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

MTA Report

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All commercial in confidence data and information are highlighted in [redacted] All academic in confidence data and information are highlighted in [redacted]

Please note that the analyses in this report are based on list prices and do not take into account any confidential pricing arrangements. This means that the cost-effectiveness results are for illustration only. For the avoidance of doubt, they will not underpin the committee decision-making.

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 were £3,757,021; £2,290,917 and £510,269 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 £1,157,437 and £1,217,660, 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 of £818,427 compared to the TEZ/IVA ICER of £1,885,946.

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.

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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 12+ 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 2020 2019, and currently 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: 10.63% 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: 37.70% 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 £3,757,021; £2,290,917 and £510,269 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 £1,157,437 and £1,217,660, 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 £818,427 compared to the TEZ/IVA ICER of £1,885,946.

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: 2,220

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.

Plain English Summary Word Count: 226

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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

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 colistimethate 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.

**[redacted]

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 83 (MEDLINE: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations) and Table 84 (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 87 of Appendix 9.1.2, and further details of the Cystic Fibrosis Trials Register are presented in Appendix 9.1.2 (including Table 85 and Table 86). 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 87 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 92 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 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.

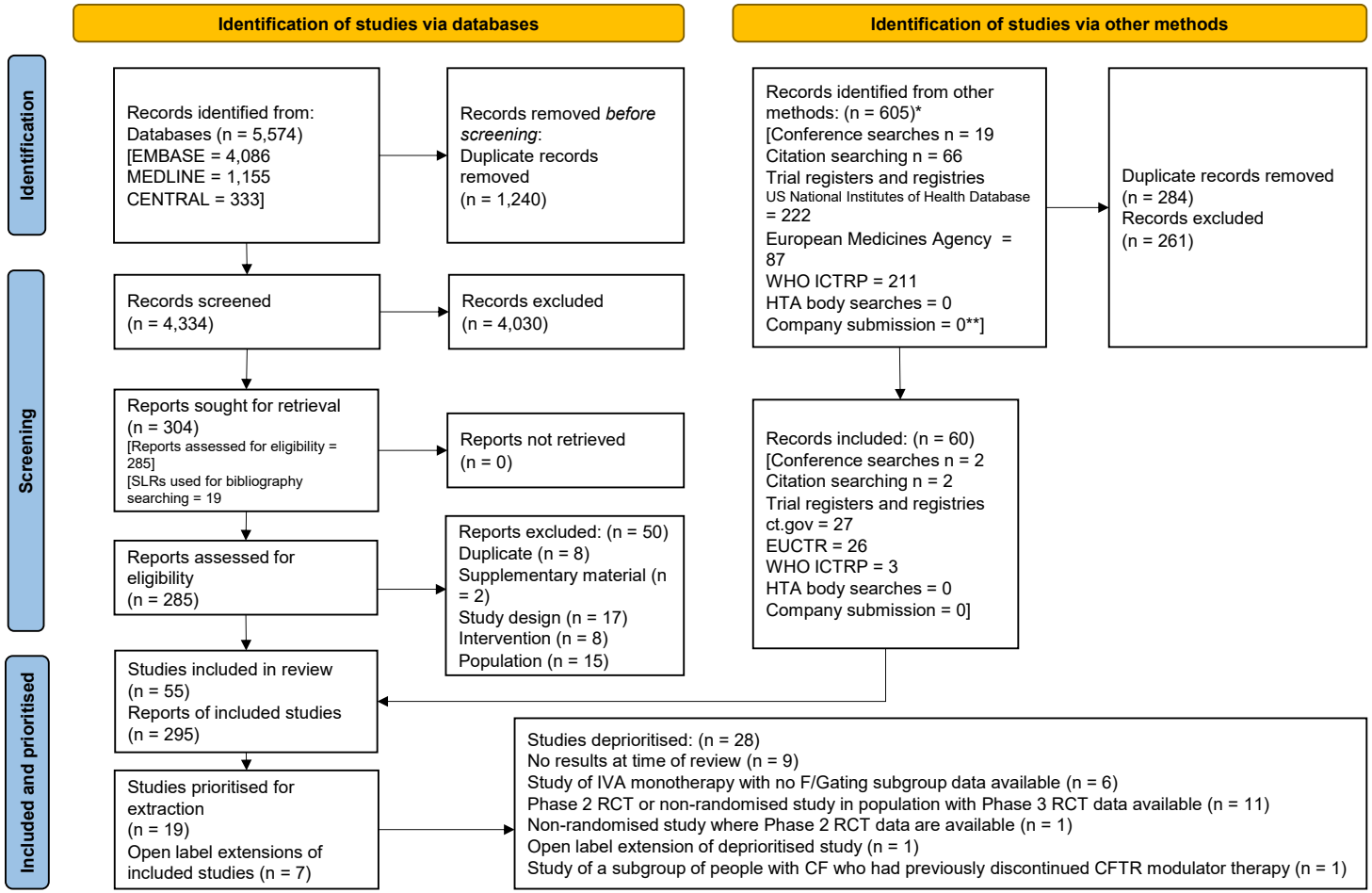
3.2 Results

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 110 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 the update to Southern *et al.* Cochrane review were screened but not included in this figure.

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 110 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) • IVA (150 mg qd)	Phase 3, randomised	Efficacy: 8 Weeks Safety: 12 Weeks

				• 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 92 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 93, Table 94 and Table 95 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].[155]

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 93, Table 94 and Table 95 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 96 to Table 105 in Appendix 9.3. 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 96), 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 (11.96, 95% CI: 10.97 to 12.94) 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 4.1 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 106 and Table 107), 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)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	2 (1.09)	2 (1.10)	2 (1.08)	2 (1.07)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	6 (3.26)	3 (1.65)	7 (3.76)	2 (1.07)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	4 (2.17)	1 (0.55)	3 (1.61)	1 (0.53)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mood swings	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal ideation	0	0	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed mood	0	3 (1.65)	NR	NR	[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 anchored 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, seven (6.8%) participants in the LUM/IVA arm experienced a pulmonary exacerbation requiring IV antibiotics through Week 24, compared to 6 (5.9%) participants in the placebo arm. In Zemanick 2022, one (1.5%) 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.

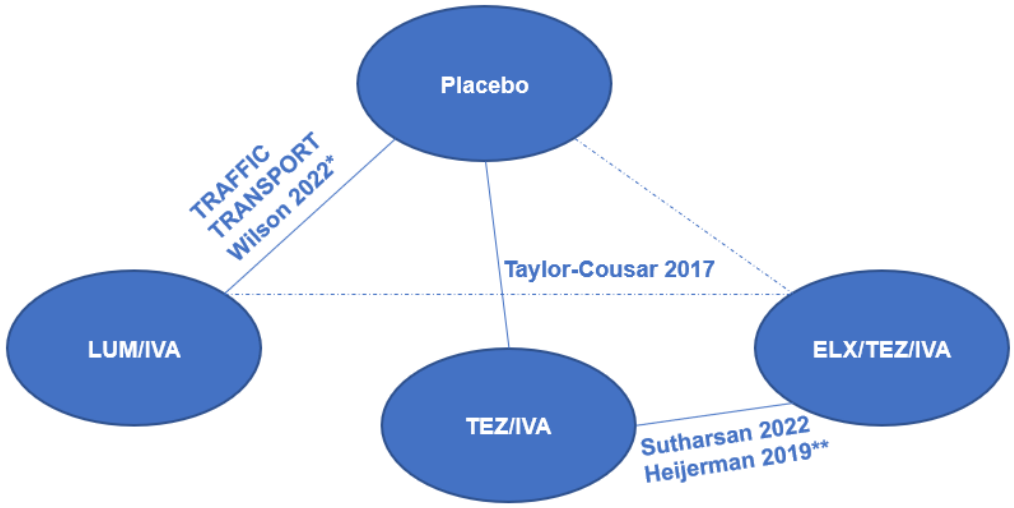
In the economic model, the Company does not apply a direct treatment effect on pulmonary exacerbations requiring IV antibiotics for people aged <12 years, although an indirect effect through $ppFEV_1$ is observed (section 4.2.1.5.3). The EAG considers this a reasonable, although potentially

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 101) and a similar disease severity indicated by a similar baseline ppFEV$_1$ and CFQ-R RD score (Appendix Table 97 and Table 98). 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	–11.37 (–13.70 to –9.03)	–14.20 (–16.31 to –12.07)	–10.20 (–12.16 to –8.25)
LUM/IVA	11.37 (9.03 to 13.70)	LUM/IVA	–2.83 (–3.81 to –1.84)	1.17 (–0.13 to 2.46)
Placebo	14.20 (12.07 to 16.31)	2.83 (1.84 to 3.81)	Placebo	4.00 (3.15 to 4.85)
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.

Table 37. Results of the EAG sensitivity NMA for absolute change from baseline in $ppFEV_1$ through Week 24 in the F/F 12+ years population.

ppFEV1: F/F 12+ years: EAG sensitivity analysis	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA
ELX/TEZ/IVA	ELX/TEZ/IVA	–11.29 (–13.32 to –9.26)	–14.11 (–15.90 to –12.35)	–10.11 (–11.68 to –8.57)
LUM/IVA	11.29 (9.26 to 13.32)	LUM/IVA	–2.83 (–3.82 to –1.84)	1.17 (–0.14 to 2.48)
Placebo	14.11 (12.35 to 15.90)	2.83 (1.84 to 3.82)	Placebo	4.00 (3.15 to 4.85)
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; IVA: ivacaftor; NMA: network meta-analysis; $ppFEV_1$: percent predicted forced expiratory volume in one second: TEZ: tezacaftor.

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]

[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	[redacted]	5.45	16.42

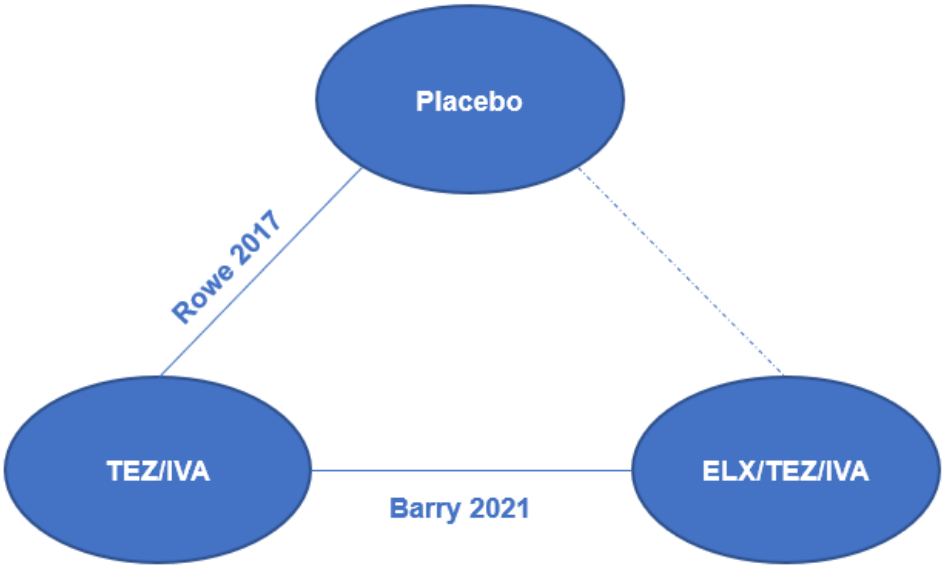
*Reported at Week 4

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 101). 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 100). 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: [redacted]) with the rate ratio estimated in the F/F population for TEZ/IVA vs placebo (Taylor-Cousar 2017: [redacted]).

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 99). 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.

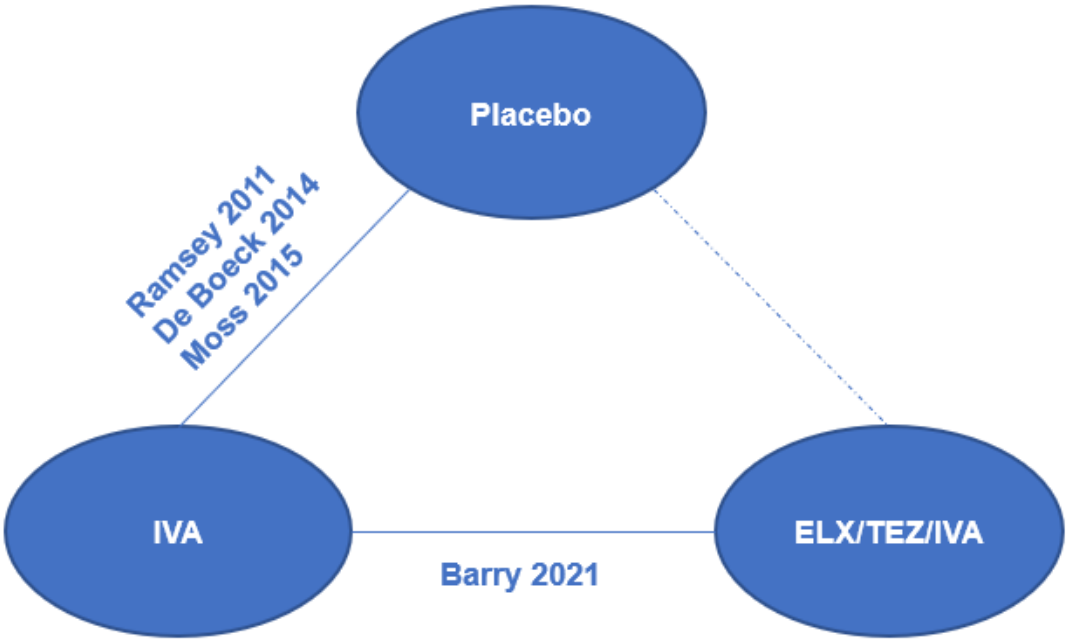
Table 40. The distribution of non-*F508del* mutations in study subgroups included in the F/Gating NMA.

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	FE: –5.80 (–8.06 to –3.53) 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	FE: –0.01 (–0.08 to 0.06) 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 93) 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 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." 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 0.77, 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 11.69;
- 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 of the IVA/TEZ/ELX treatment impact 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 demonstrated 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: [redacted][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, 181] 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 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
Newsome 2022[178]	+0.49 (95% CI: −0.15, 1.13)	• Measured from IVA treated individuals with gating or other IVA-eligible mutations • Analysis of UK CF Registry data • Unaffected by COVID-19-related confounding • Corrected for both historical and contemporaneous negative control outcomes • Unbiased estimate of IVA monotherapy treatment effect • Potentially conservative estimate of ELX/TEZ/IVA treatment effect • **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 ppFEV1 of +0.138 (calculated as 0.282*0.49), 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	+0.138	• 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 from baseline ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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.

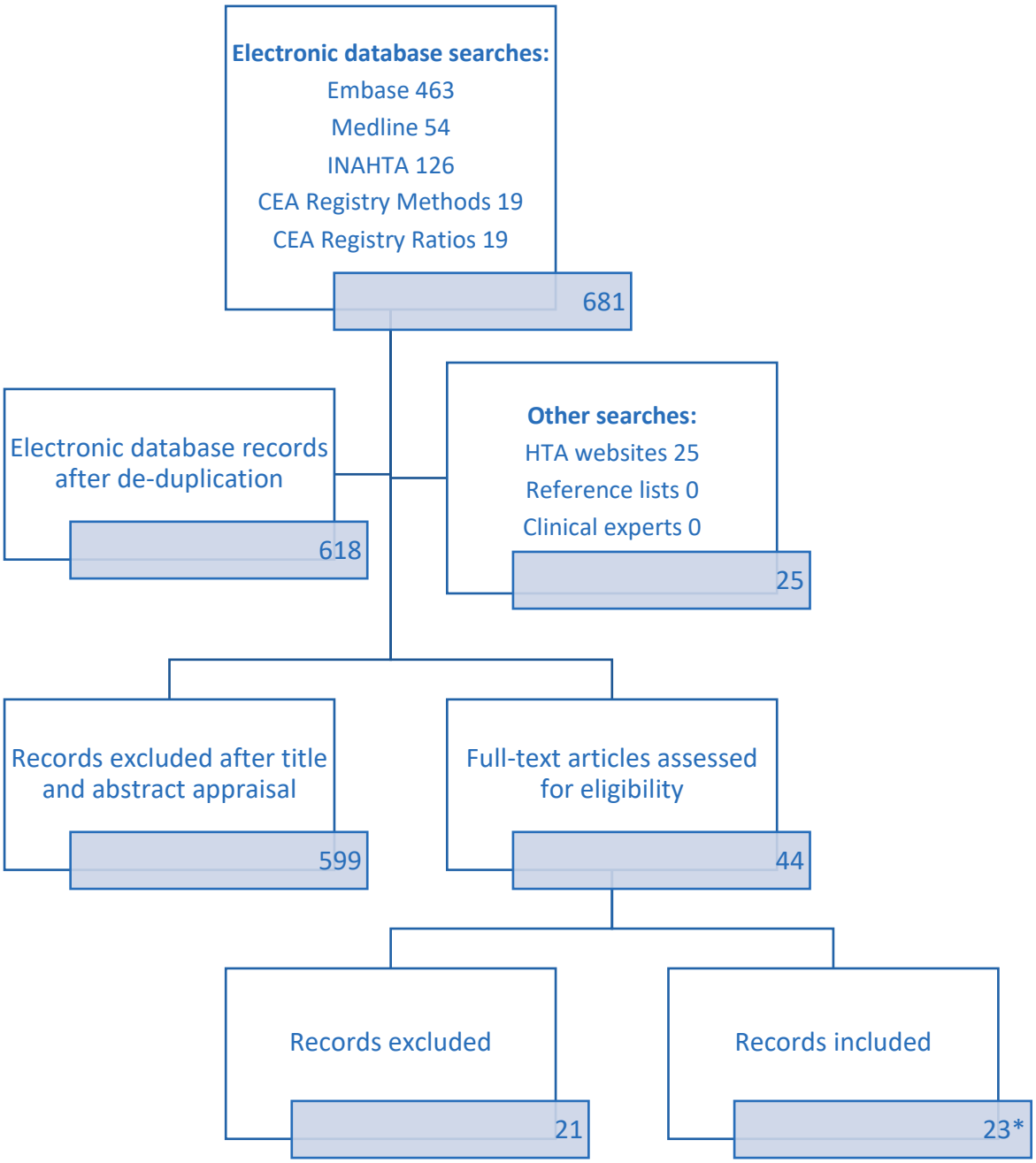
	• Direct utility elicitation tools (TTO, standard gamble, rating scale) • Generic health-related quality of life questionnaires (e.g. SF-36, SF-12). • CFQ	
Study design	• Studies reporting original HRQoL data or mapping studies • UK cost effectiveness studies	• Commentaries and letters; • Reviews (systematic 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/Tezacafor/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

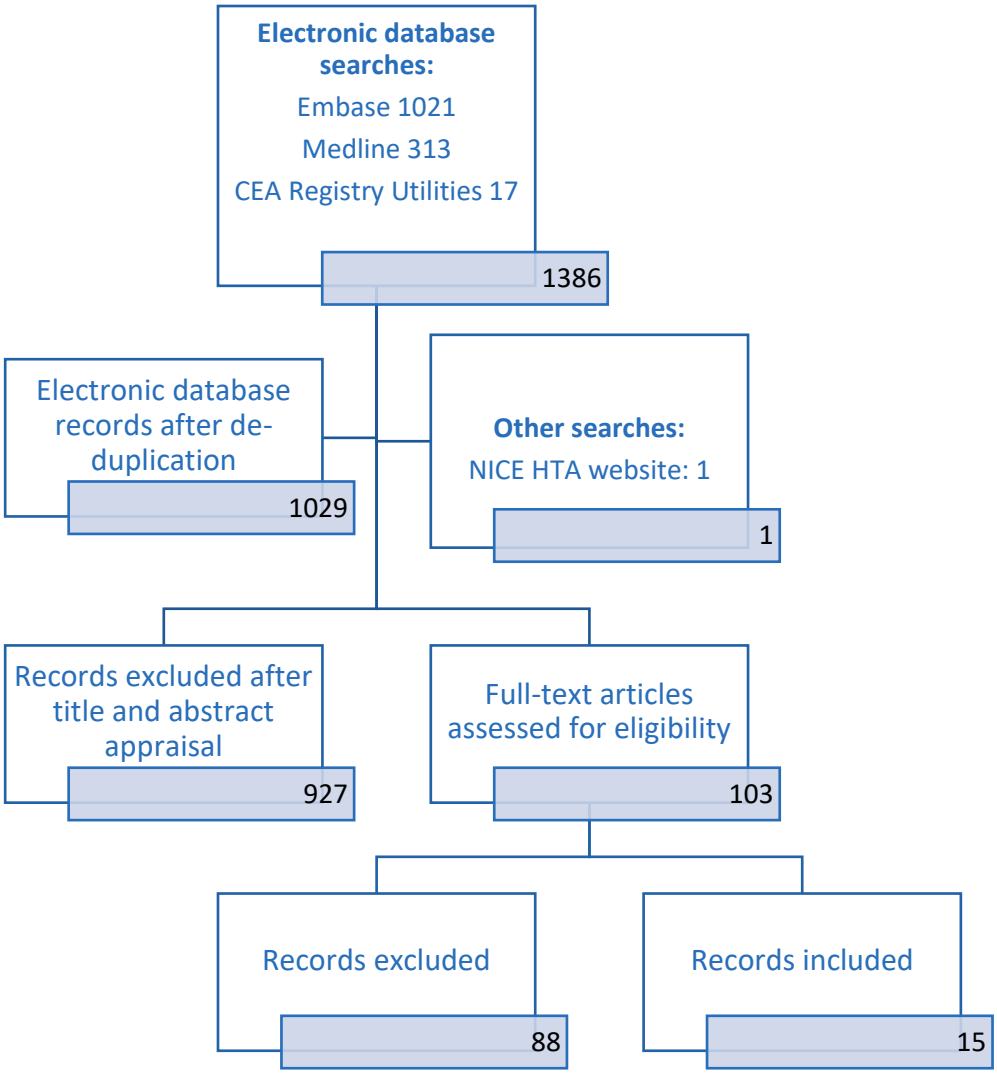
	PBAC 2019a (TEZ/IVA)[208]	CDR 2018 (LUM/IVA)[201]	CDR 2016 (LUM/IVA)[200]	NICE TA786 2016 (LUM/IVA)[202]	CDR, 2022[111]; CDR 2021[210] (ELX/TEZ/IVA and LUM/IVA)
$ppFEV_1$	0% decline in $ppFEV_1$ relative to ECM following the trial period, i.e. decline assumed equal to that of ECM instead of 42% applied 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.

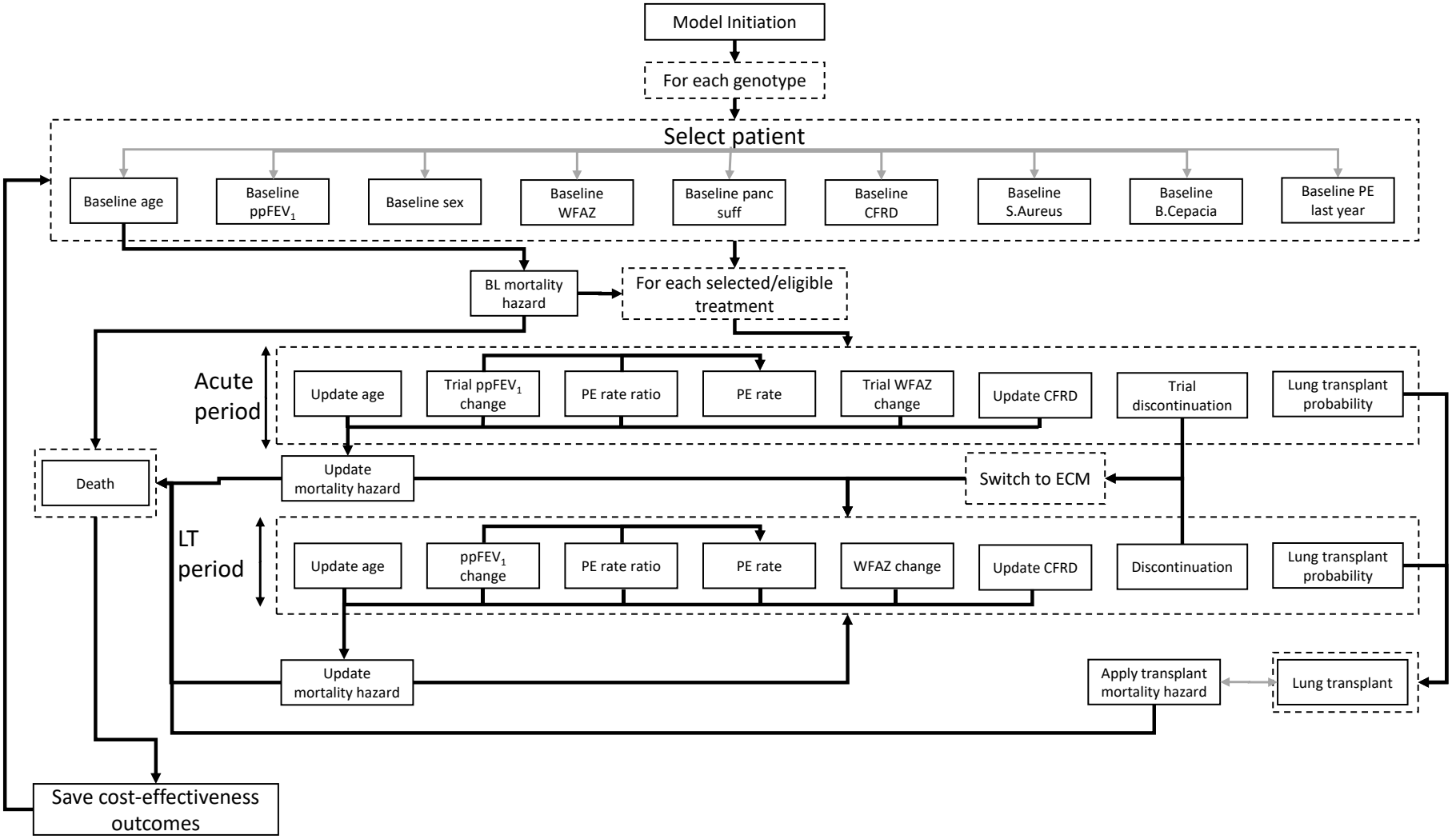
- Based on the relevant trial data, patient characteristics are defined for each individual.
- An age specific mortality hazard is assigned to the patient taken from the reference population survival curves from Keogh *et al.* 2018[236] in the first model cycle, based on patient starting age.
- Patient 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 ran 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. 2000 patients were ran 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.

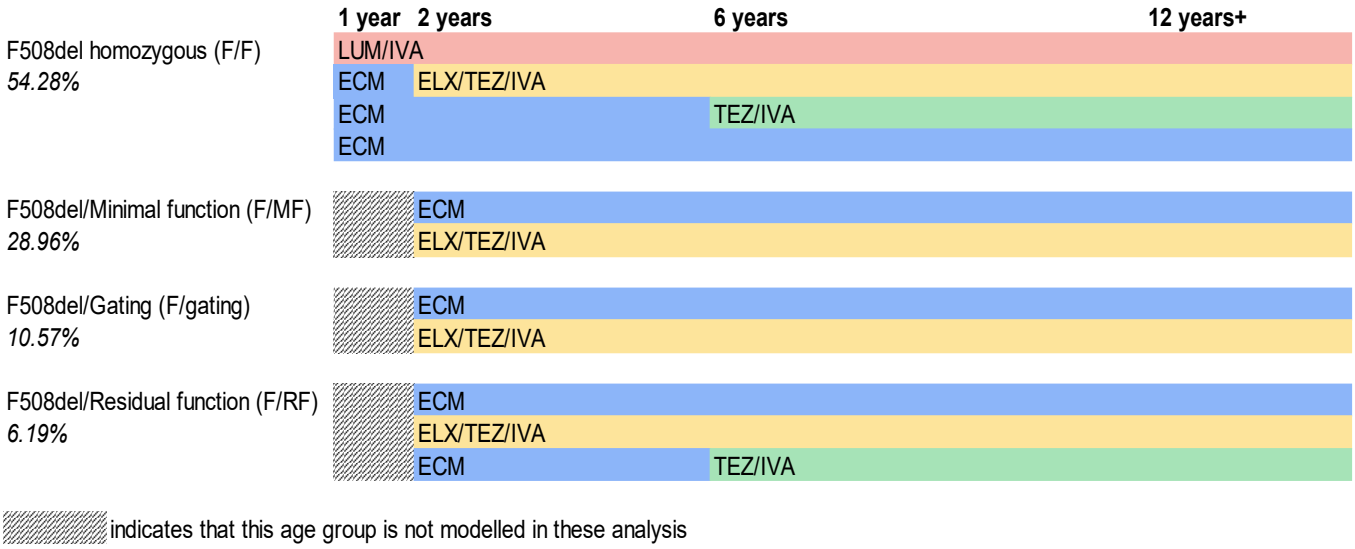
1. F/F population: ECM vs LUM/IVA vs ELX/TEZ/IVA vs TEZ/IVA. Patients will receive LUM/IVA from age 1, in line with the most recent marketing authorisation. In the ELX/TEZ/IVA treatment arm, patients aged 1-2 will receive ECM before switching to ELX/TEZ/IVA aged 2, based on expected marketing authorisation. 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. A cap is also applied in the model for the F/RF group to ensure that if the value from the applied digitised curve is lower than the value from the Sawicki 2022[3] linear model in the F/RF genotype at a particular age, then the rate of decline from the linear model for the F/RF genotype is applied instead.

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 note that applying an estimate from data based on ivacaftor monotherapy may be conservative; however, as this treatment effect is applied for the lifetime of the model the EAG believe it is the most reasonable assumption based on the data available and does not include any potential bias due to COVID-19 as would be seen with the ELX/TEZ/IVA long-term data.

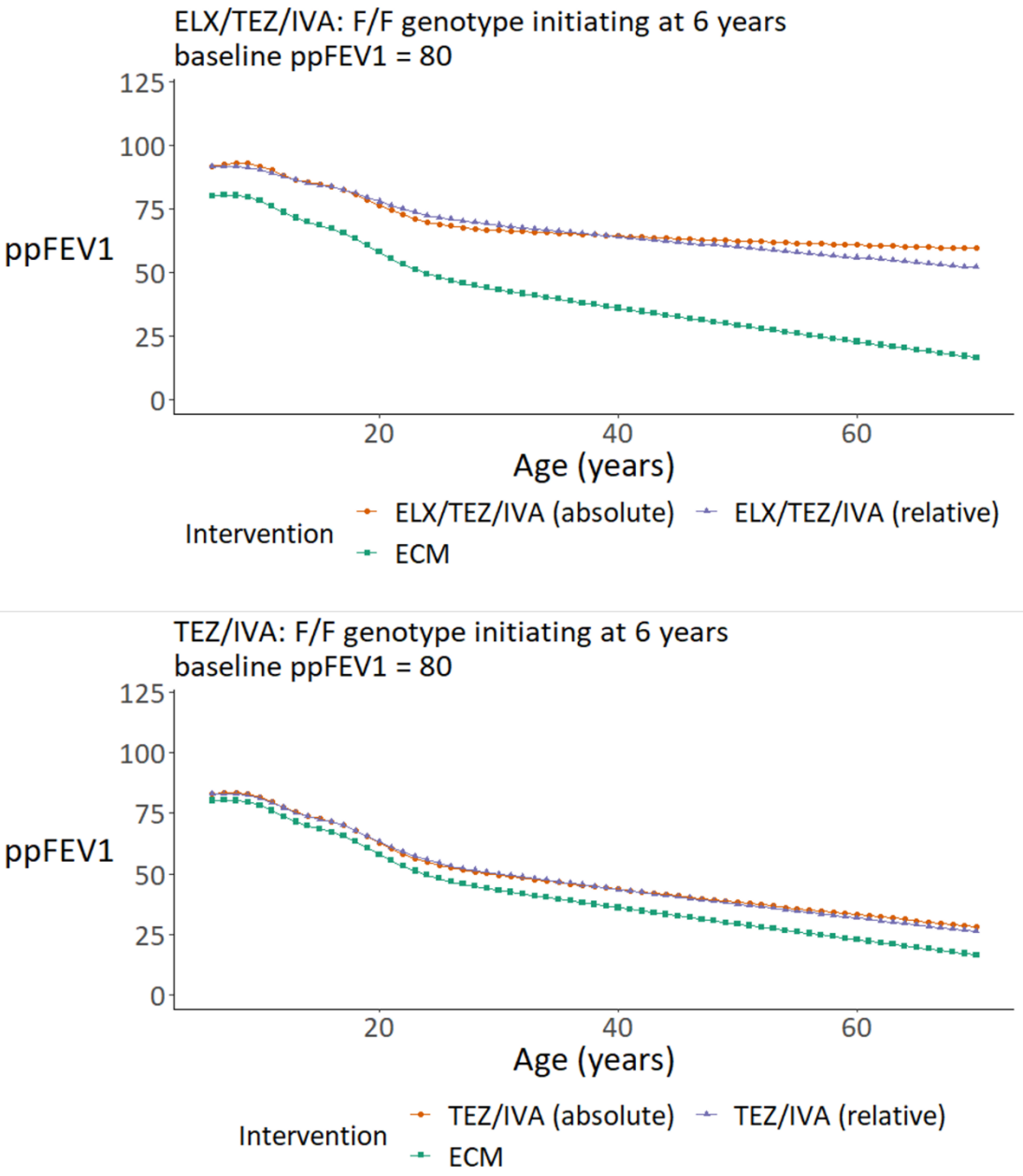
As noted in Section 3.2.2.6, the EAG does not consider the long-term data available for TEZ/IVA and LUM/IVA to provide a reliable estimate of the treatment effect in the post-acute period. For LUM/IVA, the EAG notes that no robust evidence has been presented or identified to suggest that LUM/IVA causes 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 10.63% 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 directly applying the Newsome 2022 estimate of IVA for ELX/TEZ/IVA (+0.49 per year slower decline than ECM), and scaled this estimate for TEZ/IVA (+0.138 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 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 of 0.49 for ELX/TEZ/IVA corresponds to a markedly reduced relative reduction at higher ages.

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 substantially lower than that observed for LUM/IVA, with an absolute increase of 0.02. As no change beyond the acute increase is assumed over the patient's lifetime in the model, only applying an acute increase of 0.02 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	0.025	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/MF	24	0.025	Study 445-111, Phase 3 non-randomised trial of F/F and F/MF genotype patients aged 2–5
F/Gating	24	0.025	Assumed equal to F/F and F/MF

F/RF	24	0.025	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.

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]. 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. In the Company's model the inclusion had a negligible impact on the ICER (≈ £250 in the F/F population) and therefore carer HRQoL was not included in the EAG analyses.

4.2.1.11.1 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.

4.2.1.11.2 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.

4.2.1.11.3 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).

4.2.1.12 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.

4.2.1.12.1 CFTR modulator acquisition costs

The drug acquisition costs included in the model 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.

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]

	[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]
	[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.

** [redacted]

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

4.2.1.12.2 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 latest drug costs were sourced from the BNF.[252]

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 2021/21.[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	£13,908.40	0.49	0.59	0.7	£6,815.12	£8,205.96	£9,735.88	CF Registry 2018 report, see Appendix 9.9 for further detail
Dornase alfa	£6,044.04	0.73	0.8	0.8	£4,412.15	£4,835.23	£4,835.23	Tappenden 2023, Pulmozyme 2.5mg; daily dose: 2.5mg
Hypertonic saline solution	£86.88	0.37	0.4	0.42	£32.14	£34.75	£36.49	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	£76.96	0.31	0.27	0.22	£23.86	£20.78	£16.93	Tappenden 2023, Flucloxacillin 250mg or 500mg capsules; daily dose:1g
					£11,323	**£13,155**	**£14,695**	

Abbreviations: CF, cystic fibrosis; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; g, grams; mg, milligrams; ml, millilitre

4.2.1.12.3 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

4.2.1.12.4 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				

4.2.1.12.5 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		

4.2.1.13 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 37.7% 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 10.63% 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 = 37.7% TEZ/IVA = 10.63% 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 76 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.

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]	-	-	-	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,757,021	-54.97
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,021,429	-88.55
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,078,934	-137.11
F/MF								
ECM	[redacted]	[redacted]	[redacted]	-		-	-	-
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,157,437	-136
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	-		-	-	-
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,217,660	-128
F/RF								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,885,946	-87.55
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,436,940	-114.55

*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]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,757,021
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,290,917
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£510,269
F/MF							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,157,437
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[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 survival (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

[redacted]

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	9.73	9.46	9.73	9.30
Proportional shortfall	0.43	0.42	0.43	0.44
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

Probabilistic results of the base-case analysis will be provided in a separate addendum.

4.2.2.3 One-way sensitivity analysis

One-way deterministic sensitivity analysis (DSA) results will be provided in a separate addendum.

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 81.

Table 81. EAG scenario analyses

	Scenario analysis	Base case
Clinical parameters		
1	Long-term decline in ppFEV$_1$ modelled as an absolute reduction compared to ECM	Long-term decline in ppFEV$_1$ modelled as a relative reduction in decline compared to ECM
2	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 ([redacted] and LUM/IVA ([redacted]) from the Company models	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 37.7%, scaled for TEZ/IVA (10.67% 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)
3	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	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 37.7%, scaled for TEZ/IVA (10.67% 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)
4	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)	Both an indirect effect (through ppFEV$_1$) and direct treatment effect on pulmonary exacerbations applied
5	Direct treatment effect on pulmonary exacerbations applied for the observed period equal to the long-term extension studies	Direct treatment effect on pulmonary exacerbations applied for the trial period only
6	No discontinuations beyond the observed extension study period (96 weeks or 144 weeks) as applied in the Company's model	No discontinuations beyond 5 years on treatment
HRQoL		
7	Health state utility values taken from Acaster 2015 (EQ-5D). Same as those applied in Company scenario analysis	Health state utility values (EQ-5D-3L) sourced from the LUM/IVA clinical trial
8	Pulmonary exacerbation disutility applied for 14 days	Pulmonary exacerbation disutility applied for 30 days

Abbreviations: F/F, *F508del* homozygous; MF, minimal function; RF, residual function; CF, cystic fibrosis; QALY, quality adjusted life year

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]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,757,021
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,290,917
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£510,269
Scenario 1: LT ppFEV$_1$ decline absolute reduction							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,757,021
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,096,697
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£494,656
Scenario 2: Company's estimates of LT ppFEV$_1$ decline on modulator treatments							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,109,506
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,629,027
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£569,306
Scenario 3: LT ppFEV$_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,757,021
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,290,917
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£445,891
Scenario 4: No separate PE treatment effect							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,765,111
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,289,466
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£510,348
Scenario 5: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,708,555
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,290,343
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£509,822
Scenario 6: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,776,404
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,273,837
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£511,668
Scenario 7: EQ-5D values from Acaster 2015							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-

LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,125,528
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,409,324
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£568,943
Scenario 8: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,764,160
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,294,692
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£511,058

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]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,157,437
Scenario 1: LT $ppFEV_1$ decline absolute reduction							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,100,200
Scenario 2: Company's estimates of LT $ppFEV_1$ decline on modulator treatments							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£994,703
Scenario 3: LT $ppFEV_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£960,714
Scenario 4: No separate PE treatment effect							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,157,815
Scenario 5: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,156,590
Scenario 6: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,157,510
Scenario 7: EQ-5D values from Acaster 2015							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,273,093
Scenario 8: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,159,759

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]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,217,660
Scenario 1: LT $ppFEV_1$ decline absolute reduction							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,145,961
Scenario 2: Company's estimates of LT $ppFEV_1$ decline on modulator treatments							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,031,049
Scenario 3: LT $ppFEV_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£989,864
Scenario 4: No separate PE treatment effect							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,217,822
Scenario 5: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,216,632
Scenario 6: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,217,744
Scenario 7: EQ-5D values from Acaster 2015							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,351,241
Scenario 8: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,220,315

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]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,885,946
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£818,427
Scenario 1: LT $ppFEV_1$ decline absolute reduction							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,760,086
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£683,888
Scenario 2: Company's estimates of LT $ppFEV_1$ decline on modulator treatments							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,153,559
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,092,091
Scenario 3: LT $ppFEV_1$ decline of ELX/TEZ/IVA from CF Trust FA							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,885,946
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£570,561
Scenario 4: No separate PE treatment effect							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,886,328
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£818,596
Scenario 5: PE treatment effect applied for extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,883,408
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£817,100
Scenario 6: No discontinuation beyond the extension study period							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,880,990
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£817,512
Scenario 7: EQ-5D values from Acaster 2015							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,139,002

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£892,479
Scenario 8: Pulmonary exacerbation disutility applied for 14 days							
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,886,649
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£820,562

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 not 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). 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. 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 due to the high acquisition costs of treatment.

Table 82. 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]	-	-	-	-	
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,138,713	£2,615,594
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,384,569	£1,987,141
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£875,875	£729,896
F/MF								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£927,245	£772,705
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£988,961	£824,134
F/RF								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,658,937	£1,382,448
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,194,932	£995,776

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 83. Additional exploratory scenario analyses, fully incremental analysis results

Population	Absolute			Incremental			ICER (no severity weighting applied)	ICER (severity weighting applied
	Costs	QALY	LY	Costs	QALY	LY		
F/F genotype								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,138,713	£2,615,594
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,740,393	£1,450,328
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£455,228	£379,357
F/MF								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£927,245	£722,705
F/Gating								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£988,961	£824,134
F/RF								
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	-
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,658,937	£1,382,448
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£669,678	£558,065

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

4.2.2.5 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 list prices for all drugs.

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 £510,269. LUM/IVA was the least cost-effective with an ICER of £3,757,021. 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 £1,157,437 and £1,217,660, 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 £818,427 compared to the TEZ/IVA ICER of £1,885,946.

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 by a small amount, however the EAG does not consider applying an absolute reduction of 0.49 (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 0.49, (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 to be more transportable to these individuals.

Across all populations, the assumptions on the long-term effectiveness of CFTR modulator treatments on $ppFEV_1$ decline had the greatest impact. The EAG considers the two scenarios changing the long-term effectiveness assumptions (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 [redacted] for LUM/IVA, [redacted] 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.

Both scenarios 4 and 5 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 (+~£7000). 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 £48,466. 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 a 1.29% 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 6 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 did not have a substantial impact on any of the ICERs across all genotypes.

Scenario 7 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. 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 8) did not have a substantial impact on any of the ICERs.

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], [redacted], [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 33%. 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 £3,757,021; £2,290,917 and £510,269 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 £1,157,437 and £1,217,660, 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 £818,427 compared to the TEZ/IVA ICER of £1,885,946.

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, 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 £500,000 to £3.7 million. 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. 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.

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9 Appendices

9.1 Literature search strategies

9.1.1 EAG database searches

Table 84. 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 85. 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 85 and Table 86. 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 86. 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 87. 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 88. 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 89. 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 90. 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 90.

Table 91. 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 92. 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 93. 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 [redacted]	Low [redacted]	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 [redacted]	Low [redacted]	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 [redacted]	Low [redacted]	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 [redacted]	Low [redacted]	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 [redacted]	Low [redacted]	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

	[redacted]					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 [redacted]	Low [redacted]	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 	Low 	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 94. 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 [redacted]	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 [redacted]	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 [redacted]	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 95. 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	[redacted] 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 96. 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 [redacted] 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 97. 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 98. 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	51.2	51.2	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, %										
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 99. 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%)	NR	NR	NR	NR
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 100. 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 101. 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 102. 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 103. 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 104. 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]		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 105. 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	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	As efficacy outcome	As 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]		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]		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 106. 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						
CFB sweat chloride						
Difference from reference						
CFB ppFEV1						
Difference from reference						
Pulmonary exacerbations reported						
N exacerbations						
Annualised event rate						
Difference from reference						
CFB BMI						
Difference from reference						
CFB BMI-z-score						

Difference from reference						
CFB Weight						
Difference from reference						
CFB Weight-z-score						
Difference from reference						
CFB CFQ-R Respiratory Domain						

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 107. 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	75	66	60	61	132	126	55	52	202	201	87	88
Participants with AEs	74	65	48	57	88	83	33	32	188	193	77	81

Participants with serious AEs	2	1	4	9	5	11	2	1	28	42	5	14
Alanine aminotransferase increased	8	7	3	5	8	0	[redacted]	[redacted]	20	7	6	1
Aspartate aminotransferase increased	4	[redacted]	[redacted]	[redacted]	8	0	[redacted]	[redacted]	19	4	5	0
Gamma-glutamyltransferase increased	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased bilirubin	NR	[redacted]	NR	NR	[redacted]	[redacted]	NR	NR	10	2	[redacted]	[redacted]
Hepatic enzyme increased	NR	[redacted]	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash events	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	NR	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 108. 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 109. 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. L., Lee, T., Gray, R., Vermeulen, F., Vanderhelst, E., Robinson, P. J., Smith, D. J., Mulrennan, S. A., Clements, B. S., Wark, P.	10.1016/S2213-2600%2821%2900454-9
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	2019	US National Institutes of Health Database (ClinicalTrials.gov) Record	https://clinicaltrials.gov/ct2/show/NCT04058353

F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)			
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	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

and a minimal function mutation: Results from a phase 3 clinical study			
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.,	10.1016/S0140-6736%2819%2932597-8

		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.	
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	2018	EU Clinical Trials Register Record	https://www.clinicaltrialsregister.eu/ctr-

Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age			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	Pneumologie, 2018	Fischer, R., Rowe, S. M., Davies, J. C., Nair, N., Han, L., Lekstrom-Himes, J.	10.1055/s-0037-1619210

randomized, double-blind, placebo-controlled, crossover phase 3 study			
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	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

F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation			
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	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

antibiotics, in patients with CF treated with lumacaftor in combination with ivacaftor			
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,	10.1016/S2213-2600%2817%2930215-1

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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 Care Medicine, 2022	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
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 heterozygous for F508del-CFTR and a residual function mutation	Pediatric Pulmonology, 2018	Ingenito, E., Nair, N., Yi, B., Lekstrom-Himes, J., Elborn, J., Rowe, S. M.	10.1002/ppul.24152
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 110. 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 111. 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) Lung transplant: assumed that 11.3% of patients with a $ppFEV_1$ <30% would receive a lung transplant.	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+ 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 Discontinuation rates taken from the TRAFFIC and	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

		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 favouring LUM/IVA + SoC based on short term observational studies	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

		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. Treatment compliance of 80% assumed (resulting in cost reduction only)	**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

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)	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)

			47% male 69% on a CFTR modulator, Mean ppFEV1 = 66% (SD 20.3)		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 16. 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).

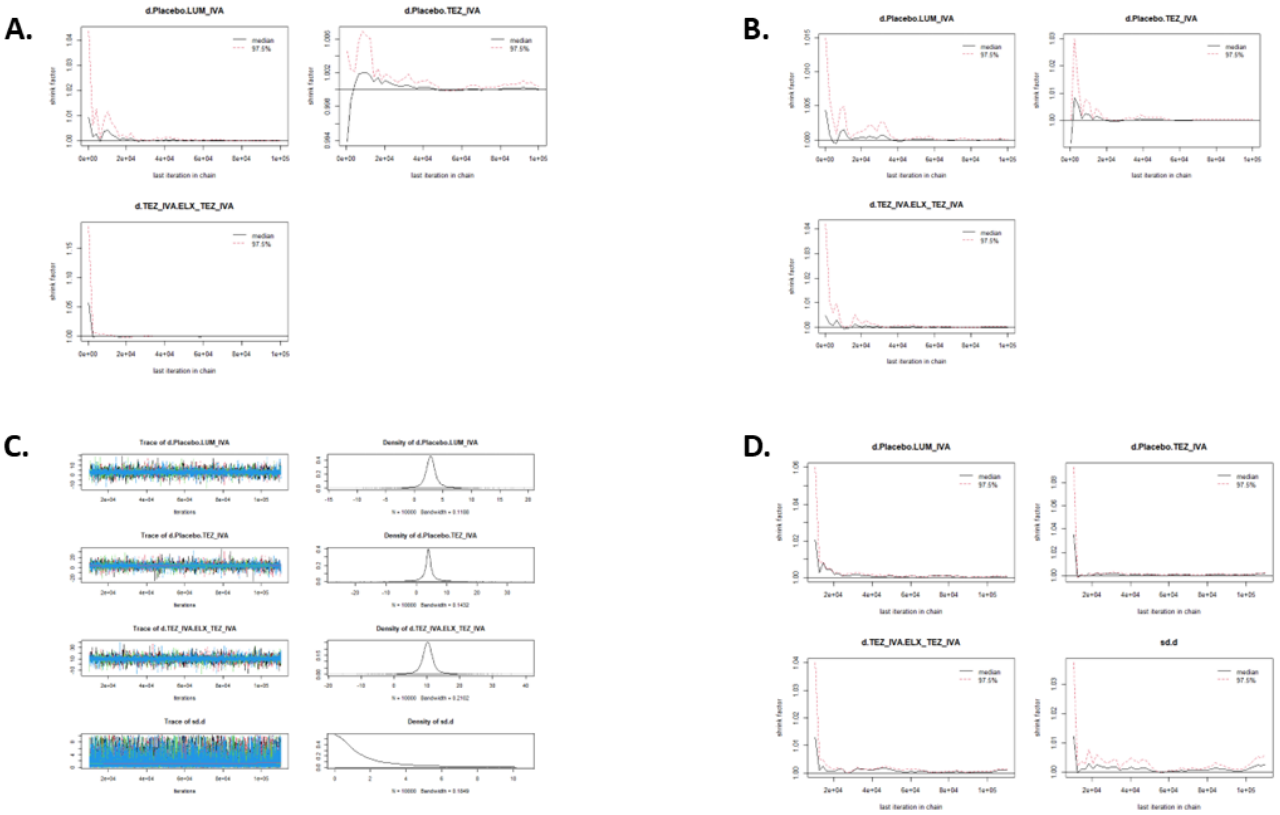
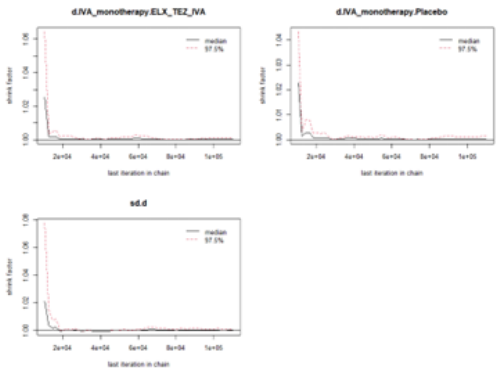
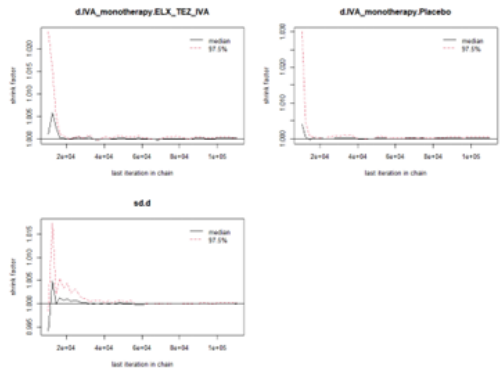


Figure 17. Brooks-Gelman-Rubin diagnostic plots for the F/Gating random effects ppFEV$_1$ analysis (A), random effects weight-for-age z-score analysis (B), fixed-effect ppFEV$_1$ analysis (C) and fixed-effect weight-for-age z-score analysis (D).

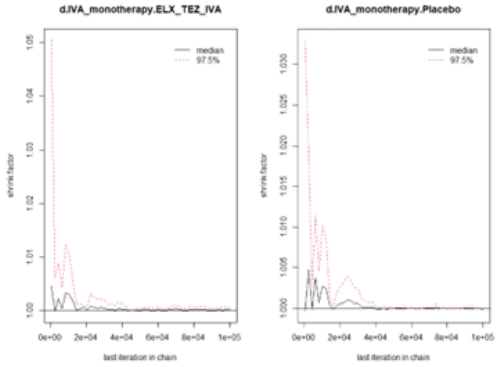
A.



B.



C.



D.

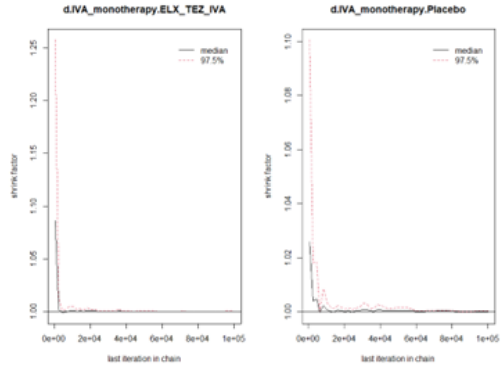
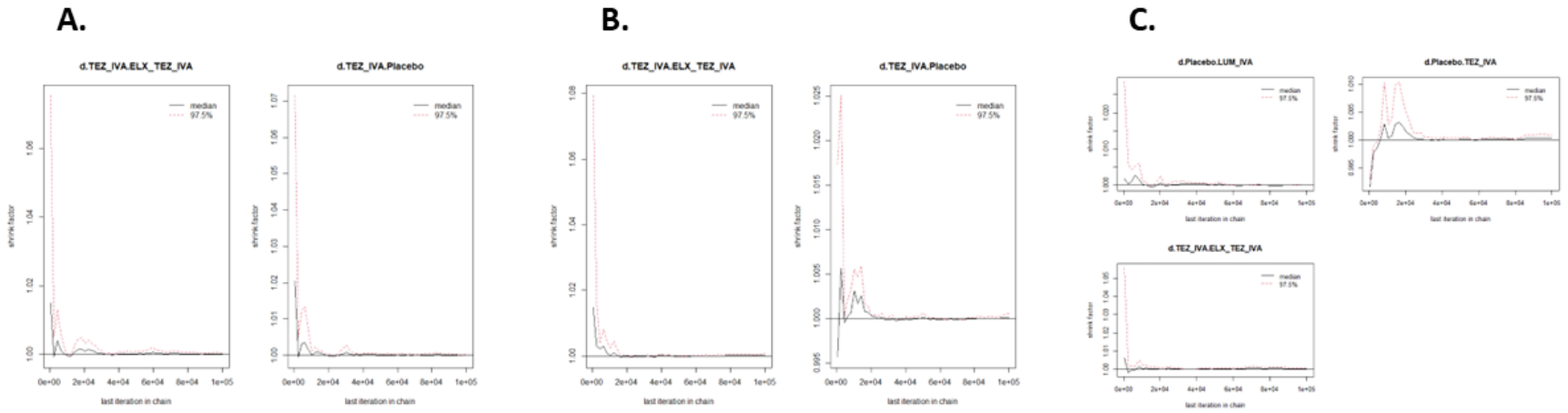


Figure 18. Brooks-Gelman-Rubin diagnostic plots for the F/RF fixed-effect ppFEV$_1$ analysis (A), fixed-effect weight-for-age z-score analysis (B), and for the F/F fixed-effect weight-for-age z-score analysis (C).



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 112. 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	£30,967.98	£5,185.71	300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution	BNF 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.	
				£13,908.40		