftor trial	Journal of Cystic Fibrosis, 2021	Wilson, J., You, X., Ellis, M., Urquhart, D. S., Jha, L., Duncan, M., Tian, S., Harris, R. A., Kotsimbos, T., Keating, D.	10.1016/j.jcf.2020.12.006
A Study of the Effects of Lumacaftor/Ivacaftor on Exercise Tolerance in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	2016	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT02875366
A Study of the Effects of Lumacaftor/Ivacaftor on Exercise Tolerance in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation	2017	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-000066-34-GB
Ratjen 2017			
Efficacy and safety of lumacaftor/ivacaftor (LUM/IVA) in patients (pts) aged 6-11 years (yrs) with cystic fibrosis (CF) homozygous for F508del-CFTR: A randomized placebo (PBO)-controlled phase 3 trial	Journal of Cystic Fibrosis, 2017	Ratjen, F., Tian, S., Marigowda, G., Hug, C., Huang, X., Stanojevic, S., Milla, C. E., Robinson, P., Waltz, D., Davies, J. C.	2017;16 S24
Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial	The Lancet Respiratory Medicine, 2017	Ratjen, F., Hug, C., Marigowda, G., Tian, S., Huang, X., Stanojevic, S., Milla, C. E., Robinson, P. D., Waltz, D., Davies, J. C., Rosenfeld, M., Starner, T., Retsch-Bogart, G., Chmiel, J., Orenstein, D., Milla, C., Rubenstein, R., Walker, S., Cornell, A., Asfour, F., Black, P., Colombo, J., Froh, D., McColley, S., Ruiz, F., Quintero, D., Casey, A., Mueller, G., Flume, P., Livingston, F., Rock, M., O'Sullivan, B., Schmidt, H., Lahiri, T., McNamara, J., Chidekel, A., Sass, L., Keens, T., Schaeffer, D., Solomon, M., Chilvers, M., Lands, L., Junge, S., Griese, M., Staab, D., Pressler, T., van Koningsburggen-Rietschel, S., Naehrlich, L., Reid, A., Balfour-Lynn, I., Urquhart, D., Lee, T., Munck, A., Gaudelus, I. S., De Boeck, C., Reix, P., Malfroot, A., Bui, S., Selvadurai, H., Robinson, P., Wainwright, C., Clements, B., Hilton, J., Hjelte, L.	10.1016/S2213-2600%2817%2930215-1
Feasibility of ultrashort echo time MRI to evaluate the effect of lumacaftor/ ivacaftor therapy in children with cystic fibrosis homozygous for f508del	Pediatric Pulmonology, 2017	Nagle, S. K., Brody, A., Woods, J. C., Johnson, K. M., Wang, L., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Owen, C.	10.1002/ppul.23840

Feasibility of ultrashort echo time (UTE) MRI to evaluate the effect of lumacaftor/ivacaftor therapy in children with cystic fibrosis (CF) homozygous for F508DEL	Thorax, 2017	Nagle, S., Brody, A. S., Woods, J., Johnson, K. M., Wang, L., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Hug, C.	10.1136/thoraxjnl-2017-210983.396
Effect of lumacaftor/ivacaftor on total, bronchiectasis, and air trapping computed tomography (CT) scores in children homozygous for F508del-CFTR: Exploratory imaging substudy	Thorax, 2017	Brody, A. S., Nagle, S., Hug, C., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Wang, L.	10.1136/thoraxjnl-2017-210983.99
Effect of lumacaftor/ivacaftor on total, bronchiectasis, and air trapping computed tomography scores in children homozygous for F508DEL-CFTR: Exploratory imaging substudy	Pediatric Pulmonology, 2017	Brody, A., Nagle, S. K., Owen, C., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Wang, L.	10.1002/ppul.23840
Safety, tolerability, and pharmacodynamics of combination lumacaftor/ivacaftor therapy in patients aged 6-11 yrs with CF homozygous for the F508DEL-CFTR mutation	Pediatric Pulmonology, 2016	Milla, C., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., Rosenfeld, M.	10.1002/ppul.23576
Ultrashort echo time MRI can evaluate treatment effect of Lumacaftor/Ivacaftor	Respirology, 2018	Wainwright, C., Nagle, S., Brody, A., Woods, J., Johnson, K., Wang, L., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Hug, C.	10.1111/resp.13268
Effect of lumacaftor/ivacaftor on ct scores: Exploratory imaging substudy	Respirology, 2018	Wainwright, C., Brody, A., Nagle, S., Hug, C., Marigowda, G., Waltz, D., Goldin, J., Ratjen, F., Wang, L.	10.1111/resp.13267
A Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects With CF, Homozygous for the F508del-CFTR Mutation	2015	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT02514473
Corrections: Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial (The Lancet Respiratory Medicine (2017) 5(7) (557-567)(S2213260017302151)(10.1016/S2213-2600(17)30215-1))	The Lancet Respiratory Medicine, 2017	Anonymous	10.1016/S2213-2600%2817%2930270-9

Change in low-dose chest Computed Tomography (CT) scores after 72 weeks of tezacaftor/ivacaftor (TEZ/IVA) in patients (pts) with cystic fibrosis and ppFEV1 >=70%: an exploratory phase 2 study	Journal of Cystic Fibrosis, 2019	Wainwright, C., Stick, S., Goldin, J., Lekstrom-Himes, J., Wang, L., Campbell, D., Wang, L. T., Harris, R. S., Owen, C. A., Brody, A.	10.1016/S1569-1993%2819%2930152-3
A study in children aged 6 Through 11 Years With Cystic Fibrosis to assess the efficacy and safety of a combination of two experimental drugs	2015	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2015-000543-16-SE
Stahl 2022			
A Study of the Effects of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del	2018	EU Clinical Trials Register Record	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-003761-99-DE
A Study to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/show/NCT03625466
Long-term efficacy of lumacaftor/ivacaftor (LUM/IVA) in children aged 2 through 5 years with cystic fibrosis (CF) homozygous for the F508del-CFTR mutation (F/F): a phase 2, open-label extension study	Journal of Cystic Fibrosis, 2022	Stahl, M., Roehmel, J., Eichinger, M., Doellinger, F., Naehrlich, L., Kopp, M. V., Dittrich, A. M., Sommerburg, O., Ray, P., Maniktala, A., Duncan, M. E., Xu, T., Wu, P., Joshi, A., Mascia, M., Tian, S., Wielputz, M. O., Mall, M. A.	10.1016/S1569-1993%2822%2900250-8
An exploratory study to determine the impact of lumacaftor/ivacaftor (LUM/IVA) on disease progression in children 2 through 5 years of age with cystic fibrosis homozygous for F508del-CFTR (F/F)	Journal of Cystic Fibrosis, 2021	Stahl, M., Roehmel, J., Eichinger, M., Doellinger, F., Naehrlich, L., Kopp, M. V., Dittrich, A. M., Lee, C., Sommerburg, O., Tian, S., Xu, T., Wu, P., Joshi, A., Duncan, M., Wielputz, M. O., Mall, M.	10.1016/S1569-1993%2821%2900981-4
Rayment 2022			
A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age with Cystic Fibrosis Homozygous for F508del-CFTR	American Journal of Respiratory and Critical	Rayment, J. H., Asfour, F., Rosenfeld, M., Higgins, M., Liu, L., Mascia, M., Paz-Diaz, H., Tian, S., Zahigian, R., McColley, S. A.	10.1164/RCCM.202204-0734OC

	Care Medicine, 2022		
Safety and pharmacokinetic study of lumacaftor/ivacaftor in subjects 1 to less than 2 years of age with cystic fibrosis, homozygous for F508del	2018	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT03601637
A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del	2017	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004794-13/results
Ramsey 2011			
A CFTR potentiator in patients with cystic fibrosis and the G551D mutation	New England Journal of Medicine, 2011	Ramsey, B. W., Davies, J., McElvaney, N. G., Tullis, E., Bell, S. C., Drevinek, P., Griese, M., McKone, E. F., Wainwright, C. E., Konstan, M. W., Moss, R., Ratjen, F., Sermet-Gaudelus, I., Rowe, S. M., Dong, Q., Rodriguez, S., Yen, K., Ordonez, C., Elborn, J. S.	10.1056/NEJMoa1105185
Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor	Journal of Cystic Fibrosis, 2018	Flume, P. A., Wainwright, C. E., Elizabeth Tullis, D., Rodriguez, S., Niknian, M., Higgins, M., Davies, J. C., Wagener, J. S.	10.1016/j.jcf.2017.06.002
Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis	Health and Quality of Life Outcomes, 2016	Solem, C. T., Vera-Llonch, M., Liu, S., Botteman, M., Castiglione, B.	10.1186/s12955-016-0465-z
Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: Patient-reported outcomes in the STRIVE randomized, controlled trial	Health and Quality of Life Outcomes, 2015	Quittner, A., Suthoff, E., Rendas-Baum, R., Bayliss, M. S., Sermet-Gaudelus, I., Castiglione, B., Vera-Llonch, M.	10.1186/s12955-015-0293-6
Efficacy and safety of VX-770 in subjects with cystic fibrosis and the G551D-CFTR mutation	Pediatric Pulmonology, 2011	Ramsey, B., Dong, Q., Yen, K., Elborn, J.	10.1002/ppul.21583

VX-770, an investigational CFTR potentiator, in subjects with CF and the G551D mutation	European Respiratory Journal, 2011	Plant, B. J., Ramsey, B., Yen, K., Dong, Q., Rodriguez, S., Elborn, J. S.	38: 4655
Patient-reported treatment effects of ivacaftor beyond respiratory symptoms in patients with cystic fibrosis (CF)	Pediatric Pulmonology, 2014	Suthoff, E., Rendas-Baum, R., Vera-Llonch, M., Bayliss, M., Sermet-Gaudelus, I., Quittner, A. L.	10.1002/ppul.23108
Impact of pulmonary exacerbations on EQ-5D measures in patients with cystic fibrosis	Value in Health, 2014	Solem, C. T., Vera-Llonch, M., Liu, S., Botteman, M., Lin, F. J., Castiglione, B.	10.1016/j.jval.2014.08.1707
Responsiveness of the EQ-5D index and visual analog scale to changes in lung function in patients with cystic fibrosis	Value in Health, 2014	Solem, C. T., Vera, LLonch M., Liu, S., Botteman, M. F., Lasch, K., Rodriguez, S., Castiglione, B.	10.1016/j.jval.2014.03.1038
Effect of ivacaftor on circulating inflammatory indices in CF patients with the G551D-CFTR mutation	Pediatric Pulmonology, 2013	Seliger, V. I., Accurso, F. J., Konstan, M. W., Dong, Q., Lubarsky, B., Mueller, P.	10.1002/ppul.22898
Pulmonary exacerbations in a Phase 3 trial of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR mutation	Journal of Cystic Fibrosis, 2012	Griese, M., Ramsey, B., Rodriguez, S., Yen, K., Elborn, J. S.	10.1016/S1569-1993%2812%2960213-6
Study of Ivacaftor in Cystic Fibrosis Subjects Aged 12 Years and Older With the G551D Mutation	2009	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT00909532
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of VX 770 in Subjects with Cystic Fibrosis and the G551D Mutation	2009	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007416-15/GB
De Boeck 2014			
Ivacaftor, a CFTR potentiator, in cystic fibrosis patients who have a non-G551D-CFTR gating mutation: Phase 3, part 1 results	Pediatric Pulmonology, 2013	De Boeck, K., Paskavitz, J., Chen, X., Higgins, M.	10.1002/ppul.22898

Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation	Journal of Cystic Fibrosis, 2014	De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., Higgins, M.	10.1016/j.jcf.2014.09.005
The effect of ivacaftor, a CFTR potentiator, in patients with cystic fibrosis and a non-G551D-CFTR gating mutation, the KONNECTION study	Journal of Cystic Fibrosis, 2014	De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Chan, J., Gilmartin, G.	10.1016/S1569-1993(14)60004-7
Study of Ivacaftor in Subjects With Cystic Fibrosis (CF) Who Have a Non-G551D CF Transmembrane Conductance Regulator (CFTR) Gating Mutation	2012	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT01614470
A Phase 3, Two-Part, Randomized, Double-Blind, Placebo-Controlled, Crossover Study With an Open-Label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D CFTR Gating Mutation	2012	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000388-26/results
Moss 2015			
Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: A double-blind, randomised controlled trial	The Lancet Respiratory Medicine, 2015	Moss, R. B., Flume, P. A., Elborn, J. S., Cooke, J., Rowe, S. M., McColley, S. A., Rubenstein, R. C., Higgins, M.	10.1016/S2213-2600%2815%2900201-5
Ivacaftor treatment in patients with cystic fibrosis who have an R117H-CFTR mutation, the KONDUCT study	Journal of Cystic Fibrosis, 2014	Moss, R. B., Flume, P. A., Elborn, J. S., Cooke, J., Rowe, S. M., McColley, S. A., Rubenstein, R. C., Higgins, M.	10.1016/S1569-1993(14)60137-5
Effects of ivacaftor in CF patients with R117H-CFTR	Pediatric Pulmonology, 2014	Moss, R., Flume, P. A., Elborn, J., Cooke, J., Rowe, S. M., McColley, S. A., Rubenstein, R. C., Pilewski, J. M., Higgins, M.	10.1002/ppul.23108
Study of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation (KONDUCT)	2012	US National Institutes of Health Database (ClinicalTrials.gov) Record (duplicate of record below, erroneously included in review)	https://clinicaltrials.gov/ct2/show/NCT01614457
Study of Ivacaftor in Subjects With Cystic Fibrosis (CF) Who Have the R117H-CF Transmembrane Conductance Regulator (CFTR) Mutation (KONDUCT)	2012	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT01614457

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis who Have the R117H-CFTR Mutation	2012	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-000387-19
Pooled analyses			
Improved FEV1 based on airway recruitment and reduced airway narrowing in patients with CF receiving CFTR modulator therapy	Pediatric Pulmonology, 2016	Ingenito, E. P., Waltz, D., Higgins, M., Lekstrom-Himes, J., Huang, X., Liu, L., Elborn, J. S., Ramsey, B., McKee, C.	10.1002/ppul.23576
Patient-reported outcomes in Phase 3 trials of ivacaftor in subjects with CF who have the G551D-CFTR mutation	Journal of Cystic Fibrosis, 2012	Quittner, A. L., Ramsey, B., Dong, Q., Yen, K., Elborn, J. S.	10.1016/S1569-1993%2812%2960212-4
Patient-reported outcomes in phase 3 trials of ivacaftor in subjects with CF who have the G551D-CFTR mutation	Pediatric Pulmonology, 2012	Quittner, A., Ramsey, B., Rodriguez, S., Yen, K., Elborn, J. S.	10.1002/ppul.22682
Pulmonary effects of the investigational CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the G551D-CFTR mutation	American Journal of Respiratory and Critical Care Medicine, 2012	Elborn, S., Wainwright, C., Sermet-Gaudelus, I., Nasr, S., Rodriguez, S., Yen, K., Ramsey, B.	10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A2464
Lung function, weight, and sweat chloride responses in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor: A secondary analysis	European Respiratory Journal, 2013	Elborn, S., Plant, B., Konstan, M., Aherns, R., Rodriguez, S., Munck, A., Johnson, C.	42: 5059
Lung function, weight, and sweat chloride responses in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor: a secondary analysis	Journal of cystic fibrosis, 2013	Plant, B. J., Konstan, M., Aherns, R., Rodriguez, S., Munck, A., Elborn, J. S., Johnson, C. M.	10.1016/S1569-1993(13)60195-2
Effects of the CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the G551D-CFTR mutation	European Respiratory Journal, 2012	Elborn, J. S., Wainwright, C., Sermet-Gaudelus, I., Rodriguez, S., Yen, K., Ramsey, B.	40: 184

Effect of ivacaftor in patients with cystic fibrosis and the G551D-CFTR mutation who have baseline FEV1 >90% of predicted	Pediatric Pulmonology, 2013	Elborn, J. S., Rodriguez, S., Lubarsky, B., Gilmartin, G., Bell, S.	10.1002/ppul.22898
Nutritional status measures among persons with CF carrying the G551D-CFTR mutation who received ivacaftor or placebo in phase 3 clinical trials	Pediatric Pulmonology, 2012	Borowitz, D., Ramsey, B., Rodriguez, S., Yen, K., Elborn, J. S.	10.1002/ppul.22682
Measures of nutritional status in two Phase 3 trials of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR mutation	Journal of Cystic Fibrosis, 2012	Borowitz, D., Ramsey, B., Dong, Q., Yen, K., Elborn, J. S.	10.1016/S1569-1993%2812%2960041-1
Improved rate of decline in percent predicted FEV1 is not associated with acute improvement in percent predicted fev1 in patients with CF treated with ivacaftor	Pediatric Pulmonology, 2015	McKone, E., Sawicki, G., Millar, S., Pasta, D., Rubin, J., Johnson, C., Konstan, M., Wagener, J.	10.1002/ppul.23297
Efficacy response in CF patients treated with ivacaftor: Post-hoc analysis	Pediatric Pulmonology, 2015	Konstan, M. W., Plant, B. J., Elborn, J. S., Rodriguez, S., Munck, A., Ahrens, R., Johnson, C.	10.1002/ppul.23173
Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor	Digestive Diseases and Sciences, 2016	Borowitz, D., Lubarsky, B., Wilschanski, M., Munck, A., Gelfond, D., Bodewes, F., Schwarzenberg, S. J.	10.1007/s10620-015-3834-2
Pulmonary exacerbations in CF patients with the G551D-CFTR mutation treated with ivacaftor	Journal of Cystic Fibrosis, 2013	Flume, P., Wainwright, C. E., Tullis, E., Rodriguez, S., Davies, J., Wagener, J.	10.1016/S1569-1993(13)60200-3
Retrospective analysis of physiological response patterns to tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for F508DEL-CFTR or heterozygous for F508DEL-CFTR and a residual function mutation	Thorax, 2018	Ingenito, E., Nair, N., Yi, B., Lekstrom-Himes, J., Elborn, J. S., Rowe, S. M.	10.1136/thorax-2018-212555.75
Retrospective analysis of physiological response patterns to tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for F508del-CFTR or	Pediatric Pulmonology, 2018	Ingenito, E., Nair, N., Yi, B., Lekstrom-Himes, J., Elborn, J., Rowe, S. M.	10.1002/ppul.24152

heterozygous for F508del-CFTR and a residual function mutation			
Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles	ERJ Open Research, 2019	Taylor-Cousar, J. L., Mall, M. A., Ramsey, B. W., McKone, E. F., Tullis, E., Marigowda, G., McKee, C. M., Waltz, D., Moskowitz, S. M., Savage, J., Xuan, F., Rowe, S. M.	10.1183/23120541.00082-2019
Non-respiratory health-related quality of life in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor	Journal of Cystic Fibrosis, 2022	Fajac, I., Daines, C., Durieu, I., Goralski, J. L., Heijerman, H., Knoop, C., Majoor, C., Bruinsma, B. G., Moskowitz, S., Prieto-Centurion, V., Van Brunt, K., Zhang, Y., Quittner, A.	10.1016/j.jcf.2022.08.018
*Record identified as erroneously excluded at title and abstract appraisal during quality control			

9.5 Tables of excluded and deprioritised records with rationale

Table 116. Table of studies included in the SLR but deprioritised for extractions following the pre-specified prioritisation plan in the Assessment Protocol.

Study	VX Protocol	Genotype/Mutation	Age	Interventions and comparators	Phase and Randomisation	Linked references	Reason for deprioritisation
Accurso 2010[268]	VX06-770-101	*G551D*	18+	IVA, PBO	Phase 2, randomised	[268-277]	Study of ivacaftor monotherapy that did not report subgroup data for F/Gating population

Boyle 2014[278]	VX09-809-102	F/F	18+	LUM/IVA, PBO	Phase 2, randomised	278-285	Phase 3 RCT data are available for this population
Davies 2013[286]	*VX08-770-103*	*G551D*	6 to 11	IVA, PBO	Phase 3, randomised	287-294	Study of ivacaftor monotherapy that did not report subgroup data for F/Gating population
Milla 2017[295]	VX13-809-011	F/F	6 to 11	LUM/IVA	Phase 3, non-randomised	295-298	Phase 3 RCT data are available for this population
Donaldson 2018[299]	VX11-661-101	F/F F/Gating	18+ F/F 12+ F/Gating	TEZ/IVA, PBO	Phase 2, randomised	299-305	Phase 3 RCT data are available for 12+ F/F TEZ/IVA population and F/Gating is outside of marketing authorisation for TEZ/IVA
Williams 2015[264]	NA	*G551D*	18+	IVA, PBO	NR, randomised	264, 306	Study of ivacaftor monotherapy that did not report subgroup

							data for F/Gating population
McNamara 2019[307]	VX15-809-115	F/F	2 to 5	LUM/IVA	Phase 3, non-randomised	160, 307-309	PBO controlled randomised Phase 2 trial data available for LUM/IVA the F/F 2 to 5 population
Hoppe 2021[310]	VX16-809-116	F/F	2 to 5	LUM/IVA	Phase 3, non-randomised	310-313	Long-term extension study of McNamara 2019
Schwarz 2021[314]	VX16-661-114	F/F	12+	TEZ/IVA, PBO	Phase 3, randomised	314-317	Study of subgroup of people with CF who had discontinued LUM/IVA due to respiratory symptoms considered related to treatment
Keating 2019[318]	VX16-445-001	F/F F/MF	18+	ELX/TEZ/IVA, PBO	Phase 2, randomised	318-321	Phase 3 RCT data are available for this population

McNally 2022[261]	NA	F/X	6+	ELX/TEZ/IVA	Phase 4, non-randomised	261, 322	Observational Phase 4 clinical trial where RCT data are available.
Sagel 2021[262]	NA	F/F	6+	LUM/IVA	NR, non-randomised	262, 263	Observational study where RCT data are available
Walker 2019[323]	VX15-661-113	F/F F/RF	6 to 11	TEZ/IVA	Phase 3, non-randomised	323-325	Phase 3 RCT data are available for this population
NCT02730208[326]	VX15-661-112	F/F	12+	TEZ/IVA, PBO	Phase 2, randomised	326, 327	Phase 3 RCT data are available for this population
NCT02508207[328]	VX14-661-111	F/F	18+	TEZ/IVA, PBO	Phase 2, randomised	328	Phase 3 RCT data are available for this population
NCT02070744[329]	VX13-661-103	F/F	18+	TEZ/IVA, PBO	Phase 2, randomised	329	Phase 3 RCT data are available for this population

Davies 2013[330]	VX10-770-106	*G551D*	6+	IVA, PBO	Phase 2, randomised	330-341	Study of ivacaftor monotherapy that did not report subgroup data for F/Gating population
Edgeworth 2017[342]	NA	*G551D*	16 to 70	IVA, PBO	Phase 4, randomised	342-352	Study of ivacaftor monotherapy that did not report subgroup data for F/Gating population
Ng 2021[353]	NA	F/F	12 to 40	TEZ/IVA, PBO	Phase 2, randomised	353, 354	Phase 3 RCT data are available for this population
NCT02742519[355]	VX15-770-123	*G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D.*	3 to 5	IVA, PBO	Phase 3, randomised	355	Study of ivacaftor monotherapy that did not report subgroup data for F/Gating population. No randomised ELX/TEZ/IVA data in this age group.

NCT05111145[356]	VX20-445-121	NR	12+	ELX/TEZ/IVA	Phase 3, non-randomised	356	No results available at time of review.
NCT05153317[357]	VX20-445-112	NR	2+	ELX/TEZ/IVA	Phase 3, non-randomised	357	Extension study of VX20-445-111 Part B. No results available at time of review.
NCT04969224[358]	VX20-445-126	F/Gating	12+	ELX/TEZ/IVA	Phase 3, non-randomised	358	No results available at time of review.
NCT04599465[359]	VX19-445-117	F/MF	12+	ELX/TEZ/IVA	Phase 3, non-randomised	359	No results available at time of review; subgroup of people with abnormal glucose metabolism.
NCT04545515[360]	VX20-445-119	F/MF	6+	ELX/TEZ/IVA	Phase 3, non-randomised	360	No results available at time of review.
NCT04235140[361]	VX19-809-124	F/F	1+	LUM/IVA	Phase 3, non-randomised	361	No results available at time of review; Long-term extension of

							included Rayment 2022 study.
NCT03956589[265]	NA	F/F	12+	LUM/IVA	Phase 4, non-randomised	265	No results available at time of review.
DRKS00023862[266]	NA	NR	12+	LUM/IVA	Phase 4, non-randomised	266	No results available at time of review.
DRKS00022267[267]	NA	NR	2 to 12	LUM/IVA	Phase 4, non-randomised	267	No results available at time of review.

Table 117. Table of studies excluded at the full-text appraisal stage of the clinical systematic literature review.

Study	Linked References Excluded	Reason for exclusion
Clancy 2012[362]	Clancy 2010a;[363] Clancy 2010b;[364] Clancy 2010c;[365] Clancy 2011a[366] Clancy 2012;[362] Lu 2011;[367] NCT00865904;[368] EUCTR2008-006446-25[369]	Irrelevant intervention – lumacaftor monotherapy
Davies 2018[370]	Davies 2018[370]	Irrelevant intervention – VX659
Flume 2012[371]	Flume 2011a;[372] Flume 2011b;[373] Flume 2012[371]	Irrelevant genotype for intervention – Study of ivacaftor monotherapy in F/F genotype

Kerem 2021[374]	Kerem 2020;[375] Kerem 2021a;[374] Kerem 2021b[374]	Irrelevant genotype for intervention – Study of ivacaftor monotherapy in F/RF genotype
McKone 2021[376]	McKone 2021;[376] NCT02412111;[377] EUCTR2014-004838-25[378]	Irrelevant genotype for intervention – Study of TEZ/IVA in F/Gating genotype
Munck 2020[379]	Munck 2020;[379] NCT02516410;[380] EUCTR2014-004787-37[381, 382]	Irrelevant genotype for intervention – Study of TEZ/IVA in F/MF genotype
Berkers 2021[383]	Berkers 2021;[383] EUCTR2016-001585-29[384]	Irrelevant genotype for intervention – Study of LUM/IVA in people with an *A455E* mutation
McKone 2014[385]	McKone 2011;[386] McKone 2012a;[387] McKone 2012b;[388] McKone 2013;[389] McKone 2014[385]	Study design – Non-randomised study of ivacaftor monotherapy
Altes 2017[390]	Altes 2012a;[391] Altes 2012b;[392] Altes 2012c;[393] Altes 2014[394]	Study design – small N pre-post study
Sawicki 2017[395]	Sawicki 2017[395]	Study design – observational
Gilmartin 2018[396]	Gilmartin 2018[396]	Study design – in vitro study linked to excluded RCT
Nick 2020[397]	Nick 2014a;[398] Nick 2014b;[399] Nick 2020[397]	Study design – pilot study

McGarry 2015[400]	McGarry 2015[400]	Study design – N-of-one trial, ivacaftor monotherapy without relevant genotype reported
At full text appraisal, 8 further records were excluded due to being duplicates and 2 for being supplementary material associated with included studies		

9.6 Detailed data extraction tables

9.6.1 Economic evaluation searches data extraction

Author, year, country	Patient population	Key model inputs	Cost-effectiveness results
Multiple CFTR modulators			
Institute for Clinical and Economic Review (ICER), 2018, USA[195]	Patients with CF in both homogenous and heterozygous (gating mutation or RF)	Treatment effect is modelled as an immediate increase in $ppFEV_1$, weight for age z-score, and a decrease in the annual number of acute pulmonary exacerbations, sourced from the key trials relevant to the intervention Long term efficacy: assumed no decline in $ppFEV_1$ for the first 2 years on treatment followed by a decline of 50% of the ECM rate for the remainder of the model Mortality is a combination of age specific mortality based on USA life table and a CF-specific rate (function of sex, $ppFEV_1$, weight-for-age z-scores, number of acute pulmonary exacerbations, diagnosis of CF-related diabetes, pancreatic sufficiency, and B. cepacia infection based on Liou *et al.* 2021 survival model. However S.aurus infection was not included in the model as Liou found the impact was decrease mortality - ICER found no explanation as to why this would be the case and so removed this from the Liou model Adverse events not explicitly modelled in terms of costs or disutility but captured in discontinuations Compliance based on rates reported in trials	Base-case results - all CFTR modulators ICER compared to ECM alone only homozygous for the F508del mutation: LUM/IVA: $890,739 per QALY TEZ/IVA: $974,348 per QALY heterozygous for the F508del mutation with residual function: TEZ/IVA: $941,110 per QALY IVA: $840,568 per QALY heterozygous for the F508del mutation with gating function IVA: $956,762 per QALY gained

Institute for Clinical and Economic Review (ICER) 2020, USA[196]	Target population is patients both homozygous and heterozygous for the F508del mutation Patients started on a CFTR modulator when they were first eligible to receive that modulator as per the marketing authorisation and then switch to a “more effective” modulator when they become age eligible	Treatment effectiveness: Treatment effect is modelled as an immediate increase in $ppFEV_1$, weight for age z-score, and a decrease in the annual number of acute pulmonary exacerbations. Patients switching CFTR modulators are assumed to experience the net increase in $ppFEV_1$ between the two drugs, based on trial data where available. Long term treatment effect was assumed to be no $ppFEV_1$ decline whilst on the CFTR modulator for 2 years followed by a decline that is 50% of the standard care rate after this time point for all CFTR modulators. Assumed no additional costs and disutilities due to AEs but assumed those who discontinued in trials included those discontinuing due to AEs	Base-case results - all CFTR modulators ICER compared to ECM alone only homozygous for the F508del mutation: LUM/IVA: $1,480,000 per QALY TEZ/IVA: $1,380,000 per QALY ELX/TEZ/IVA: $1,160,000 per QALY heterozygous for the F508del mutation with residual function: TEZ/IVA: $1,340,000 per QALY ELX/TEZ/IVA: $1,100,000 per QALY heterozygous for the F508del mutation with minimal function ELX/TEZ/IVA: $1,050,000 per QALY gained
Elexacaftor/Tezacafor/Ivacaftor (ELX/TEZ/IVA)			

CADTH Common Drug Review, 2021, Canada[210]	Target population is patients with CF aged ≥ 12 years who have at least 1 F508del mutation in the CFTR gene. 4 genotypes considered in separate analyses: 1. Homozygous for F508del-CFTR (F/F) 2. Heterozygous for F508del-CFTR with 1 minimal function mutation (F/MF) 3. Heterozygous for F508del-CFTR with a residual mutation (F/RF) 4. Heterozygous for F508del-CFTR with a gating mutation (F/G), inclusive of R117H Also include a subgroup analysis of IVA monotherapy for patients with an F/G genotype	Treatment was assumed to impact disease progression through effects relating to $ppFEV_1$, weight for age score, and exacerbation rate. Data on effectiveness was taken from key trials and ITC (Bucher method) undertaken for ECM Patients on ELX/TEZ/IVA were assumed not to experience any decline in $ppFEV_1$ for the initial 96 weeks, after which it declined at a rate of 61.5% of the ECM decline, based on data from TEZ/IVA- CADTH analyses removed the relative reduction in $ppFEV_1$ decline post 96 weeks in their own base-case Discontinuation rates: up to the trial duration period were taken from the phase III trials for ELX/TEZ/IVA and IVA monotherapy. A 'post-acute' phase up to an additional 96 weeks used extension studies. After this point no further discontinuation occurred. Compliance rates: Taken from trials for first 24 weeks (genotype specific). Beyond the trial period taken from a study by Suthoff 2016[401] (not genotype specific). Compliance affects costs only and not treatment efficacy. The Company assumed 80% compliance whereas CADTH re-analyses assumed 100% compliance Assumed 13.2% of patients with a $ppFEV_1$ less than 40% would receive a lung transplant.	<u>Company's base case results:</u> F/F genotype: incremental costs of $4,638,324 and QALYs of 12.93. ICER = $358,763 per QALY F/MF genotype: incremental costs of $4,526,116 and QALYs of 12.59. ICER = $359,597 per QALY F/RF genotype: incremental costs of $3,782,240 and QALYs of 7.12. ICER = $531,195 per QALY <u>CADTH re-analyses base case results:</u> F/F genotype: incremental costs of $8,171,598 and QALYs of 7.13. ICER = $1,140,840 per QALY F/MF genotype: incremental costs of $7,916,634 and QALYs of 6.88. ICER = $1,150,105 per QALY F/RF genotype: incremental costs of $6,412,761 and QALYs of 3.35. ICER = $1,911,977 per QALY

CADTH Common Drug Review, 2022, Canada[111]	This is an extension of the previously submitted and reviewed submission for those are 12+ focusing on those aged 6-11 years old. Target population is patients with CF aged ≥ 6 years who have at least 1 F508del mutation in the CFTR gene. 4 genotypes considered in separate analyses: 1..Homozygous for F508del-CFTR (F/F) 2. Heterozygous for F508del-CFTR with 1 minimal function mutation (F/MF) 3. Heterozygous for F508del-CFTR with a residual mutation (F/RF) 4. Heterozygous for F508del-CFTR with a gating mutation (F/G), inclusive of R117H	Treatment effectiveness: Treatment impacts disease progression through effects relating to $ppFEV_1$, weight for age score, and exacerbation rate sourced through the relevant clinical trials. Indirect treatment comparison was undertaken on patient level data as placebo-adjusted estimates were required. Reduction in rate of $ppFEV_1$ decline for patients on CFTR modulators for patients aged 6 to 11 years receiving LUM/IVA and IVA assumed to be equal to that calculated for patients aged 12+ (47.1% and 42% reductions compared to ECM, respectively). Patients on ELX/TEZ/IVA were assumed not to experience any decline in $ppFEV_1$ for the initial 96 weeks, after which it declined at a rate of 20% of the ECM decline – CADTH analyses removed the relative reduction in $ppFEV_1$ decline post 96 weeks in their own base-case Treatment discontinuation: Taken from the relevant trials for the trial period and open label extensions up to 96 weeks. After this point no further discontinuations were assumed to occur (rates not reported) Compliance: 93% in Company base-case taken from the trials and observational data from LUM/IVA for data beyond the trial period. Costs were adjusted by the compliance rate yet efficacy was not. CADTH analyses assumed 100% compliance to account for all drug costs Adverse events: Based on trials for the relevant genotype and CFTR modulators (rates not reported)	Company's base case results: F/F genotype: incremental costs of $2,792,413 and QALYs of 8.63 when compared with LUM/IVA. ICER = $323,602 per QALY. When compared with ECM, it resulted in incremental costs of $6,662,694 and QALYS of 14.76. ICER = $451,377 per QALY. F/MF genotype: incremental costs of $6,689,307 and QALYs of 14.66. ICER = $456,394 per QALY versus ECM F/RF genotype: incremental costs of $6,678,270 and QALYs of 10.27. ICER = $650,475 per QALY versus ECM Key scenario analysis undertaken for the full indicated population for ELX/TEZ/IVA (age 6+ with at least one F508del mutation). weighted ICER accounting for prevalence of each genotype = $407,601 CADTH reanalyses base case results: F/F genotype: incremental costs of $4,043,775 and QALYs of 5.94 when compared with LUM/IVA. ICER = $680,560 per QALY. When compared with ECM, it resulted in incremental costs of $9,961,485 and QALYS of 6.94. ICER = $1,434,435 per QALY. F/MF genotype: incremental costs of $9,684,715 and QALYs of 5.86. ICER = $1,653,605 per QALY versus ECM F/RF genotype: incremental costs of $10,174,150 and QALYs of 4.17. ICER = $2,437,481 per QALY versus ECM Key scenario assessing the cost effectiveness of ELX/TEZ/IVA in the full Health Canada population (age 6+

		Lung transplant: assumed that 11.3% of patients with a ppFEV$_1$ <30% would receive a lung transplant.	with at least one F508del mutation) resulted in an overall weighted ICER of $1,136,142 per QALY. None of CADTH's scenario analyses produced an ICER below $878,073 per QALY

Pharmaceutical Benefits Advisory Committee (PBAC), 2021, Australia[211]	CF patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/any).	Treatment effectiveness was measured in terms of change in $ppFEV_1$, weight for age z score and pulmonary exacerbations Changes in ppFEV1 and weight for age score for patients on ELX/TEZ/IVA versus TEZ/IVA taken from an ITC conducted of Study 109 and EVOLVE (TEZ/IVA) in the F/F population and an ITC of Study 104 and EXPAND (TEZ/IVA) for the F/RF population. Impact on PEs taken from Study 102 for all genotypes Model assumed that short term treatment effects from the trials last for the lifetime. The long term decrease in the rate of $ppFEV_1$ decline for TEZ/IVA versus ECM (42% of ECM) was taken from a study of lumacaftor/ivacaftor. This was deemed to be uncertain and overly optimistic. For ELX/TEZ/IVA this rate was assumed to be 61.5% of that for ECM, taken from a study of TEZ/IVA patients. It is uncertain if this data is directly applicable for ELX/TEZ/IVA and overly optimistic Compliance = assumed 90%. Considered inappropriate by ESC Following resubmission to PBAC in December 2019 the following model changes were implemented: No treatment specific utility increment applied and an 80% relative rate of decline in ppFEV1 for ELX/TEZ/IVA as opposed to original 61.5%, based on longer follow up data from Study 105.	March 2019 submission (Costs and ICERs redacted): F/F population- Incremental LYs of 3.10 for ELX/TEZ/IVA versus TEZ/IVA and incremental QALYs of 4.55. Redacted ICER in the range $155,00<$255,000 F/RF population- Incremental LYs of 1.14 for ELX/TEZ/IVA versus TEZ/IVA and incremental QALYs of 2.25. Redacted ICER in the range $135,00<$155,000 F/MF population- Incremental LYs of 5.44 for ELX/TEZ/IVA versus ECM and incremental QALYs of 6.47. Redacted ICER in the range $455,00<$555,000 December 2019 resubmission: F/F population- Incremental LYs (undiscounted) of 20.56 for ELX/TEZ/IVA versus TEZ/IVA and incremental QALYs (discounted) of 4.47. Redacted ICER in the range $155,00<$255,000 F/MF population- Incremental LYs (undiscounted) of 26.79 for ELX/TEZ/IVA versus ECM and incremental QALYs (discounted) of 6.72. Redacted ICER in the range $155,00<$255,000
Lumacaftor/Ivacaftor (LUM/IVA)			

National Institute for Health and Care Excellence (NICE) - TA786. 2016[202]	Cystic fibrosis patients homozygous for the F508del mutation (age 12+)	Main measure of treatment effect was change in $ppFEV_1$. This was taken from the pooled placebo-adjusted mean change from baseline in $ppFEV_1$ measured as the average of weeks 16 and 24 from TRAFFIC and TRANSPORT studies (increases by 2.8 percentage points by week 16 compared to starting $ppFEV_1$ and assumed to remain constant until week 24, irrespective of if they remained on treatment). The committee stated that decline in $ppFEV_1$ for the treatment group post 24 weeks may overestimate the benefit as it was based on data from 4 weeks onwards which includes a period in which ppFEV1 was still improving (treatment effect peaked at 8 weeks). $ppFEV_1$ post 24 weeks for the ECM group is assumed to decline with age. This is taken from prospective multicentre observational studies in the US and Canada as they deemed the cross-sectional CF registry data inferior. $ppFEV_1$ decline post 24 weeks for the treatment group was taken from a combination of data from the TRAFFIC, TRANSPORT and PROGRESS (open-label extension) studies. The Company used a "mixed model with random intercepts and slopes for each patient to estimate the slope of $ppFEV_1$. The unadjusted slope was annualised, and the analyses determined that patients declined at an average of 0.68 (95% CI -1.58% to 0.16%) percentage points per year". The committee noted how it had not been sufficiently justified why USA/Canada data was more relevant to the clinical population in England, resulting in uncertainty. The committee also stated how exploratory analyses should have been undertaken using the $ppFEV_1$ decline for standard of care alone based on the 24-week trial data	Company's base case results (deterministic): Incremental costs of £753,570 and QALYs of 3.45. ICER = £218,248 per QALY ERG base-case: Incremental costs of £714,637 and an incremental QALY gain of 3.22. ICER = £221,992 per QALY ERG base case a combination of the following changes: - Setting the adherence rate to 96.5% rather than 90% - People could stop lumacaftor–ivacaftor treatment after 24 weeks. The rate for people stopping treatment between weeks 24–48 were taken from PROGRESS (13.5% annually), and was assumed to be 1.9% annually hereafter in line with a rate used by the Company in its scenario analysis. - The mean absolute change in $ppFEV_1$ from baseline was based on the 24-week time point data alone rather than the average of the 16-week and 24-week data

		Discontinuation rates taken from the TRAFFIC and TRANSPORT trials (6.8%) during the 24 week trial period. No change in treatment efficacy is applied for patients who discontinue during this period. Patients discontinuing after the initial 24 weeks have the same $ppFEV_1$ decline as SoC patients. Treatment adherence used by the Company is 90%. Trial adherence was 96.5% but deemed to be unrealistically high due to trial settings. The ERG and committee stated that the trial value should be used if not adjusting efficacy	

Scottish Medicines Consortium (SMC), 2016, Scotland[206]	CF patients aged 12 years and older who are homozygous for the F508del mutation	Treatment effectiveness was measured through changes in ppFEV$_1$, pulmonary exacerbations and weight for age z score taken from the TRAFFIC and TRANSPORT trials. The annual rate of pulmonary exacerbations was taken from TRAFFIC and TRANSPORT trials for the treatment arm (rate reduction) and published studies for standard care arm. The weight-for-age z-scores for the standard care arm were assumed to remain at baseline for the entire time horizon and the values reported in the studies were not used.	Company's base case ICER = £310,879 per QALY gained
Scottish Medicines Consortium (SMC), 2019a, Scotland[207]	CF patients aged 6 years and older and aged 2 to 5 years who are homozygous for the F508del mutation	Treatment effectiveness was measured through changes in ppFEV$_1$, pulmonary exacerbations and weight for age z score For patients aged 12 years + this data were from a pooled analysis of the TRAFFIC and TRANSPORT studies. For patients aged 6 to 11 years, taken from study 109 and study 011. For patients aged 2 to 5 years, there was no placebo-controlled evidence available. Treatment adherence: adherence is assumed to be 80% based on retrospective USA claims data. This results in a 20% decrease in the cost of the drug	Company's base case results: Incremental costs of £930,000 and QALYS of 4.33. ICER = £214,772 per QALY gained If treatment is initiated only in patients aged 2 the ICER = approximately £173K If treatment is initiated only in patients aged 2 to 11 years the ICER = approximately £185K

CADTH Common Drug Review (CDR), 2016, Canada[200]	CF in patients aged 12 years + who are homozygous for the F508del-CFTR mutation	Treatment effectiveness data based on TRANSPORT and TRAFFIC trials to inform changes in $ppFEV_1$, PEs and weight for age z score. Long term efficacy: Based on 24 week extension data from PROGRESS. The Company's model assumed a slower rate of decline in $ppFEV_1$ for patients on LUM/IVA versus BCS. This was revised to assume improvement in $ppFEV_1$ is maintained in the long term but the rate of decline is the same as ECM. Compliance = assumed to be 88% by the Company, applied by reducing drug price. CADTH instead assumed 100% compliance Company assumed a price reduction of 82% after 12 years to represent generic market access. CADTH removed this assumption from their analysis	Company's base case results: Incremental costs of $1,718,342 and QALYS of 3.54. ICER = $485,767 per QALY gained CDR re-analyses base case results: Incremental costs of $1,995,321 and QALYS of 0.42. ICER = $4,773,615 per QALY gained
CADTH Common Drug Review (CDR), 2018, Canada[201]	Target population is patients 6 years of age and older who are homozygous for the F508del mutation. Includes analyses for patients 6-11 and age 12+ separately	Treatment effectiveness: Treatment impacts disease progression through effects relating to $ppFEV_1$,weight for age score, and exacerbation rates. For the first 24 weeks of the model, changes in $ppFEV_1$ is taken from TRAFFIC and TRANSPORT studies for patients aged over 12 and the 809-109 study for patients aged between six and 12. Post 24 weeks, the model used extension data from PROGRESS and the CDR analyses assumed a continuous treatment effect (same rate of decline) with both LUM/IVA + SoC and SoC alone post 24 weeks. This differed to the Company's submitted model which assumed a differential rate of decline	Company's base-case ICER (age 6+) = $446,529 CDR re-analyses base case cost per QALY gained (age 12+) = $3,785,432 CDR re-analyses base case cost per QALY gained (age 6-11) = $7,258,514

		favouring LUM/IVA + SoC based on short term observational studies Data on exacerbation rate as a function of ppFEV1 is sourced from analysis of USA CF registry data (figures not reported CADTH report) Adverse event rates are taken from clinical trials data but figures not reported in CADTH report	
Pharmaceutical Benefits Advisory Committee (PBAC), 2018b, Australia[203] * *combines multiple summary documents from resubmissions, extraction details results and final model inputs from the most recent submission, utilising earlier versions for details where needed*	CF patients aged 12+ homozygous for the F508del mutation	Treatment effectiveness data taken from TRAFFIC & TRANSPORT trials to inform changes in $ppFEV_1$, PE's and weight for age z score Long term efficacy data based on PROGRESS 96 week open label extension trial to inform the rate of decline in $ppFEV_1$ (42% of that of ECM) and weight for age z score post 24 weeks. Baseline hazard function for mortality is taken from Irish CF Registry 2013 Company assumed a price reduction at patent expiry (price reduction redacted)	Incremental QALYs of 1.97. Redacted ICER in the range $105,000 - $200,000 per QALY

Pharmaceutical Benefits Advisory Committee (PBAC), 2018a, Australia[204]	CF patients aged 6-11 homozygous for the F508del mutation	Data from Study 109 informed changes in $ppFEV_1$ for patients ages 6-11 whilst changes in weight for age z score were informed by TRAFFIC and TRANSPORT trials. Long term efficacy (decline in $ppFEV_1$ post 24 weeks and changes in weight for age z score) informed by PROGRESS trial Baseline hazard function for mortality is taken from Irish CF Registry 2013	Incremental QALYs of 3.19. Redacted ICER in the range $105,000 - $200,000 per QALY
Pharmaceutical Benefits Advisory Committee (PBAC), 2019b, Australia[205]	CF patients aged 2–5 years who are homozygous for the F508del mutation	Data from Study 109 informed changes in $ppFEV_1$ for patients ages 6-11 whilst changes in weight for age z score were informed by TRAFFIC and TRANSPORT trials. Long term efficacy (decline in $ppFEV_1$ post 24 weeks (42%) and changes in weight for age z score) informed by PROGRESS trial. Baseline hazard function for mortality is taken from Irish CF Registry 2013 The only differences in the model compared to PBAC, 2018 study for patients ages 6-11 was treatment compliance of 99.20% for patients aged 2 to 5 years, informed by study 115.	Patients aged 2-5: Incremental QALYs of 2.42. Redacted ICER in the range $105,000 - $200,000 per QALY Patients aged 6+: Incremental QALYs of 1.83. Redacted ICER in the range $105,000 - $200,000 per QALY

Dilokthornsakul, P., et al. 2017, USA[197]	CF patients (25+) with homozygous phe508del mutation	Data from TRAFFIC and TRANSPORT trials was used to inform treatment effect on ppFEV$_1$ which determined the probability of moving from moderate to mild health states and severe to moderate. Transition probability table not provided in report Efficacy of LUM/IVA is assumed to remain constant in the first 2 years then reduce to 50% of that rate for subsequent years. Mortality risks for severe and moderate lung disease ad lung transplantation were sourced from the literature but not reported	Incremental life-years of 2.91 (95% CI 2.55–3.56) Incremental costs of $2,632,249 (95% CIs $1,094,846–$3,628,261) Incremental QALYs of 2.42 (95% CIs 2.10–2.98). ICER not reported
Sharma, D et al., 2018, USA[198]	12 year old CF patients with homozygous F508del mutation	Data from TRAFFIC and TRANSPORT trials informed changes in ppFEV$_1$ and pulmonary exacerbations between the two treatment arms. Long term efficacy is assumed to remain 100% throughout the model time horizon in the base case (i.e. no progression to severe health states and constant risk ration for PE reductions whilst on treatment) Lung transplant - age specific rates calculated from USA CF foundation patient registry annual report 2016 Mortality rates sourced from the literature and used age specific mortality rates for the CF population No adverse events noted	Base case analysis: Incremental costs of $1,662,765 and QALYs of 0.45 compared with usual care. ICER = $3,655,352 per QALY gained Sensitivity analyses resulted in ICERs in the range of $2,773,949 - $5,357,736, with the utility value used in the mild health state having the largest impact.

Vadagam P et al., 2018, USA[199]	CF patients 12 years + with homozygous F508del mutation	Efficacy measured a change in $ppFEV_1$ sourced from the TRAFFIC and TRANSPORT trials Risk of pulmonary exacerbations and discontinuation rates due to AEs was based on 48 week safety data Adverse events included those that occurred in at least 10% of patients in any treatment group. The most commonly reported SAE was pulmonary exacerbation Due to short time horizon of the model (1 year) no lung transplantation or mortality was included	Main outcome was incremental cost per absolute $ppFEV_1$. ICER = $95,016
Tezacaftor/Ivacaftor (TEZ/IVA)			
Scottish Medicines Consortium (SMC), 2019b, Scotland[209]	CF patients 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation with residual function	Treatment effectiveness was measured through changes in $ppFEV_1$, pulmonary exacerbations and weight for age z score (heterozygous population only) Data from the EVOLVE trial was used for homozygous patients and the EXPAND trial for heterozygous patients Long term decline in $ppFEV_1$ used proxy data from other CFTR modulator trials. For homozygous patients, data from the phase 3 trials and open label extensions for lumacaftor/ivacaftor was compared with homozygous patients from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). For heterozygous patients, a proxy for percentage reduction in long term $ppFEV_1$ decline was derived from comparing data on decline in the trials for ivacaftor monotherapy with patients with homozygous mutation in the US CFFPR.	**Company's base case results:** Homozygous populations - incremental costs of £1,528,711 and QALYs of 3.63. ICER = £421,173 per QALY gained Heterozygous population - incremental costs of £1,820,962 and QALYs of 5.05. ICER = £360,499 per QALY gained

		Treatment compliance of 80% assumed (resulting in cost reduction only)	

Pharmaceutical Benefits Advisory Committee (PBACa), 2019, Australia[208]	CF patients 12 years and older heterozygous for the F508del mutation with residual function	Treatment effects based on Study 108 Changes in treatment effect over time based on extension study PROGRESS (LUM/IVA for patients homozygous for the F508del mutation) and large longitudinal registry analyses Baseline hazard function, a Gompertz parametric distribution, was applied to extrapolate data from the Kaplan-Meier (KM) curve of patients from the Irish CF registry (not just RF patients). The hazard was then adjusted using based on patient characteristic from the Liou *et al*. 2001 survival model based on patient characteristics from Study 108 Long term decrease in the rate of decline in $ppFEV_1$ (42%) for patients on tezacaftor/ivacaftor beyond the 8 week trial period was informed by the extension trial for lumacaftor/ivacaftor (PROGRESS) - this was deemed inappropriate and removed in the ESC base-case Reduction in pulmonary exacerbations was based on Study 108. Differences between the treatment and placebo arm were insignificant and the ESC removed this in their base case.	Incremental costs and ICERs were redacted but noted to be over $200,000 (AUS$) Submission base case: Incremental QALYs = 2.44 ESC base case: Incremental QALYs = 1.57

9.6.2 HRQoL searches data extraction

Study	Author, year	Sample size	Patient population, recruitment	Instrument	Utility results
1	Acaster et al. 2015	401 participants	Self-reported clinical diagnosis of CF, 18 years or above and currently resident in the UK. Interested participants followed a link provided by the CF Trust Mean age = 28.7+/- 8.88, 39% Male	CRQ-R & EQ-5D	EQ-5D by FEV1 Mild FEV (>70%) = 0.74 +/-0.27 Moderate FEV (41%-70%) = 0.7+/- 0.26 Severe FEV (<41%) = 0.54 +/-0.29 Total sample = 0.67+/-0.28
2	Acaster et al. 2022/2019	335 participants	Mean age (SD) =47.4 (16) 49.8% Female 85.3% British	CFQ-R (TTO)	Regression model used to calculate utility based on 30 different parameters.
3	Angelis et al. 2015	74 patients	Patients recruited from the CF Trust. Mean age (SD) All patients: 18.3 (15.1) Adult patients 31.1 (10.1) 52.7% Male	EQ-5D, VAS	EQ-5D Adult CF patients (n30) = 0.64 (0.264)
4	Bradley et al. 2013	94 participants	Mean age = 28.5+/- 8.2yrs baseline FEV1 = 58.7+/-26.8% 60 patients had no pulmonary exacerbation at visit 1	EQ-5D	No exacerbations = 0.85 (0.8-0.89) Mild PE= 0.79 (0.67-0.91) Severe PE = 0.6 (0.44-0.76)
5	Bell et al. 2015	209 patients	Patients recruited from France (61), UK (54), Germany (47), Australia (38) and Ireland (9). Only patients with CF and >/1 *G551D* mutation and were receiving IVA for >/3months, or were homozygous for the *F508del* mutation and receiving SoC.	EQ-5D, WPAI	EQ-5D G551D/IVA patient group 0.9(0.02), n=72 F508del/SoC patient group 0.81(0.02), n=137

6	Cameron et al. 2021	51 patients	Patients attending a single large adult CF centre in England were invited to participate in remote interviews conducted by video call. Mean age = 33(18-66) 47% male 69% on a CFTR modulator, Mean ppFEV1 = 66% (SD 20.3)	EQ-5D measured with TTO	EQ-5D Mean = 0.82(0.2) Base case = 0.8(0.2) No exacerbations = 0.84(0.16) 3 exacerbations = 0.73(0.23) Additional nebulized medicine = 0.78(0.2) Additional physiotherapy = 0.77 (0.22)
7	NICE TA786 2016 Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]	516 patients	Pooled TRAFFIC and TRANSPORT studies LUM-IVA + SoC n=340 Mean age (SD) = 25.1 (9.33) 51.8% Male Placebo + SoC n=176 Mean age (SD) = 24.9 (10.10) 51.1% Male	EQ-5D-3L, CFQ-R	EQ-5D of all TRAFFIC and TRANSPORT patients FEV1 = mean (SD) >/90% = 0.951 (0.096) 70%-<90% = 0.933 (0.124) 40%-<70%= 0.906 (0.141) <40% = 0.878 (0.14) All patients = 0.912 (0.137)
8	Solem et al. 2016	161 patients	CF diagnosis and *G551D-CFTR* mutations Mean age = 25.5(SD 9.5) 46% Female 83% normal weight 91% history of pancreatic insufficiency 42% use inhaled cycling antibiotic	EQ-5D, VAS	EQ-5D measures by FEV1% Normal (>90): 0.931 (0.023) Mild (90% -70%): 0.923 (0.021); Moderate (70%-40%): 0.904 (0.018); severe (<40%): 0.870 (0.020)
9	Tappenden et al. 2013	Taken from Bradley et al.			FEV1% = mean EQ-5D (SD) >70 = 0.864 (0.165) 40-70 = 0.81 (0.216) <40 = 0.641 (0.319) Disutility from major exacerbation = 0.174 (0.341)

					Disutility from minor exacerbation = 0.015 (0.048)
10		Stahl et al. 136 patients	Mean age = 64.3 Predicted mean FEV1 % = 62% 41% Female	EQ-5D	FEV1% = mean EQ-5D (SD) >79 = 0.84(0.15) 60-79 = 0.73(0.23) 40-59 = 0.74 (0.25) <40 = 0.52 (0.26)
11	Tappenden et al. 2017 & 2014	Taken from Bradley et al.			Same as those taken from Bradley et al, in Tappenden, 2013
12	Tappenden et al. 2023	Used a using a de novo function developed to map from absolute FEV1% pred. scores to the 3-Level Euroqol 5-Dimensions (EQ-5D-3L) using data collected during clinic visits in the CFHH trial in Wildman et al. 2021 Unlike Wildman, only used patients with no missing EQ-5D values.			FEV1 > 70% predicted. = 0.82; FEV1 40–69% pred. = 0.79; FEV1 < 40% pred. = 0.71
13	Whiting et al. 2014	Ivacaftor clinical trial 167 in adult study 52 in child study	Mean age = 20 52% Female baseline predicted FEV1 = 71%	EQ-5D	Normal (percentage predicted FEV1 ≥ 90%) = 0.97 Mild (percentage predicted FEV1 70–89%) = 0.95 Moderate (percentage predicted FEV1 40–69%) = 0.93 Severe (percentage predicted FEV1 < 40%) = 0.91
14		Gee et al 223 adolescent patients	Patients recruited from two specialist adult CF units in Manchester and Leeds Mean age = 25.15yrs (14 to 52 years old) 46% Male Mean BMI = 20.88 (SD 2.6) Mean FEV1 = 55.63 (SD 23.5)	SF-36	Utility values (SD) used in basecase, based on SF-36: Mild (percentage predicted FEV1 > 70%) = 0.803 (20.1) Moderate (percentage predicted FEV1 40–69%) = 0.749 (20.5) Severe (percentage predicted FEV1 < 40%) = 0.688 (20.2)

15	Wildman et al. 2021	607 patients	>16 with cystic fibrosis, on the cystic fibrosis registry, not post lung transplant or on the active transplant list, who were able to consent and not using dry-powder inhalers Baseline FEV1% predicted Control 56.9 (SD 23) Intervention 60.6 (24.2)	EQ-5D	Control 0.81 (0.18) Intervention 0.84(0.15)
Abbreviations: CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire – revised; EQ-5D, EuroQoL-5D; FEV_1, forced expiratory volume; SoC, standard of care.					

9.7 NMA diagnostic plots

Figure 23. Brooks-Gelman-Rubin diagnostic plots for the F/F fixed-effect ppFEV$_1$ base case analysis (A), fixed-effect ppFEV$_1$ sensitivity analysis (B), random effects ppFEV$_1$ analysis (D) and the trace plots and posterior distributions of the random effects analysis (C).

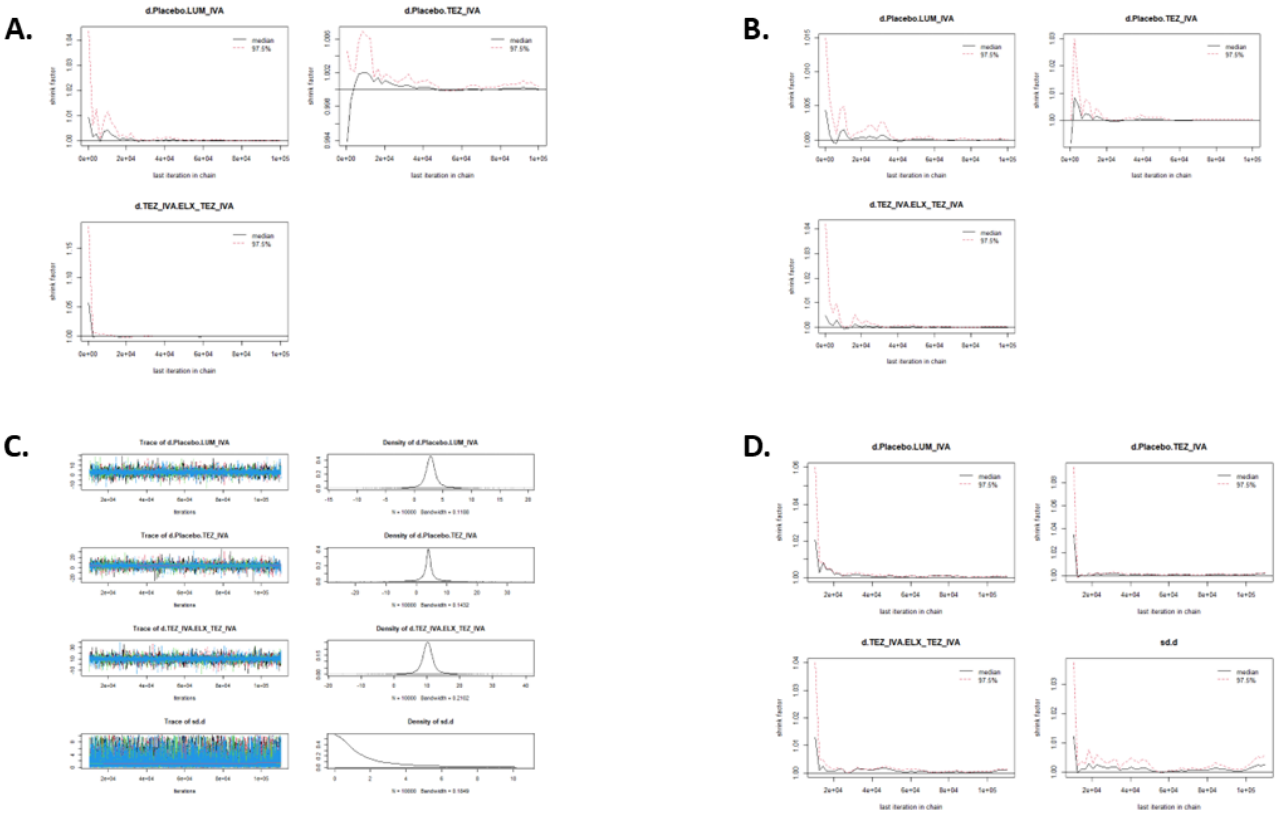


Figure 24. Brooks-Gelman-Rubin diagnostic plots for the F/Gating random effects ppFEV$_1$ analysis (A), random effects weight-for-age z-score analysis (B), fixed-effect ppFEV$_1$ analysis (C) and fixed-effect weight-for-age z-score analysis (D).

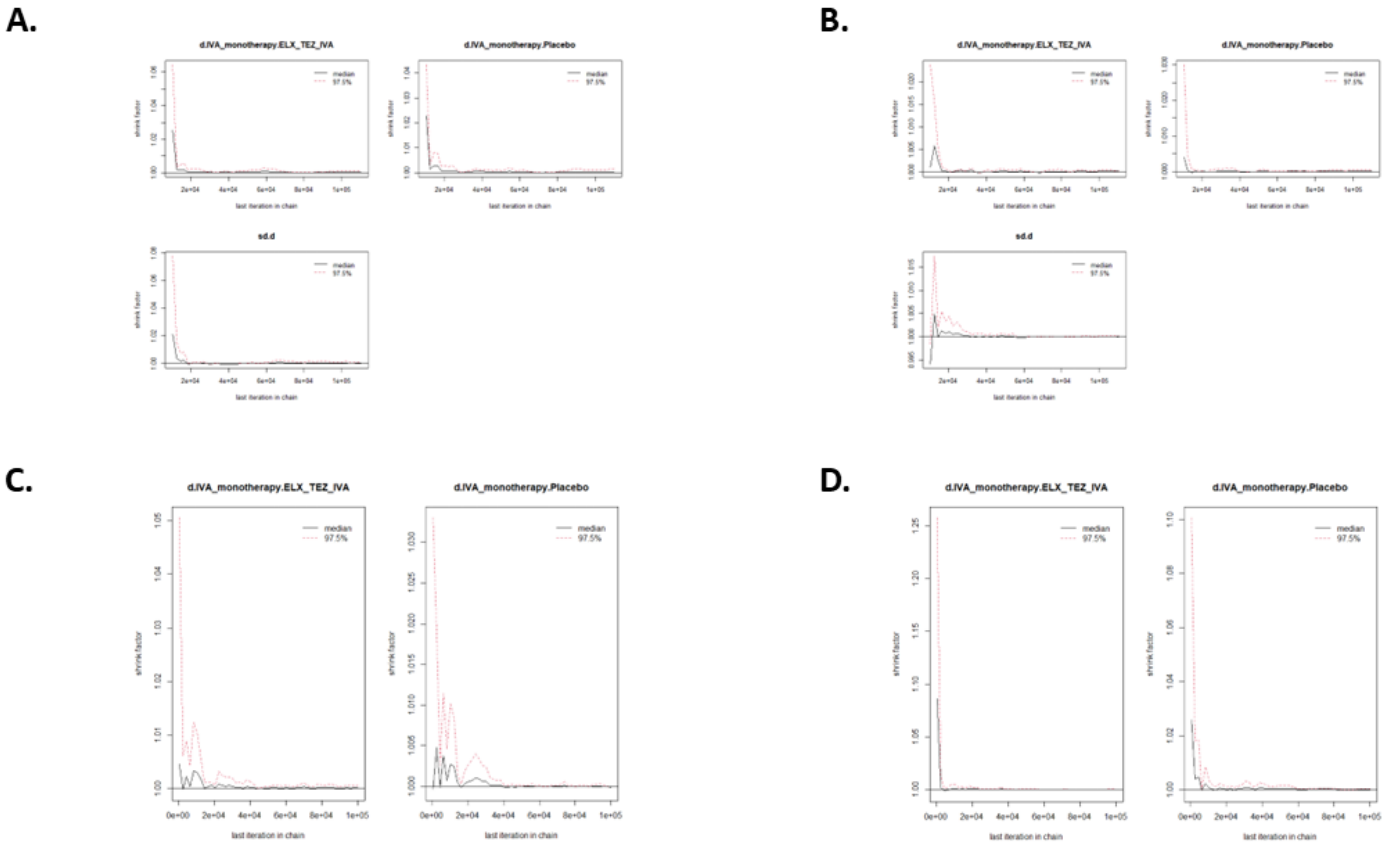
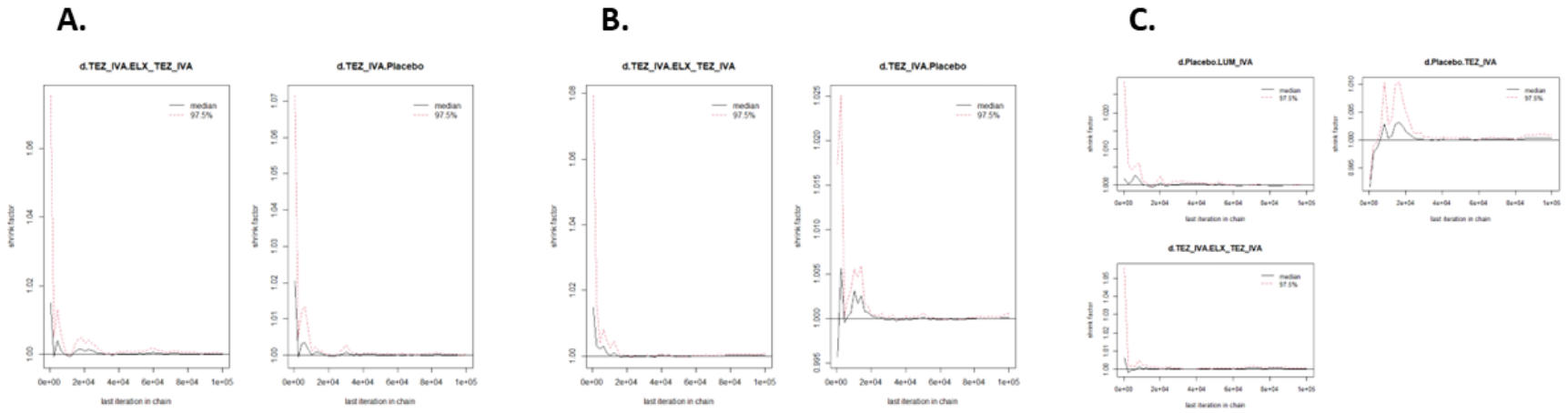


Figure 25. Brooks-Gelman-Rubin diagnostic plots for the F/RF fixed-effect ppFEV$_1$ analysis (A), fixed-effect weight-for-age z-score analysis (B), and for the F/F fixed-effect weight-for-age z-score analysis (C).



9.8 Age distribution of patients for each genotype in CF Registry 2018 to inform model population produced by the Company

	All patients aged ≥6 N (%)	Patients aged 6–12 N (%)	Patients aged >12 N (%)
F/F	4000 (100)	828 (20.7)	3172 (79.3)
F/MF	7304 (100)	1471 (20.1)	5833 (79.9)
F/RF	423 (100)	66 (15.6)	357 (84.4)
F/Gating	446 (100)	111 (24.9)	335* (75.1)
F/Gating (patients with *R117H* mutation)	545 (100)	88* (16.1)	457* (83.9)

Source: Cystic Fibrosis Trust 2018. Number of individuals eligible by genotype for CFTR modulating therapy in each nation of the UK, defined by centre attended[240]

* When figures were reported as <5 in the CF Registry, a value of 3 was assumed

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; N, number

9.9 Health economic established clinical management costs

Table 118. Weighted cost of inhaled antibiotics

Inhaled Antibiotics	All patients	Proportion taking drug of those on treatment	Cost per year	Weighted annual cost	Assumptions	Source
Tobramycin solution	638	0.167	£20,085.76	£3,363.44	300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution	BNF and eMIT drug costs CF Registry report 2018 number taking inhaled antibiotics. Drug dose from Tappenden 2023 and confirmed by clinical experts
Colistin	647	0.170	£4,733.64	£803.85	2 million units per day	
Promixin	797	0.209	£9,934.80	£2,078.22	1–2 million units 2–3 times a day, for specific advice on administration using nebulisers—consult product literature; maximum 6 million units per day.	
Aztreonam	645	0.169	£14,228.64	£2,408.79	75 mg 3 times a day for 28 days, doses to be administered at least 4 hours apart, subsequent courses repeated after 28-day interval without aztreonam nebuliser solution	
Colistimethate dry powder	448	0.118	£12,637.65	£1,486.00	1.66 million units twice daily.	
Tobramycin dry powder	635	0.167	£11,674.96	£1,945.83	112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder.	
				£12,086		

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Addendum- Fully incremental scenario analysis table

October 2023

1.1 EAG scenario analyses – fully incremental results with dominated treatments removed

1.1.1 F/F population

	Absolute			Incremental			ICER	NHB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Base case								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: LT ppFEV$_1$ decline absolute reduction								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: No separate PE treatment effect								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: PE treatment effect applied for extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No discontinuation beyond the extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Lower long-term CFTR modulator compliance								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: EQ-5D values from Acaster 2015*								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Pulmonary exacerbation disutility applied for 14 days								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: CFQ-R utility values from company model								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	

LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 15: 1.5% discount rate (costs and QALYs)†								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 16: No long-term ppFEV$_1$ decline in ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Severity modifier of 1.2 applied. ICER for ELX/TEZ/IVA when not applied is £[redacted]

† Severity modifier of 1.2 applied. ICER for ELX/TEZ/IVA when not applied is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

1.1.2 F/MF population

	Absolute			Incremental			ICER	NHB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Base case								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: LT ppFEV$_1$ decline absolute reduction								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds								

ECM	[redacted]							
IVA/TEZ/ELX	[redacted]							
Scenario 5: No separate PE treatment effect								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 6: PE treatment effect applied for extension study period								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 7: No discontinuation beyond the extension study period								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 8: Lower long-term CFTR modulator compliance								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 9: EQ-5D values from Acaster 2015*								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 10: Pulmonary exacerbation disutility applied for 14 days								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 11: CFQ-R utility values from company model								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 15: 1.5% discount rate (costs and QALYs)†								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							
Scenario 16: No long-term ppFEV$_1$ decline in ELX/TEZ/IVA								
ECM	[redacted]							
ELX/TEZ/IVA	[redacted]							

*Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

† Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

1.1.3 F/Gating population

	Absolute			Incremental			ICER	NHB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Base case								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: LT ppFEV$_1$ decline absolute reduction								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: No separate PE treatment effect								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: PE treatment effect applied for extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No discontinuation beyond the extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Lower long-term CFTR modulator compliance								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: EQ-5D values from Acaster 2015*								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Pulmonary exacerbation disutility applied for 14 days								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: CFQ-R utility values from company model								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 15: 1.5% discount rate (costs and QALYs)†								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 16: No long-term ppFEV$_1$ decline in ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

† Severity modifier of 1.2 applied. ICER without a severity modifier is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

1.1.4 F/RF population

	Absolute			Incremental			ICER	NHB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Base case								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: LT ppFEV$_1$ decline absolute reduction								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: LT ppFEV$_1$ decline of ELX/TEZ/IVA and TEZ/IVA from EAG lower bounds								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: No separate PE treatment effect								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: PE treatment effect applied for extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No discontinuation beyond the extension study period								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 8: Lower long-term CFTR modulator compliance								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: EQ-5D values from Acaster 2015								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Pulmonary exacerbation disutility applied for 14 days								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: CFQ-R utility values from company model								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Carer QoL utility increment for ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: 23% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 14: 40% reduction in ECM medication costs when on CFTR modulators								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 15: 1.5% discount rate (costs and QALYs)*								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 16: No long-term ppFEV$_1$ decline in ELX/TEZ/IVA								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Severity modifier of 1.2 applied. ICER without severity modifier for ELX/TEZ/IVA is £[redacted]

Abbreviations: ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; LUM/IVA, Lumacaftor/ivacaftor; TEZ/IVA, Tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; EQ-5D, Euroqol 5-dimension; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; LT, long-term; FA, final analysis; CF, cystic fibrosis

1.2 QALY shortfall estimates using EAG base-case with 1.5% discount rate

	F/F	F/MF	F/Gating	F/RF
Mean age (years)	20.15	20.91	20.71	28.61
Female (%)	51	51	52	55
QALYs with CF	[redacted]	[redacted]	[redacted]	[redacted]
QALYs without CF	34.91	34.51	34.51	31.11
Abs. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
Prop. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1.2	1.2	1.2	1.2

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; CF, cystic fibrosis; QALY, quality adjusted life year

1.3 Additional EAG model validation

The EAG noted the concerns raised during the stakeholder engagement process about the reliability of the EAG's model. As an additional quality assurance step, the EAG used the Company's preferred parameter estimates and assumptions for ELX/TEZ/IVA within the EAG model. This could only be compared to the Company's originally submitted model with list prices and age of patients aged 6+ as the EAG had not received an updated model following stakeholder engagement. As the EAG model was not built to be an exact replicate of the Company's model, it would be expected that there would be some differences that cannot be accounted for in how the model has been set up. The results shown below compare the Company's preferences and inputs used in the EAG model versus the Company's own model results. As shown, although there are some differences in costs in both the ECM and ELX/TEZ/IVA arms between the two models, the results are largely similar and resulting ICERs broadly comparable, providing evidence of reliability of the EAG model.

Table 1. Comparison of company model results for ELX/TEZ/IVA (originally submitted, list price) versus Company preferences and inputs applied in EAG model

	F/F population		F/MF population		F/gating population		F/RF population	
	EAG model with company preferences	Company model	EAG model with company preferences	Company model	EAG model with company preferences	Company model	EAG model with company preferences	Company model
ECM LYs*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA LYS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA QALYS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (no severity modifier)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Undiscounted

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; EAG, evidence review group; QALY, quality adjusted life year; ECM, established clinical management; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LY, life years