NIHR | National Institute for Health and Care Research

Journals Library

Check for updates

Health Technology Assessment

Volume 29 • Issue 19 • May 2025

ISSN 2046-4924

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation

Steven J Edwards, Benjamin G Farrar, Kate Ennis, Nicole Downes, Victoria Wakefield, Isaac Mackenzie, Archie Walters and Tracey Jhita

DOI 10.3310/CPLD8546

NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Extended Research Article

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation

Steven J Edwards,* Benjamin G Farrar, Kate Ennis, Nicole Downes, Victoria Wakefield, Isaac Mackenzie, Archie Walters and Tracey Jhita

BMJ-TAG, BMJ Group, London, UK

*Corresponding author sedwards@bmj.com

Published May 2025
DOI: 10.3310/CPLD8546

This report should be referenced as follows:

Edwards SJ, Farrar BG, Ennis K, Downes N, Wakefield V, Mackenzie I, *et al.* Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation. *Health Technol Assess* 2025;**29**(19). https://doi.org/10.3310/CPLD8546

Health Technology Assessment

NICE TAR and DAR

ISSN 2046-4924 (Online)

Impact factor: 3.5

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.5 and is ranked 30th (out of 174 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as award number NIHR135829. The protocol was agreed in February 2023. The draft manuscript began editorial review in September 2023 and was accepted for publication in October 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

Abstract

Background: Cystic fibrosis is a life-limiting genetic condition that affects over 9000 people in England. Cystic fibrosis is usually diagnosed through newborn screening and causes symptoms throughout the body, including the lungs and digestive system. Around 90% of individuals with cystic fibrosis have at least one copy of the *F508del* mutation on the cystic fibrosis transmembrane conductance regulator gene.

Objectives: To appraise the clinical effectiveness and cost-effectiveness of elexacaftor–tezacaftor–ivacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor within their expected marketing authorisations for treating people with cystic fibrosis and at least one *F508del* mutation, compared with each other and with established clinical management before these treatments.

Methods: A de novo systematic literature review (search date February 2023) was conducted searching electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials), bibliographies of relevant systematic literature reviews, clinical trial registers, recent conferences and evidence provided by Vertex Pharmaceuticals (Boston, MA, USA). Data on the following outcomes were summarised: acute change in per cent predicted forced expiratory volume in 1 second (change in weight-for-age *z*-score; and change in pulmonary exacerbation frequency requiring intravenous antibiotics. Network meta-analyses were conducted where head-to-head data were not available. Data from clinical trials and real-world evidence were examined to assess long-term effectiveness. A patient-level simulation model was developed to assess the cost-effectiveness of the three modulator treatments. The model employed a lifetime horizon and was developed from the perspective of the National Health Service.

Results: Data from 19 primary studies and 7 open-label extension studies were prioritised in the systematic literature review. Elexacaftor/tezacaftor/ivacaftor was associated with a statistically significant increase in predicted forced expiratory volume in 1 second and weight-for-age *z*-score and a reduction in pulmonary exacerbations compared with established clinical management, lumacaftor/ivacaftor and tezacaftor/ivacaftor, and also led to a reduction in the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management, although the magnitude of this decrease was uncertain. Lumacaftor/ivacaftor and tezacaftor/ivacaftor were also associated with a statistically significant increase in predicted forced expiratory volume in 1 second and reduction in pulmonary exacerbations relative to established clinical management, but with a smaller effect size than elexacaftor/tezacaftor/ivacaftor. There was some evidence that tezacaftor/ivacaftor reduced the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management, but little evidence that lumacaftor/ivacaftor reduced the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management. The incremental cost-effectiveness ratios from the economic analysis were confidential. However, for all genotypes studied the incremental cost-effectiveness ratios were above what would be considered cost-effective based on the National Institute for Health and Care Excellence threshold of £20,000–30,000 per quality-adjusted life-year gained.

Conclusions: Despite the improved clinical benefits observed, none of the cystic fibrosis transmembrane conductance regulator gene modulators assessed would be considered cost-effective based on the National Institute for Health and Care Excellence threshold of £20,000–30,000 per quality-adjusted life-year gained. This is largely driven by the high acquisition costs of cystic fibrosis transmembrane conductance regulator gene modulator treatments.

Study registration: This study is registered as PROSPERO CRD42023399583.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: NIHR135829) and is published in full in *Health Technology Assessment*; Vol. 29, No. 19. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/CPLD8546).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CENTRAL	Cochrane Central Register of Controlled Trials
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFRD	cystic fibrosis-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CFTRm	cystic fibrosis transmembrane conductance regulator modulator
CPH	Cox proportional hazards
CRD	Centre for Reviews and Dissemination
CrI	credible interval
DIC	deviance information criterion
DPI	dry powder for inhalation
EAG	External Assessment Group
ECM	established clinical management
ELX	elexacaftor
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions three-level version
EQ-5D-5L	EuroQol-5 Dimensions five-level version
F	*F508del*
FEV_1	forced expiratory volume in 1 second
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IV	intravenous
IVA	ivacaftor
$LCI_{2.5}$	Lung Clearance Index 2.5%
LUM	lumacaftor
MF	minimal function
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PBAC	Pharmaceutical Benefits Advisory Committee
$ppFEV_1$	per cent predicted forced expiratory volume in 1 second
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
RCT	randomised controlled trial
SF-36	36-Item Short-Form Health Survey
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TEZ	tezacaftor
WTP	willingness to pay

Note

This manuscript is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain language 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 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 than 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 United Kingdom 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 National Health Service. The analysis found that based on the current prices of these treatments, they are unlikely to be considered good value for money for the National Health Service.

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.

Scientific summary

Background

Cystic fibrosis (CF) is a life-limiting genetic condition that is most often diagnosed through newborn screening. There are over 9000 people with CF in England, and 89% of these people have 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. Most people with CF experience progressive lung function loss over their lifetime, and lung disease is the primary cause of death for people with CF.

Before the availability of CFTR modulator therapies, established clinical management (ECM) of 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, dietitians and social workers, in addition to specialist nurses and doctors.

Cystic fibrosis transmembrane conductance regulator gene modulator therapies treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators have been available through the NHS via managed access agreements:

- Lumacaftor/ivacaftor (LUM/IVA) has been available for people aged ≥ 6 years with CF and two *F508del* copies (F/F genotype) since October 2019, and currently it is available for people aged ≥ 1 year 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 it is available for people aged ≥ 6 years with CF and an F/F or F/RF genotype.
- Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been available for people aged ≥ 12 years with CF and a single *F508del* copy with another eligible mutation [F/F, F/RF, F/minimal function (F/MF) or F/Gating genotype] since August 2019 through compassionate access, and more widely since August 2020. Currently, ELX/TEZ/IVA is available for people aged ≥ 2 years with CF and an F/F, F/RF, F/MF or F/Gating genotype.

The clinical effectiveness and safety of CFTR modulator combination therapies has been studied in clinical trials, and through real-world data collection, notably through a data collection agreement between the National Institute for Health and Care Excellence (NICE), the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals (Boston, MA, USA), NHS England and NHS Improvement.

Objectives

The objective of this research is to compare the clinical effectiveness and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA with each other and with ECM for treating CF in England 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 (Cochrane Central Register of Controlled Trials)] 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 included in the SLR. Two independent reviewers appraised the titles and abstracts of identified records and performed an evaluation of full texts, with a third reviewer used to resolve discrepancies. Data from included studies were extracted by one reviewer and validated by a second. Study quality was assessed by a single reviewer

at both the study and outcome level using standard checklists, and was then validated by a second reviewer. Where sufficient data were available for an outcome measure within a genotype and age-group of interest, Bayesian network meta-analyses (NMAs) were performed using Markov chain Monte Carlo simulations. The key outcomes of the clinical effectiveness review were changes in per cent predicted forced expiratory volume in 1 second ($ppFEV_1$); changes in weight-for-age *z*-score; and the frequency of pulmonary exacerbations requiring intravenous (IV) antibiotics. Additional real-world evidence was obtained through targeted searches of electronic databases, a data request to the UK CF Registry and 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 (CPH) model developed by Liou *et al*. (Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;**153**:345–52) 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 EuroQol-5 Dimensions (EQ-5D) data. Costs were obtained from standard UK sources, with the costs of CFTR modulator treatments provided by the company, including confidential commercial discounts.

The economic model used a lifetime horizon (up to a maximum of 100 years), and the analysis is from an NHS perspective. Costs and quality-adjusted life-years (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.

Results

Nineteen relevant studies and seven associated open-label extension studies were included for data extraction from the SLR. Sixteen of these were Phase III (n = 14), Phase II (n = 1) or Phase IV (n = 1) randomised controlled trials, most of which were assessed to be high quality. Three non-randomised Phase III 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.

Across genotypes, treatment with ELX/TEZ/IVA led to large and statistically significant acute increases in $ppFEV_1$, weight-for-age *z*-score and pulmonary exacerbations requiring IV antibiotics compared with ECM, and LUM/IVA and TEZ/IVA where available. Clinical experts advised the External Assessment Group (EAG) that the magnitude of these effects with ELX/TEZ/IVA is clinically meaningful and likely to lead to increased survival relative to ECM. LUM/IVA and TEZ/IVA were also associated with acute increases in $ppFEV_1$, and reductions in pulmonary exacerbations requiring IV antibiotics compared with ECM. LUM/IVA was associated with an increase in weight-for-age *z*-score relative to ECM. The effect sizes for LUM/IVA and TEZ/IVA were smaller than for ELX/TEZ/IVA. Nevertheless, the effects are still expected to be clinically meaningful and be associated with better long-term lung function and increased survival than ECM.

The main outstanding clinical uncertainty is the long-term effect of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the 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 was often limited to 2–3 years. Real-world data collection as part of the data collection agreement did not result in robust long-term data for LUM/IVA or TEZ/IVA because of the rapid transition 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 that LUM/IVA meaningfully reduces the long-term rate of $ppFEV_1$ decline compared with ECM (EAG preferred assumption: 0% reduction in rate of $ppFEV_1$ decline compared with ECM)
- some evidence that TEZ/IVA reduces the long-term rate of $ppFEV_1$ decline compared with ECM, with a small effect size (EAG preferred assumption: 17.18% reduction in rate of $ppFEV_1$ decline compared with ECM)
- good evidence that ELX/TEZ/IVA reduces the long-term rate of $ppFEV_1$ decline compared with ECM, with a highly uncertain magnitude (EAG preferred assumption: 61.00% reduction in rate of $ppFEV_1$ decline compared with 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 (AE) profile of CFTR modulators, specifically regarding mental health outcomes, hypertension and cataracts and lens opacities.

The NICE typically considers interventions a cost-effective use of the NHS resources if the incremental cost-effectiveness ratio (ICER) sits below a cost-per-QALY threshold of £20,000–30,000. None of the EAG's base-case ICERs (either pairwise vs. ECM alone or full incremental results, used when more than two alternative treatments are available) 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 showed that both LUM/IVA and TEZ/IVA were extendedly dominated in the F/F population (i.e. the ICERs were higher than a more effective treatment, ELX/TEZ/IVA). In the F/RF population, TEZ/IVA was also extendedly dominated by ELX/TEZ/IVA.

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 with ECM.

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 than 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

Elexacaftor/tezacaftor/ivacaftor 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 on discontinuation. There is currently a lack of both clinical effectiveness 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 AE 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 CPH model used to model the impact of changes in patient characteristics over time on survival in the UK population.

Study registration

This study is registered as PROSPERO CRD42023399583.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: NIHR135829) and is published in full in *Health Technology Assessment*; Vol. 29, No. 19. See the NIHR Funding and Awards website for further award information.

Chapter 1 Background

Description of health problem

Brief statement describing the health problem

Cystic fibrosis (CF) is a life-limiting genetic condition affecting over 9000 people in England,[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]

Aetiology, pathology and prognosis

Cystic fibrosis 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 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 cell plasma membranes.[5] *F508del* homozygous individuals (F/F genotype) constitute 47.7% of people with CF in the UK, and 41.3% of individuals are *F508del* heterozygous, including the following other mutation groups:[1]

- *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 constitute 10.7% of people with CF in England.[1] These individuals, on average, have milder disease than patients with at least one *F508del* copy, having a higher best forced expiratory volume in 1 second (FEV_1) and a lower probability of pancreatic insufficiency or chronic *Pseudomonas* infection.[6]

Since 2007, all babies born in England have been screened for CF using a blood spot immunoreactive trypsin test.[2] 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. If necessary, further genetic testing for a larger number of CF mutations may be conducted, and, in rare cases, a diagnosis of CF can be made on 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, that is, they require pancreatic enzyme replacement therapy.[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, including bloating, cramps and malnutrition.[14] Approximately 35% of adults with CF have cystic fibrosis-related diabetes (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 among people with CF, with 38.0% of people with CF in the UK receiving hospital-based intravenous (IV) antibiotics in 2019.[15] 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 per cent predicted forced expiratory volume in 1 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 12–30 years, after which the rate of decline may decrease.[3,16]

In 2020, 101 (1.0%) of people with CF registered in the UK Cystic Fibrosis Registry died, with a median age at death of 36 years. Among people born with CF between 2015 and 2019, the median predicted survival is 49.1 years, 7.6 years longer than the median predicted survival of individuals born between 2007 and 2011.[15]

Epidemiology

Incidence and/or prevalence

The UK CF 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.[1,17] The registry provides comprehensive and up-to-date data on the incidence and prevalence of CF in England. The CF Registry manages data submitted by UK CF centres from patient annual reviews, including details on pulmonary function and infections. Since a 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), NHS England and NHS Improvement, encounter-based data have been more systematically captured by the UK CF Registry.[18,19]

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 3 years), including 9044 people with CF in England.[1] Across the UK in 2021, there were 188 new diagnoses of CF. Genotyping was available for at least one mutation for 99.0% of registered individuals, and for both mutations for 96.3% of registered individuals. The prevalence of different CF genotypes in England in 2021 was:

- F/F – 49.2%
- F/Gating, including F/*G551D* – 4.4%
- F/*R117H* – 4.6%
- F/Other, including F/MF and F/RF – 31.1%
- non-*F508del* combinations – 10.7%.

The *R117H* mutation is a non-gating residual function mutation, but it is within the marketing authorisation for ivacaftor monotherapy, alongside other gating mutations, and not within the marketing authorisation for tezacaftor/ivacaftor, unlike other residual function mutations.

Impact of health problem

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 (interquartile range 12–34 days) receiving hospital-based IV antibiotics, and 18 days (interquartile range 12–34 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:[14,20]

- 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,[21] and some patients may develop CF-associated liver disease.[22] Such longer-term outcomes can introduce a significant clinical and psychological burden of disease to people with CF, including burden associated with infertility, transplant and shortened life expectancy:

- Infertility affects around 98% of men with CF as a result of 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 result from CF-related illnesses.[23]
- People with CF with severe organ damage, most commonly of the lungs, may require a transplant. In 2019 in the UK, 241 people with CF were evaluated for a transplant and 96 were accepted, with 49 people aged ≥ 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,[24] with physiotherapy for airway clearance occurring at least twice daily for 10–30 minutes.[25] The high treatment burden associated with CF care was noted in multiple stakeholder submissions.[25–30] Such a high treatment burden is often translated into a large caregiver burden for caregivers of children with CF, who often must co-ordinate, 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 with population norms in both Germany and the UK,[31] and a high incidence of anxiety and depression among CF caregivers.[32] In addition, a survey by CF Voices in the UK in spring 2020 highlighted that:[27]

- the work, life and financial well-being 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[33]
- 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 in spring 2022 on the cost of living with CF reported that 77% of parents, carers and spouses felt that their caring responsibilities for family members with CF had an effect on their employment.[34]

The psychological burden of CF is complex. The NICE guideline on the diagnosis and management of CF (NG78) recommends that 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*.[35]

The Standards highlight a diversity of psychological and behavioural burdens that a person with CF may experience, including the psychosocial impact of segregation from others with CF; eating difficulties; issues concerning needle aversion/phobia; difficulty adhering 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 among people with CF.[36–38] Stakeholder submissions also foregrounded difficulties in psychological adjustment that may be particularly relevant when new, highly effective therapies are introduced.[30]

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 EuroQol-5 Dimensions three-level version (EQ-5D-3L) was 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.[39,40] EQ-5D-3L score was highest for

those with ppFEV$_1$ ≥ 90% (0.95), followed by those with ppFEV$_1$ 70–90% (0.93) and 40–70% (0.91), and was lowest for those with ppFEV$_1$ < 40% (0.88). Similar values were reported using the EuroQol-5 Dimensions five-level version (EQ-5D-5L) scale in the STRIVE clinical trial.[41] These values are approximately in line with UK population norms for ages < 25 years (0.94) and 35–44 years (0.91).[42]

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a CF-specific HRQoL measure that has versions available for adolescents and adults aged ≥ 14 years, children, and parents of children with CF.[43,44] It comprises nine HRQoL domains, three symptom scales and one health status perception scale. The CFQ-R has been validated across CF cohorts, including parent cohorts, and displays sensitivity to differences in the HRQoL related to lung function.[45,46] That CF patients can experience difficulties throughout the domains of the CFQ-R was highlighted across stakeholder submissions, and also by the External Assessment Group's (EAG) clinical experts, especially for those with a high treatment burden.[25–30] Other, system-specific CF patient-reported outcome measures have also been developed, such as the CFAbd-Score for abdominal symptoms.[47]

The EAG's clinical experts highlighted how chronic diseases with symptom burdens such as CF may limit the earning potential of many patients. The financial burden of CF on patients and their families was explored in a 2023 report conducted by the University of Bristol and CF Trust,[48] in which 59% of adults with CF surveyed noted that they had incurred loss in income because they had needed to reduce work hours, attend routine appointments or leave employment completely. It was estimated that a typical family with a member with CF will lose £6768 per year due to the additional costs associated with travel for medical appointments, prescriptions, dietary requirements and higher energy bills.[48] Another recent CF Trust report found that 7 in 10 people with CF reported receiving benefits, with 25% of those reporting having to use their benefits to pay for prescriptions.[34]

Significance for the NHS

There are 30 paediatric and 26 regional CF centres, 4 standalone clinicals and 76 networked clinics in the UK.[1] A multidisciplinary team is involved in the care of people with CF, including a medical consultant, a clinical nurse specialist, a physiotherapies, a dietitian, a clinical psychologist, a social worker and a pharmacist.[35] 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 2–3 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.[15] Home care for CF is also offered by most specialist CF services in the UK and 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.

Owing to the multidisciplinary nature of CF and the wide range of symptoms and associated comorbidities, the costs to the NHS are substantial. A cost-of-illness study conducted in 2012 estimated that the average annual direct healthcare cost for a person with CF in the UK was €20,854 (costs presented in euros in 2012).[31] In 2019, a confidential commercial arrangement between NHS England and Vertex resulted in access to the three CFTR modulator combination therapies for an estimated 5000 patients. Although the price 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.

Measurement of disease

An overview of common indicators of CF severity and quality of life in people with CF is in *Table 1*.

Current service provision

Management of disease

Established clinical management (ECM) of CF involves managing both CF symptoms and symptoms associated with CF treatments. No ECM therapy treats the underlying cause of the disease by restoring CFTR protein function. ECM for CF is co-ordinated by a multidisciplinary team, which includes prescribing and administering medication, planning diets,

TABLE 1 Common measurements of the severity of CF

Measure	Description
Disease severity	
$ppFEV_1$	$ppFEV_1$ 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 ethnicity. A variety of reference equations for calculating $ppFEV_1$ have been developed, including by Knudson *et al.*,[49] Hankinson *et al.*,[50] Wang *et al.*,[51] Stanojevic *et al.*,[52] and the Quanjer *et al.*[53] 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,[54] and is a point at which the EAG's clinical experts stated patients would be considered for lung transplant
$LCI_{2.5}$	The $LCI_{2.5}$ 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, in whom $ppFEV_1$ can be difficult to measure and unreliable.[55] Abnormal $LCI_{2.5}$ in those aged 3–5 years may be a more sensitive predictor of later spirometry abnormalities than $ppFEV_1$ at the same age.[56] The $LCI_{2.5}$ is therefore a preferred measure of lung function in young children
Pulmonary exacerbations	Pulmonary exacerbations are a cause of lung function decline in CF, are associated with reduced quality of life, and are the primary cause of hospitalisation for people with CF[41,57–59] The EAG's clinical experts stated that pulmonary exacerbations are acute worsening of CF symptoms usually associated with infection and often require the use of IV antibiotics. 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 (IV, inhaled, or oral) for any four 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; 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'[60] • 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[61]
Pulmonary bacterial colonisation	Many people with CF will experience 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* Among these, *B. cepacia* infection is a severe infection predictive of a rapid decline in lung function and, subsequently, mortality.[62] The EAG's clinical experts also highlighted how age at *Pseudomonas* acquisition can influence future lung function decline and clinical outcomes
Pancreatic insufficiency and CFRD	Pancreatic insufficiency is often measured indirectly through the need for 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 CFRD, with 8.3% of people with CF in the UK in 2021 aged 10–15 years and 35.2% of those aged ≥ 16 years receiving treatment for CFRD[1]
Weight-, height- and BMI-for-age *z*-scores	Measurements of weight, height and BMI are markers of the effects of CF 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 *Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis, 2nd Version*[7] A sweat chloride concentration of < 40 mmol/l is considered normal, whereas a concentration of > 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 parents of children with CF.[43,44] It comprises nine HRQoL domains, three symptom scales and one health status perception scale[45,46]

BMI, body mass index; $LCI_{2.5}$, Lung Clearance Index 2.5%; PERT, pancreatic enzyme replacement therapy.

co-ordinating physical therapy such as airway clearance, and providing social and psychological support. The 2021 UK CF 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 2*. People with CF who are pancreatic insufficient will receive pancreatic enzyme replacement therapy, and those with CFRD will receive insulin.

TABLE 2 Proportion of people with CF receiving non-CFTR modulator treatments reported in the 2021 UK CF Registry annual report[1]

Therapy[a]	Percentage of people with CF using therapy in 2021 (*N* = 10,175)
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 people with CF are reported. Therapies are not mutually exclusive.
Source
UK CF Registry annual report 2021.[1]

The existing NICE guidance for diagnosing and managing CF (NG78) recommends:[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, 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, the following two therapies have been approved through NICE Single Technology Appraisals:

- 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, that is, a FEV1 decline of > 2% annually and
  - for whom other osmotic agents are not considered appropriate.[63]

- 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.[64]

In 2021, mannitol use was 5.0% for people with CF in the UK aged ≥ 18 years and 0.1% for those aged < 18 years. Of people with CF who had a chronic *P. aeruginosa* infection, 18.1% were treated with tobramycin DPI, and 18.0% were treated with sodium DPI.

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 currently receive a CFTR modulator treatment. The annual cost per patient based on current list prices for elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), tezacaftor/ivacaftor (TEZ/IVA) and lumacaftor/ivacaftor (LUM/IVA) is £200,187, £173,414 and £104,357, respectively. Based on the available data from the CF Trust in December 2021 on the number of patients taking each CFTR modulator,[1] this is an annual cost of £1.2B. A summary of the variation in services for CF care across England and current national guidelines is provided in *Report Supplementary Material 1*, *Description of health problem*.

Description of technology under assessment

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).

The CFTR modulators treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators fall into one of 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 weighing 5–25 kg,[65] and for adults, adolescents and children aged ≥ 6 years and weighing ≥ 25 kg with CF who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene:[66] *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. This prevents the CFTR protein being targeted for degradation in people with an *F508del* mutation and increases CFTR expression at the cell membrane.[67–71]

The LUM/IVA combination therapy (Orkambi®, Vertex) is a systemic protein modulator comprising 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'.[72] LUM/IVA granules also have a marketing authorisation for treating children with CF who are homozygous for *F508del* and are aged ≥ 1 year.[73] LUM/IVA has previously been appraised by NICE. In TA398, LUM/IVA was not recommended within its marketing authorisation for treating CF in people aged ≥ 12 years who are homozygous for the *F508del* mutation in the *CFTR* gene.[74]

TEZ/IVA combination therapy (Symkevi®, Vertex) is a systemic protein modulator comprising 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.*
>
> *Electronic Medicines Compendium*[75]

The ELX/TEZ/IVA combination therapy (Kaftrio®, Vertex Pharmaceuticals (Europe) Limited, 2 Kingdom Street, London, W2 6BD, UK) is a systemic protein modulator comprising elexacaftor, a CFTR corrector, tezacaftor and ivacaftor. ELX/TEZ/IVA is administered orally and has a marketing authorisation in the UK as tablets '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',[76] and as granules 'in a combination regimen with ivacaftor for the treatment of CF in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the CFTR gene'.[77]

Table 3 outlines the dosing recommendations for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within their current UK marketing authorisations.

Identification of important subgroups

The NICE final scope included the following subgroups:[78]

- 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 notes that CF genotype is a clinically meaningful subgroup, and that the marketing authorisation of some CFTR modulators are limited to certain CF genotypes, which is reflected in the inclusion criteria of key clinical trials. The EAG considers the following subgroups to be most relevant to the MTA:

- 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 (≥ 2 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 (≥ 2 years) have marketing authorisation for this genotype.

TABLE 3 Dosing recommendations for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA[65,66,72,73,75–77]

		LUM/IVA	TEZ/IVA		ELX/TEZ/IVA	
Age	Weight	Morning and evening dose	Morning dose	Evening dose	Morning dose	Evening dose
1–2 years	7 kg to < 9 kg	One sachet of lumacaftor 75 mg/ivacaftor 94 mg	NA	NA	NA	NA
	9 kg to < 14 kg	One sachet of lumacaftor 100 mg/ivacaftor 125 mg				
	≥ 14 kg	One sachet of lumacaftor 150 mg/ivacaftor 188 mg				
2–5 years	< 14 kg	One sachet of lumacaftor 100 mg/ivacaftor 125 mg			One sachet of ivacaftor 60 mg/tezacaftor 40 mg/elexacaftor 80 mg granules	One sachet of ivacaftor 59.5 mg granules
2–5 years	≥ 14 kg	One sachet of lumacaftor 150 mg/ivacaftor 188 mg			One sachet of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg granules	One sachet of ivacaftor 75 mg granules
6 to < 12 years	< 30 kg	Two tablets containing lumacaftor 100 mg/ivacaftor 125 mg	One tablet containing tezacaftor 50 mg/ivacaftor 75 mg	One tablet containing ivacaftor 75 mg	Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets	One ivacaftor 75 mg tablet
6 to < 12 years	≥ 30 kg		One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet
≥ 12 years	-	Two tablets containing lumacaftor 200 mg/ivacaftor 125 mg	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet

NA, not applicable.

- 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 (≥ 2 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 (≥ 2 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.'[78] The EAG's clinical experts considered it plausible that:

- the potential effectiveness of CFTR modulator therapies may be limited in people with existing irreversible lung damage, but that
- 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 sooner after 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 a result, 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 $ppFEV_1$.

Current usage in the NHS

All three CFTR modulator therapies that are considered in this MTA (LUM/IVA, TEZ/IVA and ELX/TEZ/IVA) are currently available on the NHS through a managed access agreement.[79] 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 10,251 individuals registered and who had an annual review in 2022 in the UK CF Registry, 7950 (77.6%) were taking a CFTR modulator by December 2022, including:[80]

- 6846 people taking ELX/TEZ/IVA
- 227 people taking TEZ/IVA
- 464 people taking LUM/IVA
- 413 people taking ivacaftor monotherapy.

These figures demonstrate widespread uptake of CFTR modulator therapy and that this uptake now primarily consists of individuals receiving ELX/TEZ/IVA. Between January 2021 and December 2022, the number of people receiving ELX/TEZ/IVA rose from 4195 to 6846, whereas the use of TEZ/IVA and LUM/IVA declined during this period. 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.

Chapter 2 Definition of the decision problem

Decision problem

The National Institute for Health and Care Excellence (NICE) issued a final scope containing the decision problem to be addressed in this MTA. In the following sections, the EAG highlights any differences between the decision problem outlined in the NICE final scope and (1) the decision problem addressed by the EAG in this assessment report and (2) the decision problem addressed by Vertex in a company submission to NICE during the appraisal.

Critique of Company adherence to the NICE final scope

The EAG considered the Company to have adhered to the NICE final scope in terms of the intervention, population and outcomes. While the Company (CS, page 19) stated '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 deviated from the NICE Final Scope in the comparators and economic analysis. Specifically, the Company:

- provided a cost-effectiveness analysis of ivacaftor monotherapy compared with ECM in the F/Gating population, which is outside the NICE final scope
- deviated from the NICE reference case in using a differential annual discount rate of 1.5% for health outcomes and 3.5% for costs.

Decision problem addressed in the External Assessment Group assessment report

Interventions

The interventions relevant to this MTA as listed in the NICE final scope are:

- LUM/IVA
- TEZ/IVA
- ELX/TEZ/IVA.

Details of these interventions, including their marketing authorisations, have been presented in *Summary of intervention*.

Population including subgroups

The population relevant to this MTA is people with CF with at least one *F508del* mutation. Relevant genotype subgroups are based the marketing authorisation for each CFTR modulator combination therapy, and these are presented in *Table 4*.

TABLE 4 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

As outlined in *Chapter 1*, the EAG will consider the relationship between lung function and clinical effectiveness in the following ways:

- If data are available, the EAG will present clinical efficacy data by trial-reported lung function subgroup.
- 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 $ppFEV_1$.

Relevant comparators

The comparators of interest listed in the NICE final scope are:[78]

- each of the interventions under consideration in the MTA:
  - LUM/IVA
  - TEZ/IVA
  - ELX/TEZ/IVA

- ECM, including:
  - best supportive care
  - mannitol DPI
  - inhaled mucolytics
  - nebulised hypertonic saline
  - anti-inflammatory agents
  - bronchodilators
  - vitamin supplements
  - pancreatic enzymes.

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 them. As CFTR modulator therapies are an addition to ECM, participants in clinical trials informing this appraisal will have had access to all the ECM therapies available at the time of the trial, both in the placebo arms and in 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 2*. The EAG also notes that the availability of some ECM therapies varies with age. For example, rhDNase is only indicated for people with CF who are > 5 years of age and have a $ppFEV_1$ > 40%, and mannitol DPI is indicated for the treatment of CF in adults aged ≥ 18 years. Although not a relevant comparator in the NICE final scope, the EAG notes that as of December 2021 a number of people with CF (n = 606) were noted in the CF Trust Register as receiving ivacaftor monotherapy.[1] The EAG considers ivacaftor monotherapy relevant to the appraisal because of the likelihood that evidence from placebo randomised controlled trials of ivacaftor will form a connected evidence network with ivacaftor monotherapy active-controlled trials with ELX/TEZ/IVA.

Outcomes

The NICE final scope states that the following outcomes should be addressed in this MTA:

- mortality
- lung function, including $ppFEV_1$, forced vital capacity, Lung Clearance Index 2.5% ($LCI_{2.5}$), 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 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 CF, the CFQ-R, a minimally important difference has been reported for the respiratory domain for people with stable CF (4 points).[81] No minimally clinically important difference has been established for other domains of the CFQ-R.[81] The EAG did not find evidence that a minimally important difference has been established for lung-function outcomes in CF such as $ppFEV_1$ or $LCI_{2.5}$, although the short-term variability of $ppFEV_1$ has been reported as around 6.3%.[82] The EAG's clinical experts also noted that although patients may not feel a difference of 5% in $ppFEV_1$, this may lead to other measurable differences over time, for example less time spent doing physiotherapy. The 2012 European Medicines Agency report of the workshop on end points of CF 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.[83] 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 exacerbations will necessitate treatment with IV antibiotics either at home or in hospital.

Treatment effect modifiers

The EAG's clinical experts did not consider any clinical variable likely to be a treatment effect modifier of CFTR modulators. The EAG's clinical experts outlined that ceiling effects for some outcome measures in some individuals, for example $ppFEV_1$ 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.

Equality, diversity and inclusion

Existing research highlighted several equality, diversity and inclusion disparities relevant to this research, including the following:

- Approximately 10% of people with CF are currently ineligible for CFTR modulator therapy because they do not have an *F508del* copy. These individuals are more likely to be from black, Asian and minority ethnicity groups.[6]
- Disparities may exist in the time to diagnosis between ethnicities, which may correlate with differences in CF genotype and phenotype between ethnicities.[84,85]
- The EAG's clinical experts noted that socioeconomic status was a predictor of outcomes for people with CF.
- A submission from CF Voices provided survey data suggesting that 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.[27]
- A public consultation as part of the NICE MTA process raised the following:[86]
  - Age: as each therapy is available through routine commissioning for the prevalent CF population, the recommendations of this MTA will differentially impact those who are currently too young to receive therapy.
  - People with neurological conditions such as attention deficit hyperactivity disorder or autism, and their carers, may be disproportionately affected by CF.

Over 99% of the prevalent UK CF population are represented in the UK CF Registry. In 2022:

- 95.7% of registrant ethnicities were recorded as white, 2.7% as Asian, 0.3% as black, 0.4% as mixed and 0.9% as other.
- 37.1% of registrants were < 16 years of age, and 66.1% of those aged ≥ 16 years were in work or studying.
- 53.1% of registrants were male.[80]

As a secondary data analysis, the present study did not enrol participants. However, the full UK CF population was considered in this MTA. In addition to the review of clinical trial data, data from the UK CF Registry were available from the UK CF Registry annual data reports, and a data analysis was performed as part of the data collection agreement

(DCA) between NICE, the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals, NHS England and NHS Improvement.[87] These data ensured that the diversity of participants with an *F508del* mutation was represented. While the results of the Vertex data analysis were marked as confidential and so could not be directly reported, they were predominantly in line with the clinical trial data.

Stakeholder comments were considered during the process from a range of patient and professional bodies, and included:[88]

- Association of Chartered Physiotherapists in Cystic Fibrosis
- Cystic Fibrosis Dietitians Specialist Group of the British Dietetic Association
- Cystic Fibrosis Nursing Association
- Cystic Fibrosis Trust
- Cystic Fibrosis Voices
- UK Cystic Fibrosis Medical Association
- United Kingdom and Ireland Cystic Fibrosis Pharmacy Group
- UK Psychosocial Professionals in Cystic Fibrosis Committee.

Overall aims and objectives of the assessment

The purpose of this MTA is to assess the clinical effectiveness and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within their marketing authorisations for treating CF, compared with each other and with ECM.

Chapter 3 Assessment of clinical effectiveness

This manuscript contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Method of reviewing effectiveness

The EAG performed a systematic literature review (SLR) of the clinical effectiveness evidence of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA for treating CF, and reports it in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[89] The protocol for the systematic review was registered on PROSPERO (registration number CRD42023399583), and an expanded version was published on the NICE website.[90] There were no changes to this protocol during the appraisal.

Identification of studies

The EAG performed systematic searches of MEDLINE, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials), 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 CF and LUM/IVA, TEZ/IVA and ELX/TEZ/IVA. For CENTRAL, the EAG identified the Cystic Fibrosis Trials Register as an up-to-date systematic search repository for CF RCTs.[91] The EAG's search strategies for MEDLINE, EMBASE and CENTRAL, as well as further details of the Cystic Fibrosis Trials Register, are presented in *Report Supplementary Material 1*.

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 in the Cystic Fibrosis Trials Register. Deduplication was performed using a custom script in R 4.2.0.[92] 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. 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. Conference proceedings, clinical trial registries, review databases and health technology assessment (HTA) bodies were searched by a single reviewer and are outlined in *Report Supplementary Material 1*, *Literature search strategies*.

Company submission

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.

Types of studies included and prioritised

Randomised controlled trials (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 that the evidence base would be of different sizes in terms of 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.
- If no Phase III or Phase IV RCT data were available for an intervention within a group of interest, relevant Phase II RCT data were extracted.
- If no Phase II, Phase III or Phase IV RCT data were available, then data from relevant non-randomised Phase III or Phase IV clinical trials were extracted.

Data collection agreement

In addition to the data collected as part of the EAG's SLRs, the EAG was provided with a confidential report of a Company analysis of UK CF Registry data collected as part of the data collection agreement.[87] The agreement was between NICE, the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals, NHS England and NHS Improvement. The agreement 'intended to capture the data that may address the clinical uncertainties in the evidence base concerning LUM/IVA, TEZ/IVA and ELX/TEZ/IVA to inform a future health technology appraisal by NICE',[18] with the following relevant uncertainties highlighted:[18]

- long-term (more than 1 year) treatment effects on absolute ppFEV$_1$
- the impact of treatment on lung function decline
- discontinuation rates of Vertex therapies and reasons for discontinuation
- compliance rates with Vertex therapies
- comparative outcomes for different disease severities
- comparative treatment pathway costs
- patient and caregiver quality-of-life impact, including patient age-related differences
- the rate of pulmonary exacerbations.

The EAG received the final report, and associated workbooks, produced by Vertex in July 2023, and had access to an interim report from February 2023. The report and data sheets were prepared by Vertex, and therefore the EAG only had access to the data and analyses presented by the Company.

Inclusion and exclusion criteria

Table 5 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 might have been 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 5 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 with each other or established clinical management	Any other comparator
Outcomes	Outcomes listed in *Table 6*	No outcomes listed in *Table 6*

MA, meta-analysis.
a SLRs and MAs were included past the abstract-screening stage to enable bibliography searching but were excluded at full-text stage.

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 the involvement of a third reviewer when necessary. Outcome data were prioritised for extraction at the following time points: week 4, week 24, week 48, and the time point of the primary outcome or end of study. Where key relevant data for the economic model were not reported, Vertex was contacted for further details. If Vertex was unable to provide the data, it was assumed that the data were not available.

For clinical efficacy outcomes, data were preferentially extracted for the intention-to-treat 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 were reported, then estimates based on multiple imputation or mixed-effects models were preferred over last observation carried forward, or variants of this method.

Table 6 lists the outcomes included in the NICE final scope and the variables that were extracted for these outcomes as part of the SLR.[78] The EAG prioritised variables likely to be included in the economic model for extraction.

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 the key outcome level. At the study level, risk of bias was assessed using the risk-of-bias tables presented in *Report Supplementary Material 1*, *Study-level quality assessment*. At the outcome level, risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB-2).[93] 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 (AEs). A quality assessment was not initially 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. Following peer reviewer comments, an adapted ROBINS-I checklist for uncontrolled pre–post studies was completed for the non-randomised studies of CFTR modulators in children.[94,95]

TABLE 6 Outcomes and corresponding data extracted as part of the SLR

Outcomes included in NICE final scope[78]	Data extracted, if reported
Mortality	All-cause mortality
Lung function	Absolute and change from baseline: • ppFEV$_1$ • LCI$_{2.5}$ 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
BMI	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

continued

TABLE 6 Outcomes and corresponding data extracted as part of the SLR (*continued*)

Outcomes included in NICE final scope[78]	Data extracted, if reported
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 AE (grade 3 and above) • Any serious treatment-emergent AE (grade 3 and above) • Any trial-defined AE of special interest • AE of particular importance as identified by the EAG's clinical experts, including: ◦ AEs 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 • 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 CFRD

AE, adverse event; EQ-5D, EuroQol-5 Dimensions; SF-36, 36-Item Short Form Health Survey.

Methods of data synthesis

The extracted data and a quality assessment for each study of clinical effectiveness are presented in *Critical review and synthesis of information* and detailed data tables are presented in *Report Supplementary Material 1*, *Clinical data extraction tables*.

The EAG conducted a feasibility assessment for network meta-analyses (NMAs) 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 (6–11 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; discontinuation frequency; clinical trial setting; and study design.[96]

Network meta-analyses 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 (see *Adverse effects of treatment*) and were performed following the techniques outlined in the NICE Decision Support Unit Technical Support Document 2.[97] Contrast-based NMAs were performed using a Bayesian Markov chain Monte Carlo simulation, implemented in JAGS using the '*gemtc*' package (version 1.0-1) in R 4.2.0.[98] 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 < 1.05.[99] The '*gemtc*' default uninformative prior distributions were used for all treatment effects.[98]

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. 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 in 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 in 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, the results of both 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 (CIs). Where the Company also submitted indirect treatment comparisons, the consistency of the Company estimates with the EAG estimates is commented on. Owing to the limited number of studies informing the NMAs, the EAG and Company estimates are often aligned.

Results

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 5574 records. After deduplication, 4334 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,[40,100–114] 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 *Report Supplementary Material 1*, *Tables of excluded and deprioritised records with rationale*. Grey literature searching identified a further 60 records, including two relevant conference abstracts, two records identified from the Cochrane review[91] 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 *Report Supplementary Material 1*, *Critique of Company's SLR*.

Of the 54 studies included in the SLR, 19 were prioritised for extraction based on the pre-specified data extraction hierarchy, and seven further studies were open-label extension studies associated with the prioritised studies. The 29 studies that were deprioritised are presented in *Report Supplementary Material 1*, *Tables of excluded and deprioritised records with rationale*, 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 II RCT or non-randomised study in population with Phase III RCT data available (*n* = 11)
- non-randomised study where Phase II 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).

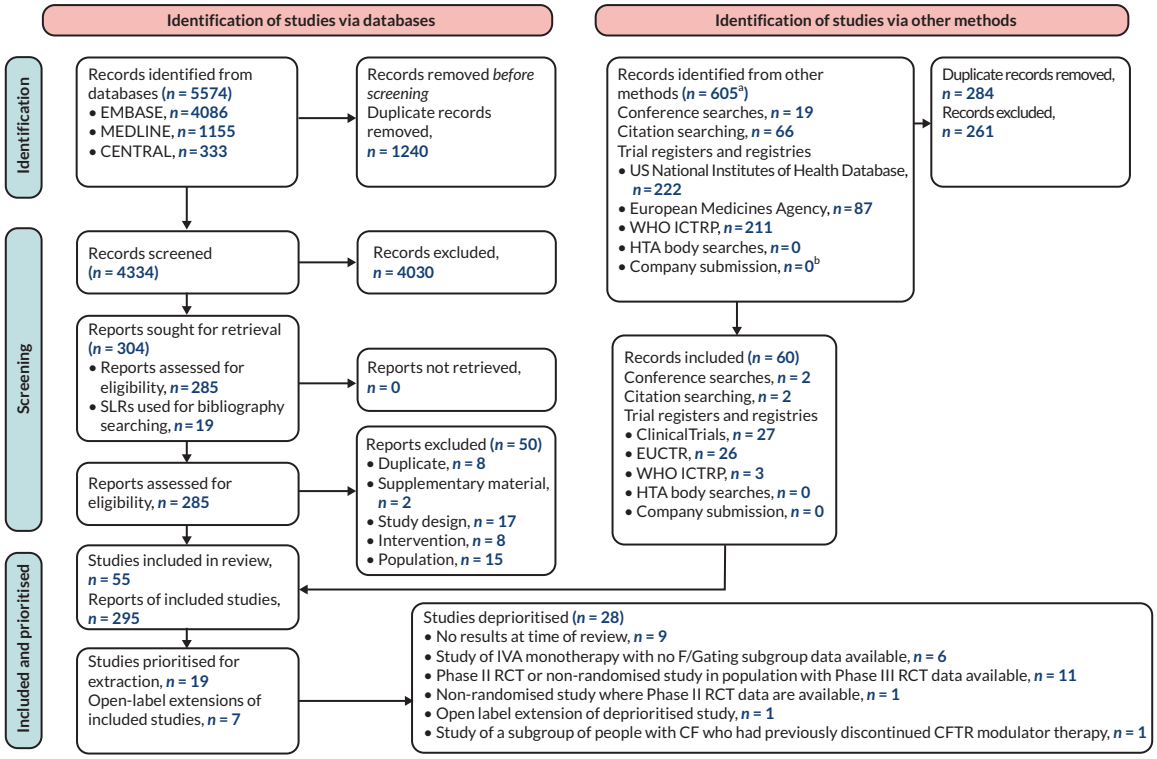

FIGURE 1 The PRISMA flow diagram of records included in the clinical SLR. a, All records from Southern *et al.* were screened but not included in records identified from other methods; b, The company provided clinical study reports for each company-sponsored study included in the SLR.

Table 7 provides a brief overview of the studies included in the SLR, and *Table 8* lists the open-label extension studies. Linked references to the studies prioritised in the SLR can be found in *Report Supplementary Material 1*, *Linked references of prioritised studies*.

Quality assessment

An overview of the study-level quality assessment performed by the EAG is presented in *Table 9*. Detailed quality assessment tables are presented in *Report Supplementary Material 1*.

Of the 16 RCTs included from the SLR, 12 were rated as being at low risk of bias. Four RCTs were identified as being at a higher risk of bias for the following reasons:

- Davies *et al*. was assessed as being at a high risk of bias because the placebo (*n* = 10) and IVA (*n* = 3) control groups were used for blinding purposes only. Efficacy data were reported only for TEZ/IVA. As a result, the outcome data from this trial are uncontrolled and are approximately equivalent to a single-arm trial.
- Ramsey *et al*., De Boeck *et al*. and Moss *et al*. were RCTs of IVA monotherapy compared with placebo, and the quality assessment was conducted of the F/Gating subgroup analysis provided by the Company. As unspecified, post hoc subgroup analyses without stratified randomisation, each of these analyses was rated as being at a risk of bias of an unpredictable magnitude and direction. However, the EAG notes that these analyses followed the same methods as the pre-specified analyses performed across the CFTR modulator clinical trials, reducing the risk of bias.

At the outcome level, the EAG completed RoB-2 assessments for ppFEV$_1$/LCI$_{2.5}$; pulmonary exacerbations; and AE reporting. These are presented in *Report Supplementary Material 1*. 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 AE only, and not in accordance with a detailed trial protocol.[115]

TABLE 7 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	Primary end point
Studies including ELX/TEZ/IVA							
Sutharsan 2022[116]	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 III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in CFQ-R from baseline through week 24
Barry 2021[117]	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 III, randomised	Efficacy: 8 weeks Safety: 12 weeks	Absolute change in $ppFEV_1$ from baseline to week 8 for the ELX/TEZ/IVA group
Middleton 2019[60]	VX17-445-102	F/MF	12 +	• ELX/TEZ/IVA (200 mg qd/100 mg qd/150 mg q12h) • Placebo	Phase III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $ppFEV_1$ from baseline at week 4
Heijerman 2019[118]	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 III, randomised	Efficacy: 4 weeks Safety: 8 weeks	Absolute change in $ppFEV_1$ from baseline at week 4
Mall 2022[119]	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 III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $LCI_{2.5}$ from baseline to week 24
Zemanick 2021[120]	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 III, non-randomised	Efficacy: 24 weeks Safety: 28 weeks	Part B: safety and tolerability as assessed by treatment emergent and serious AEs from day 1 until week 28
NCT04537793[121]	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 III, non-randomised	Safety: 28 weeks	Part B: safety and tolerability from day 1 until week 28

continued

TABLE 7 Summary of studies prioritised from the systematic review of clinical effectiveness (*continued*)

Study	Vertex protocol	Genotype/ mutation	Age, years	Interventions, comparators and doses	Phase and randomisation	Follow-up duration	Primary end point
Studies including TEZ/IVA, excluding those including ELX/TEZ/IVA							
Taylor-Cousar 2017[122]	VX14-661-106	F/F	12 +	• TEZ/IVA (100 mg qd/150 mg q12h) • Placebo	Phase 3, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $ppFEV_1$ from baseline to week 24
Rowe 2017[123]	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 III, randomised	Crossover trial consisting of two 8-week treatment periods with an 8-week washout period between	Absolute change in $ppFEV_1$ from baseline through the average of week 4 and week 8 in each treatment period
Davies 2021[124]	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) • Placebo	Phase III, randomised	Efficacy: 8 weeks Safety: 12 weeks	Within-group change from baseline in $LCI_{2.5}$ from baseline through week 8
Studies including LUM/IVA							
TRAFFIC Wainwright 2015[39]	VX12-809-103	F/F	12 +	• LUM/IVA (400 mg q12h/250 mg q12h) • LUM/IVA (600 mg qd/250 mg q12h) • Placebo	Phase III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $ppFEV_1$ from baseline to week 24
TRANSPORT Wainwright 2015[39]	VX12-809-104	F/F	12 +	• LUM/IVA (400 mg q12h/250 mg q12h) • LUM/IVA (600 mg qd/250 mg q12h) • Placebo	Phase III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $ppFEV_1$ from baseline through week 24
Wilson 2021[125]	VX15-809-112	F/F	12 +	• LUM/IVA (400 mg q12h/250 mg q12h) • Placebo	Phase IV, randomised	Efficacy: 24 weeks Safety: 28 weeks	Relative change from baseline in maximum oxygen consumption (VO_{2max}) during cardiopulmonary exercise testing at week 24
Ratjen 2017[126]	VX14-809-109	F/F	6 to 11	• LUM/IVA (200 mg q12h/250 mg q12h) • Placebo	Phase III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $LCI_{2.5}$ from baseline through week 24

TABLE 7 Summary of studies prioritised from the systematic review of clinical effectiveness (*continued*)

Study	Vertex protocol	Genotype/ mutation	Age, years	Interventions, comparators and doses	Phase and randomisation	Follow-up duration	Primary end point
Stahl 2021[127]	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/188 mg q12h) • Placebo	Phase II, randomised	Efficacy: 48 weeks Safety: 48 weeks	Absolute change from baseline in magnetic resonance imaging global chest score at week 48
Rayment 2022[128]	VX16-809-122	F/F	1 to 2	• Part B • LUM/IVA (if 7 to < 9 kg: 75 mg qd/94 mg g12h) • LUM/IVA (if 9 to < 14 kg: 100 mg qd/125 mg q12h • LUM/IVA (if ≥ 14 kg: 150 mg qd/188 mg q12h	Phase III, non-randomised	Efficacy: 24 weeks Safety: 26 weeks	Part B: safety and tolerability from day 1 until week 26
Placebo controlled studies of IVA monotherapy							
Ramsey 2011[129]	VX08-770-102	F/Gating, *G551D* mutation	12 +	• IVA 150 mg q12h • Placebo	Phase III, randomised	Efficacy: 48 weeks Safety: 48 weeks	Absolute change in $ppFEV_1$ from baseline to week 24
De Boeck 2014[130]	VX12-770-111	F/Gating, non-*G551D* mutation	6 + (12 + subgroup data provided by Company)	• IVA 150 mg q12h • Placebo	Phase III, randomised	Crossover trial consisting of two 8-week treatment periods with a 4 to 8-week washout period between	Absolute change in $ppFEV_1$ from baseline to weeks 8 and 24
Moss 2015[131]	VX11-770-110	F/*R117H* mutation	6 + (12 + subgroup data provided by Company)	• IVA 150 mg q12h • Placebo	Phase III, randomised	Efficacy: 24 weeks Safety: 28 weeks	Absolute change in $ppFEV_1$ from baseline through week 24

q12h, once every 12 hours; qd, once daily.

TABLE 8 Open-label extension studies of studies included in the systematic review of clinical effectiveness

OLE study	Vertex protocol number	Genotype	Intervention	Age group (years)	Parent studies
Griese 2022[132]	VX17-445-105	F/F F/MF	ELX/TEZ/IVA	≥ 12	Heijerman 2019[118], Middleton 2019[60]
Ratjen 2021[133]	VX19-445-107	F/F F/MF	ELX/TEZ/IVA	≥ 6	Zemanick 2021[120]
Study 445–110[134]	VX18-445-110	F/RF F/Gating	ELX/TEZ/IVA	≥ 12	Barry 2021[117]
Flume 2021[135]	VX14-661-110	F/F F/RF	TEZ/IVA	≥ 12	Taylor-Cousar 2017[122]
Sawicki 2022[136]	VX17-661-116	F/F F/RF	TEZ/IVA	≥ 6	Davies 2021[124], Walker 2019[137]
Konstan 2017[138]	VX12-809-105	F/F	LUM/IVA	≥ 12	TRAFFIC, TRANSPORT
Chilvers 2021[139]	VX15-809-110	F/F	LUM/IVA	≥ 6	Ratjen 2017[126], Milla 2017[140]

OLE, open-label extension.

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 in the trials were calculated only for participants aged ≤ 20 years. Change from baseline in weight-for-age *z*-score was calculated for the full trial populations in post hoc analyses 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 the age of 20 years. To calculate a weight-for-age *z*-score for people aged ≥ 21 years, the Company applied the growth statistics from patients aged ≥ 20 years. Overall, the EAG considers the measurement of change from baseline in weight-for-age *z*-score likely to be robust across studies. The EAG considers the use of a change from baseline statistic, rather than absolute values, to mitigate the effects of using growth statistics of 20-year-olds for older participants.

Following the assessment protocol, the EAG considered all single-arm trials to be 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 therefore preserved, or even improved, lung function, compared with the period prior to the pandemic, across respiratory disorders.[141,142] Hence, the occurrence of COVID-19 is a confounder when interpreting the results of single-arm clinical trials that collected data from 2020 onwards. *Table 10* 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 III trials of ELX/TEZ/IVA in people under 12 years and Phase III single-arm trials of LUM/IVA in infants aged 1–2 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 rated as being at high risk of bias due to COVID-19-related confounding.

Following comments from a peer reviewer, the EAG also completed a ROBINS-I outcome-level risk-of-bias assessment for each of the three single-arm parent studies. In line with the EAG's concerns about COVID-19-related confounding, pulmonary exacerbation data were rated at being at critical risk of bias in Zemanick *et al.*,[120] NCT04537793 and Rayment *et al.*[128] For the same reason, $LCI_{2.5}$ from NCT04537793 and $ppFEV_1$ from Zemanick *et al.*[120] were rated as being at serious risk of bias, whereas Rayment *et al.*[128] did not report a lung function outcome. Weight-for-age *z*-score outcomes were rated as being at moderate risk of bias for each study. Free-text responses for each of the ROBINS-I domains for each outcome are presented in *Report Supplementary Material 1*.

TABLE 9 The EAG's study-level quality assessment of RCTs included in the clinical effectiveness SLR

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Sutharsan 2022[116]	Low	Low	Low	Low	Low	Low	Low
Barry 2021[117]	Low	Low	Low	Low	Low	Low	Low
Middleton 2019[60]	Low	Low	Low	Some concerns	Low	Low	Low
Heijerman 2019[118]	Low	Low	Low	Low	Low	Low	Low
Mall 2022[119]	Low	Low	Low	Some concerns	Low	Low	Low
Taylor-Cousar 2017[122]	Low	Low	Low	Some concerns	Low	Low	Low
Rowe 2017[123]	Low	Low	Low	Some concerns	Low	Low	Low
Davies 2021[124]	Low	Low	Low	Some concerns	Some concerns	Low	Some concerns
TRAFFIC	Low.	Low	Low	Some concerns	Low	Low	Low
TRANSPORT	Low	Low	Low	Some concerns	Low	Low	Low
Wilson 2021[125]	Low	Low	Low	Some concerns	Some concerns	Low	Low
Ratjen 2017[126]	Low	Low	Low	Some concerns	Low	Low	Low
Stahl 2021[127]	Low	Low	Low	Some concerns	Low	Low	Low
Ramsey 2011[129] (F/Gating subgroup)	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
De Boeck 2014[130] (F/Gating ≥ 12 subgroup)	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Moss 2015[131] (F/Gating ≥ 12 subgroup)	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns

IVRS, interactive voice response system; IWRS, interactive web response system.

TABLE 10 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 (years)	Start date	Primary completion date
Primary single-arm clinical trials					
Zemanick 2021[120]	ELX/TEZ/IVA	F/F, F/MF	6–11	2 October 2018	7 August 2020
NCT04537793	ELX/TEZ/IVA	F/F, F/MF	2–5	19 November 2020	3 June 2022
Rayment 2022[128]	LUM/IVA	F/F	1–2	7 September 2018	29 October 2021
Extension studies					
Griese 2022[132]	ELX/TEZ/IVA	F/F, F/MF	12 +	9 October 2018	9 January 2023
Ratjen 2021[133]	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[136]	TEZ/IVA	F/F, F/RF	6 +	25 April 2018	28 October 2020

External Assessment Group's assessment of clinical effectiveness

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 *Report Supplementary Material 1*. In the following section, the key clinical outcome data that inform the economic model, and change from baseline in sweat chloride, are presented by age group. Where data were available, the EAG chose to present them through to week 24, aligning the primary end point of the key trials of LUM/IVA and TEZ/IVA. The EAG notes that there is no consensus on the time it takes for the acute effect of CFTR modulators to fully manifest, but that week 24 is likely sufficient to have allowed the full acute response on $ppFEV_1$ to be realised, and likely to have been a more appropriate time point than, for example, week 4 or week 8 for measuring changes in weight-for-age *z*-score and exacerbation frequency.

The following pre-specified outcomes were also reported in clinical trials and are presented in the detailed data extraction tables in *Report Supplementary Material 1*:

- change from baseline in BMI, BMI-for-age *z*-score, weight and CFQ-RD
- prior and concomitant CF medications.

The following pre-specified outcomes were rarely reported across the clinical trials and are not presented:

- need for lung transplantation
- changes in frequency of *Pseudomonas* colonisation
- hospitalisation measures other than requirement for IV antibiotics
- CFQ total scores
- development of CFRD.

The EAG notes that these infrequently reported outcomes typically require longer-term follow-up than the acute periods of the clinical trials, and the EAG notes that some data were available from the confidential data collection agreement (see *Data collection agreement*) and has recommended further collection for some outcomes, such as the development of CFRD diabetes, as future research priorities (see *Suggested research priorities*).

1–5 years

Three studies reported outcomes for people with CF aged 1–5 years.

- LUM/IVA:
  - Rayment *et al.* (VX16-809-122) was a Phase III non-randomised trial of people with CF aged 1–2 years with an F/F CF genotype.[128]
  - Stahl *et al.* (VX16-809-121) was a placebo-controlled Phase II RCT of LUM/IVA in children with CF aged 2–5 years with an F/F CF genotype.[127]

- ELX/TEZ/IVA:
  - NCT04537793 (VX20-445-111) was a Phase III non-randomised trial of people with CF aged 2–5 years with either an F/F or an F/MF genotype.[121,143]

The clinical outcomes studies of patients aged 1–5 years are presented in *Table 11*.

6–11 years

Four studies reported clinical outcomes following CFTR modulator therapy for people with CF aged 6–11 years.

TABLE 11 Clinical efficacy outcomes of studies of LUM/IVA and ELX/TEZ/IVA in participants aged 1–5 years

	Study			
	Rayment 2022[128]: Part B, FAS	Stahl 2021[127]: FAS		NCT04537793: Part B, FAS
Outcome	LUM/IVA (*n* = 46)	LUM/IVA (*n* = 35)	Placebo (*n* = 16)	ELX/TEZ/IVA (*n* = 75)
Genotype	F/F (*n* = 46)	F/F (*n* = 35)	F/F (*n* = 16)	F/F (*n* = 23), F/MF (*n* = 52)
Age group included, years	1–2	2–5		2–5
Time point	Week 24	Week 48	Week 24	
Absolute change from baseline in sweat chloride, mmol/l, LS mean (95% CI)	−29.1 (−34.8 to −23.4), *n* = 24	−25.4 (NR)	1.0 (NR)	−57.9 (−61.3 to −54.6)
Difference from placebo	NA	−26.4[a]	NA	
Absolute change from baseline in $LCI_{2.5}$, LS mean (95% CI)	NR	−0.37 (−0.85 to 0.10)	0.32 (−0.20 to 0.84)	−0.83 (−1.01 to −0.66)
Difference from placebo	NA	−0.69[a]	NA	
Number of protocol-defined PE events (event rate per year)	NR	26 (0.75)	19 (1.17)	12 (16%)
Number of participants with PE AE (not including serious), *n* (%). *Reported as AE through to week 48*	10 (21.2%)	15 (42.86)	9 (56.25)	NR
Number of participants with serious PE AE, *n* (%). *Reported as AE through to week 48*	3 (6.5%)	3 (8.57)	1 (6.25)	NR
Number of participants with PE requiring hospitalisation or IV antibiotics, *n* (%)	NR	NR	NR	Confidential information has been removed
Absolute change from baseline in weight-for-age *z*-score (95% CI)	0.06 (−0.05 to 0.17), *n* = 38	0.13 (−0.01 to 0.27)	−0.07 (−0.24 to 0.11)	0.02 (−0.04 to 0.09)
Difference from placebo	NA	0.20[a]	NA	NA

FAS, full analysis set; LS, least squares; NA, not applicable; NR, not reported; PE, pulmonary exacerbation.
a Calculated by EAG.

- LUM/IVA:
  - Ratjen *et al*. (VX14-809-109) was a placebo-controlled Phase III RCT of LUM/IVA in children with CF aged 6–11 years with an F/F CF genotype.[126]

- TEX/IVA:
  - Davies *et al*. (VX16-661-115) was a Phase III RCT of TEZ/IVA in children aged 6–11 years with either an F/F or an 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.[124]

- ELX/TEZ/IVA:
  - Zemanick *et al*. (VX18-445-106) was a Phase III non-randomised trial of ELX/TEZ/IVA in children aged 6–11 years with either an F/F or an F/MF CF genotype.[120]
  - Mall *et al*. (VX19-445-116) was a placebo-controlled Phase III RCT of ELX/TEZ/IVA in children with CF aged 6–11 years with an F/MF CF genotype.[119]

The outcomes of these studies are presented in *Table 12*. For all outcomes, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA led to improvements from baseline, with the magnitude of the improvements being notably larger following ELX/TEZ/IVA than following LUM/IVA and TEZ/IVA.

≥ 12 years

Nine studies reported clinical outcomes following CFTR modulator therapy for people with CF aged ≥ 12 years. Five of these were placebo-controlled RCTs of either LUM/IVA or TEZ/IVA compared with placebo,[39,123,125,144] and four were RCTs of ELX/TEZ/IVA compared with placebo, TEZ/IVA or IVA monotherapy.[60,116–118] The results of the five LUM/IVA or TEZ/IVA RCTs are presented in *Table 13*, and the results of the 5 ELX/TEZ/IVA RCTs are presented in *Table 14*. Compared with placebo, LUM/IVA and TEZ/IVA were associated with improvements in $ppFEV_1$ and weight-for-age *z*-scores, as well as with reductions in the frequency of pulmonary exacerbations requiring IV antibiotics. ELX/TEZ/IVA was associated with improvements in each clinical outcome compared with placebo, and of a larger magnitude than was observed with LUM/IVA and TEZ/IVA.

Data collection agreement

The analyses directed by the Company as part of the data collection agreement were marked as confidential.[87] The EAG considered them to be largely in line with the clinical trial data presented. A discussion of the similarity of the DCA data to the clinical trial data is provided in the *Report Supplementary Material 1*; however, it is heavily redacted due to the confidentiality markings placed by the Company.

Relationship between clinical efficacy and baseline lung function

Differences in the absolute change from baseline in $ppFEV_1$ between lung function subgroups were reported as pre-specified outcomes in eight pivotal Phase III RCTs of people with CF aged ≥ 12 years.[39,60,116–118,122,123] These subgroup data are presented in *Table 15*. 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 for the $ppFEV_1$ ≥ 70 at baseline group, but 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, with a smaller absolute increase observed for those with already high baseline $ppFEV_1$. However, for such individuals, the benefit of CFTR modulators may be more visible in the prevention or delaying of lung function decline rather than through an acute increase in $ppFEV_1$.

Generalisability of clinical trial data to clinical practice in England

The clinical trials informing the cost-effectiveness analysis were international, multicentre trials, primarily consisting of sites across North America, Europe and Australia (see *Report Supplementary Material 1*). The EAG's clinical experts considered clinical practice across these regions to be generalisable to clinical practice in England, and did not consider that variables that may differ across countries were likely to modify the treatment effect of CFTR modulators. The

TABLE 12 Clinical efficacy outcomes of studies of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA in participants aged 6–11 years

Outcome	Study							
	Ratjen 2017,[126] FAS at week 24		Davies 2021,[124] mITT at week 8			Zemanick 2021,[120] mITT at week 24	Mall 2022,[119] FAS at week 24	
	LUM/IVA (*n* = 103)	Placebo (*n* = 101)	TEZ/IVA (*n* = 54)	IVA (*n* = 3)	Placebo (*n* = 10)	ELX/TEZ/IVA (*n* = 66)	ELX/TEZ/IVA (*n* = 60)	Placebo (*n* = 61)
Genotype	F/F (*n* = 103)	F/F (*n* = 101)	F/F (*n* = 42), F/RF (*n* = 12)	F/RF (*n* = 3)	F/F (*n* = 10)	F/F (*n* = 29), F/MF (*n* = 37)	F/MF (*n* = 60)	F/MF (*n* = 61)
Age group, years	6 to 11		6 to 11			6 to 11	6 to 11	
Time point	Week 24 (week 4 for sweat chloride)		Week 8			Week 24	Week 24	
Absolute change from baseline in sweat chloride, mmol/l, LS mean (95% CI)	−20.0 (−22.0 to −18.1)	0.8 (−1.2 to 2.8)	−12.3 (−15.3 to −9.3)	−1 (SD 9)	−1 (SD 12.3)	−60.9 (−63.7 to −58.2)	−52.1 (−55.0 to −49.2)	−0.9 (−3.8 to 2.0)
Difference from placebo	−20·8 (−23.4 to −18.2)		NR			NA	−51.2 (−55.3 to −47.1)	
Absolute change from baseline in $LCI_{2.5}$, LS mean (95% CI)	−1.01 (−1.3 to −0.8)	0.08 (−0.2 to 0.3)	−0.51 (−0.74 to −0.29)	−0.61 (SD 0.88)	0.10 (SD 1.16)	−1.71 (−2.11 to −1.30)	−2.29 (−2.60 to −1.97)	−0.02 (−0.34 to 0.29)
Difference from placebo	−1.09 (−1.43 to −0.75)		NR	NR	NR	NA	−2.26 (−2.71 to −1.81)	
Absolute change from baseline in $ppFEV_1$, LS mean (95% CI)	1.1 (−0.4 to 2.6)	−1.3 (−2.8 to 0.2)	2.8 (1.0 to 4.6)	−0.4 (SD 6.0)	−3.7 (SD 6.1)	10.2 (7.9 to 12.6)	9.5 (6.6 to 12.4)	−1.5 (−4.4 to 1.4)
Difference from placebo (95% CI)	2.4 (0.4 to 4.4)		NR			NA	11.0 (6.9 to 15.1)	
Number of participants with PEs, *n* (%)	Confidential information has been removed	Confidential information has been removed	NR	NR	NR	4 (6%)	NR	NR
Number of participants with PE AE (not including serious), *n* (%). *Reported as AE through safety follow-up*	16 (15.84)	13 (12.62)	3 (5.56)	0	2 (20.0)	NR	1 (1.67)	14 (22.95)
Number of participants with serious PE AE, *n* (%). *Reported as AE through safety follow-up*	5 (4.95)	8 (7.77)	0	0	0	NR	0 (0.00)	3 (4.92)
Number of participants with PE requiring hospitalisation or IV antibiotics, *n* (%)	Confidential information has been removed	Confidential information has been removed	NR	NR	NR	Confidential information has been removed	NR	NR
Absolute change from baseline in weight-for-age *z*-score (95% CI)	Confidential information has been removed	Confidential information has been removed	−0.04 (SD 0.17)	0.03 (SD 0.23)	−0.02 (SD 0.15)	0.25 (0.16 to 0.33)	Confidential information has been removed	Confidential information has been removed
Difference from placebo (95% CI)	Confidential information has been removed					NA	Confidential information has been removed	

FAS, full analysis set; mITT, modified intention to treat; NA, not applicable; NR, not reported; SD, standard deviation.

TABLE 13 Clinical efficacy outcomes of RCTs of LUM/IVA and TEZ/IVA in people with CF aged ≥ 12 years

Outcome	Study									
	TRAFFIC (Wainwright 2015),[39] FAS		TRANSPORT (Wainwright 2015),[39] FAS		Wilson 2021,[125] FAS		Taylor-Cousar 2017,[122] mITT		Rowe 2017,[123] FAS	
	LUM/IVA (n = 182)	Placebo (*n* = 184)	LUM/IVA (*n* = 187)	Placebo (*n* = 187)	LUM/IVA (*n* = 34)	Placebo (*n* = 36)	TEZ/IVA (*n* = 248)	Placebo (*n* = 256)	TEZ/IVA (*n* = 161)	Placebo (*n* = 161)
Genotype	F/F (*n* = 182)	F/F (*n* = 184)	F/F (*n* = 187)	F/F (*n* = 187)	F/F (*n* = 34)	F/F (*n* = 36)	F/F (*n* = 248)	F/F (*n* = 256)	F/RF (*n* = 161)	F/RF (*n* = 161)
Age group, years	≥ 12		≥ 12		≥ 12		≥ 12		≥ 12	
Time point	Week 24		Week 24		Week 24		Week 24		Week 8	
Absolute change from baseline in sweat chloride, mmol/l, LS mean (95% CI)	NR	NR	NR	NR	NR	NR	−9.9[b] (−10.9 to −8.9)	0.2[c] (−0.8 to 1.2)	−9.9 (−11.8 to −8.0)	−0.4 (−2.3 to 1.5)
Difference from placebo	NR		NR		NR		−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)	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)	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)	2.6 (1.18 to 4.01)		3.0 (1.56 to 4.44)		3.4 (−1.2 to 8.1)		4.0 (3.1 to 4.8)		6.8 (5.7 to 7.8)	
Number of participants with PE AE (not including serious), *n* (% of SAS)	54 (29.67)	58 (31.52)	50 (26.74)	74 (39.78)[a]	8 (23.53)	6 (16.67)	57 (22.7)[d]	75 (29.1)[d]	19 (11.73)[e]	25 (15.43)[e]
Number of participants with serious PE AE, *n* (% of SAS)	17 (9.34)	41 (22.28)	24 (12.83)	48 (25.81)[a]	8 (23.53)	6 (16.67)	23 (9.16)[d]	32 (12.4)[d]	4 (2.47)[e]	8 (4.94)[e]
Number of protocol-defined PE events (annualised event rate)	73 (0.71)	112 (1.08)	79 (0.67)	139 (1.18)	NR	NR	78 (0.64)	122 (0.99)	11 (0.34)	20 (0.63)
Number protocol-defined PE events requiring hospitalisation (annualised event rate)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	NR	NR	NR	NR	NR	NR

TABLE 13 Clinical efficacy outcomes of RCTs of LUM/IVA and TEZ/IVA in people with CF aged ≥ 12 years (*continued*)

Outcome	Study									
	TRAFFIC (Wainwright 2015),[39] FAS		TRANSPORT (Wainwright 2015),[39] FAS		Wilson 2021,[125] FAS		Taylor-Cousar 2017,[122] mITT		Rowe 2017,[123] FAS	
	LUM/IVA (n = 182)	Placebo (*n* = 184)	LUM/IVA (*n* = 187)	Placebo (*n* = 187)	LUM/IVA (*n* = 34)	Placebo (*n* = 36)	TEZ/IVA (*n* = 248)	Placebo (*n* = 256)	TEZ/IVA (*n* = 161)	Placebo (*n* = 161)
Number protocol-defined PE events requiring IV antibiotics (annualised event rate)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	NR	NR	NR	NR	NR	NR
Rate ratio of PE events requiring IV antibiotics vs. placebo	Pooled: 0.44 (0.32 to 0.59)		NR		NR		0.53 (0.34 to 0.80)		0.54 (0.26 to 1.13)	
Absolute change from baseline in weight-for-age *z*-score	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Difference from placebo (95% CI)	Confidential information has been removed						Confidential information has been removed		Confidential information has been removed	
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	NR	NR	NR	NR
Difference from placebo (95% CI)	0.0095 (−0.011 to 0.030)	NR	−0.0009 (−0.019 to 0.017)	NR	NR	NR	NR	NR	NR	NR

FAS, full analysis set; mITT, modified intention to treat; NR, not reported; SAS; safety analysis set; SD, standard error; SE, standard error.
a *n* = 186 for this outcome.
b *n* = 240 for this outcome.
c *n* = 242 for this outcome.
d Reported as AE in SAS through to week 28, SAS *n* = 251 TEZ/IVA, SAS *n* = 256 placebo.
e Reported as AE in SAS through to week 28, SAS *n* = 162 for both TEZ/IVA and placebo.

TABLE 14 Clinical efficacy outcomes of RCTs of ELX/TEZ/IVA in people with CF aged ≥ 12 years

	Sutharsan 2022,[116] mITT		Heijerman 2019,[118] FAS		Barry 2021,[117] FAS		Barry 2021,[117] FAS		Middleton 2019,[60] FAS	
	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)
Genotype	F/F (*n* = 87)	F/F (*n* = 88)	F/F (*n* = 55)	F/F (*n* = 52)	F/RF (*n* = 82)	F/RF (*n* = 81)	F/Gating (*n* = 50)	F/Gating (*n* = 45)	F/MF (*n* = 200)	F/MF (*n* = 203)
Age group, years	12 +		12 +		12 +		12 +		12 +	
Time point	Week 24		Week 4		Week 8		Week 8		Week 24	
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 PE AE (not including serious), *n* (% of SAS)	10 (11.49)[a]	32 (36.36)[a]	0[b]	5 (9.62)[b]	Combined across genotypes:[c] ELX/TEZ/IVA = 2 (1.52%); active control = 10 (7.94%)				41 (20.30)[d]	83 (41.29)[d]
Number of participants with serious PE AE, *n* (% of SAS)	1 (1.15)[a]	9 (10.23)[a]	1 (1.82)[b]	1 (1.92)[b]	Combined across genotypes:[c] ELX/TEZ/IVA = 2 (1.52%); active control = 7 (5.56%)				11 (5.45)[d]	33 (16.42)[d]
Number of participants with protocol-defined PE, (%)	NR	NR	NR	NR	NR	NR	NR	NR	41 (20.5)	113 (56.5)
Annual event rate PE requiring IV antibiotics	NR	NR	NR	NR	NR	NR	NR	NR	Confidential information has been removed	Confidential information has been removed

TABLE 14 Clinical efficacy outcomes of RCTs of ELX/TEZ/IVA in people with CF aged ≥ 12 years (*continued*)

	Sutharsan 2022,[116] mITT		Heijerman 2019,[118] FAS		Barry 2021,[117] FAS		Barry 2021,[117] FAS		Middleton 2019,[60] FAS	
	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)
Difference from TEZ/IVA or placebo (rate ratio, 95% CI)	NR		NR		NR		NR		Confidential information has been removed	
Absolute change from baseline in weight-for-age *z*-score	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Difference from TEZ/IVA or placebo (95% CI)	Confidential information has been removed		Confidential information has been removed		Confidential information has been removed		Confidential information has been removed		Confidential information has been removed	

FAS, full analysis set; mITT, modified intention to treat; NR, not reported; SAS; safety analysis set; SE, standard error.
a Reported as AE through to week 28.
b Reported as AE through to week 8.
c Reported as AE through to week 12b.
d *n* SAS = 202 (ELX/TEZ/IVA); *n* SAS = 201n/n/(placebo).

TABLE 15 Between-treatment difference in absolute change from ppFEV$_1$, by ppFEV$_1$ subgroup, for people with CF aged ≥ 12 years

				Between treatment difference in absolute change from ppFEV$_1$, by ppFEV$_1$ subgroup				
Study	**Intervention**	**Genotype**	**Time point**	**ppFEV$_1$ < 40**	**ppFEV$_1$ ≥ 40**	**≥ 40 ppFEV$_1$ < 70**	**ppFEV$_1$ < 70**	**ppFEV$_1$ ≥ 70**
Middleton 2019[60]	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[117]	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[116]	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[118]	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[122]	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[123]	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)

NR, not reported.

EAG notes that the doses used across the trials in the EAG's SLR matched the doses outlined in the product Summary of Product Characteristics (SmPC), except a minor difference between the SmPC and the dose thresholds used for TEZ/IVA in Davies *et al*.[124]

The EAG's clinical experts noted that clinical outcomes for people with CF continually improved in the decade before CFTR modulators were routinely available, and therefore data from recent clinical trials are more likely to be generalisable to clinical practice in England than data from early trials of CFTR modulators.[1] The EAG notes that the median predicted survival of individuals with CF consistently increased in the 2000s[15] and that the use of dornase alfa and hypertonic saline solution – key mucolytic therapies used in ECM – consistently increased from 2008 to 2018.[145] However, the EAG considers that in RCTs, changes to ECM and the baseline survival of CF patients are likely to have similar impacts across intervention and control arms, and as a result the relative treatment effects from earlier CFTR modulator RCTs are likely to be still generalisable to clinical practice in England today.

The EAG notes that the inclusion criteria of the clinical trials for people with CF aged ≥ 12 years included a criterion of 40–90% $ppFEV_1$ at screening. This was noted in TA398 as possibly limiting the generalisability of the trial results to patients with severe lung disease (< 40% $ppFEV_1$) or those with very mild CF (≥ 90% $ppFEV_1$).[146] Following discussion with its clinical experts, the EAG considers that:

- People with a $ppFEV_1$ outside 40–90% 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.
  - In the TEZ/IVA and LUM/IVA trials where subgroup data reported participants with baseline $ppFEV_1$ < 40%, the magnitude of the treatment response was similar to that in the overall cohorts (see *Table 15*).
  - 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.[144]
  - In the final analysis of the UK DCA, participants who initiated ELX/TEZ/IVA with a baseline $ppFEV_1$ < 40% experienced an increase in $ppFEV_1$ after 1 year that was similar in magnitude to the increase observed in clinical trials in participants with a higher baseline $ppFEV_1$.[87]

The EAG notes that the clinical trial data presented in *Results* may have limited generalisability to the incident population of children who initiate ELX/TEZ/IVA aged 2 years, but that limited data are available for such children. The EAG's clinical experts considered that if ELX/TEZ/IVA was initiated very early, that is before substantial lung or pancreatic damage has occurred, it is plausible that ELX/TEZ/IVA may prevent most lung function and other clinical decline in these individuals. Although plausible, the EAG notes substantial uncertainty regarding the long-term clinical outcomes of people aged 2 years initiating ELX/TEZ/IVA due to:

- The lack of any data on the long-term clinical outcomes of people aged 2 years initiating ELX/TEZ/IVA.
- The likelihood of irreversible severe pancreatic and other organ damage prior to the age of 2 years,[147] with substantial damage likely occurring in utero.[148]
- 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.[149]

Hence, while the EAG notes that children initiating ELX/TEZ/IVA at the age of 2 years may have even more positive clinical outcomes than people initiating ELX/TEZ/IVA at an older age, the magnitude and consistency of the long-term treatment response is uncertain.

Adverse effects of treatment

Data on the adverse effects of CFTR modulator treatments from trials identified in the SLR are presented in *Report Supplementary Material 1*. For ELX/TEZ/IVA, the number of participants experiencing AEs and serious AEs was smaller in the ELX/TEZ/IVA arms than in the placebo or TEZ/IVA control arms of RCTs. For LUM/IVA and TEZ/IVA, the number of participants experiencing AEs and serious adverse events was similar in the CFTR modulator arms and the control arms of RCTs. However, as pulmonary exacerbations were recorded as AEs in CFTR modulator clinical trials, and CFTR modulator therapies reduce the rate of pulmonary exacerbations, the incidence of non-pulmonary exacerbations AE

is an important consideration. The EAG therefore extracted data on AEs highlighted as important by the EAG's clinical experts – liver AEs, cataracts and lens opacities, and hypertension – and AEs of special interest reported throughout the CFTR modulator clinical trial programme – liver AEs 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 than for placebo, and similar for LUM/IVA and placebo. The EAG notes that:

- The magnitude of the increase in number of liver AEs was larger for ELX/TEZ/IVA than for TEZ/IVA.
- The main cost of these non-serious liver AEs is likely to be realised in the likelihood of discontinuation because of the AEs, rather than in treating or investigating the AE itself.

In RCTs, rash events were more frequent in the ELX/TEZ/IVA and LUM/IVA arms than in placebo arms, but were not elevated in TEZ/IVA arms compared with 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 (see *Report Supplementary Material 1*), but the safety analysis period for most trials was only 28 weeks, which may have been insufficient to detect meaningful elevations related to the long-term use of CFTR modulators. The EAG viewed confidential data on the incidence of cataracts, lens opacities and hypertension from the clinical study reports of the CFTR modulator extension studies, and noted that:

- No placebo-controlled data are available for a comparative analysis.
- The reporting of cataracts, lens opacities and hypertension was inconsistent across clinical study reports.
- Follow-up data are still limited to the length of the extension studies and are not available over a patient's lifetime.

Owing to these limitations, the EAG considers the magnitude of any increase in cataracts, lens opacities and hypertension following CFTR modulator to be uncertain in existing data, but notes that there is currently no evidence that such AEs are frequent enough to incur large costs.

Mental health

Serious AEs relating to mental health were not common in the CFTR modulator clinical trials. 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'.[150] However, the submission also reported anecdotal evidence of mental health difficulties developing, or increasing in severity, following CFTR modulator therapy. Such concerns were also reported in the CF Trust submission,[26] 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 the 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 in future research. The EAG notes that the psychiatric disorder AEs reported confidentially in the clinical study reports of RCTs with 28-week safety follow-up were infrequent, and there was little evidence to suggest that any were elevated over placebo.[39,60,116,122] However, the EAG considers that mental health AEs are unlikely to be captured adequately in the short-term clinical trial data currently available. The EAG notes:

- While there is uncertainty around the rates of mental health AEs related to CFTR modulator therapies, the overall rates of serious AEs are likely to be low.
- The costs of such AEs may be captured in the rate of discontinuation of therapy, and combined with a low overall event rate costs beyond those associated with discontinuation are unlikely to have a meaningful impact on the average cost-effectiveness of treatment with CFTR modulator therapy.

Indirect treatment comparisons

A connected evidence network was available for the following populations:

- F/F genotype aged ≥ 12 years
- F/RF genotype aged ≥ 12 years
- F/Gating genotype aged ≥ 12 years.

The EAG therefore conducted indirect treatment comparisons within these populations for the following variables entering the economic model: change from baseline in $ppFEV_1$ and weight-for-age *z*-score. NMAs were not possible for the frequency of pulmonary exacerbations requiring IV antibiotics owing to a lack of reporting of this outcome across studies in the networks. All NMA models converged, and Brooks–Gelman–Rubin diagnostic plots for each model are presented in *Report Supplementary Material 1*.

F/F ≥ 12 years

Six studies reported a change from baseline in $ppFEV_1$, and the EAG conducted a base-case analysis including the five studies reporting this outcome through to week 24. In a sensitivity analysis, the EAG also included Heijerman *et al.*,[118] who reported the change from baseline in $ppFEV_1$ at week 4. Across the studies included in the NMA, patients had similar non-CFTR modulator prior medications and similar baseline $ppFEV_1$ and CFQ-R RD score (see *Report Supplementary Material 1*). The key $ppFEV_1$ eligibility criterion was the same, 40–90%, across all studies, study discontinuation was infrequent, and in placebo-controlled trials the placebo response was similar. Each included study was assessed to be at a low risk of bias at both the study level and the $ppFEV_1$ outcome level, except Wilson *et al.*, which was rated as having 'some concerns' as 11% of participants were missing outcome data for $ppFEV_1$. Overall, the EAG did not consider there to be evidence of any meaningful violation of the transitivity assumption of the NMA. Four of the Phase III trials, TRAFFIC, TRANSPORT, Taylor-Cousar *et al.*[122] and Sutharsan *et al.*,[116] reported a change in weight-for-age *z*-score at week 24 and were included in the weight-for-age *z*-score NMA. A network diagram is presented in *Figure 2*.

The results of the EAG's base-case NMA for the absolute change in $ppFEV_1$ through to week 24 are presented in *Table 16*. For each CFTR modulator, the treatment effect compared with placebo was positive and the 95% credible intervals (CrIs) excluded 0. For the two contrasts informed by indirect evidence only, the mean estimated increase in $ppFEV_1$ through to week 24 was 14.20 (95% CrI 12.07 to 16.31) between ELX/TEZ/IVA and placebo and 11.37 (95% CrI 9.03 to 13.70) between ELX/TEZ/IVA and LUM/IVA. The only contrast for which the 95% CrIs 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).

The results of the EAG sensitivity analysis and an NMA provided by the Company were directly in line with the EAG's base-case analysis and are presented in *Report Supplementary Material 1*.

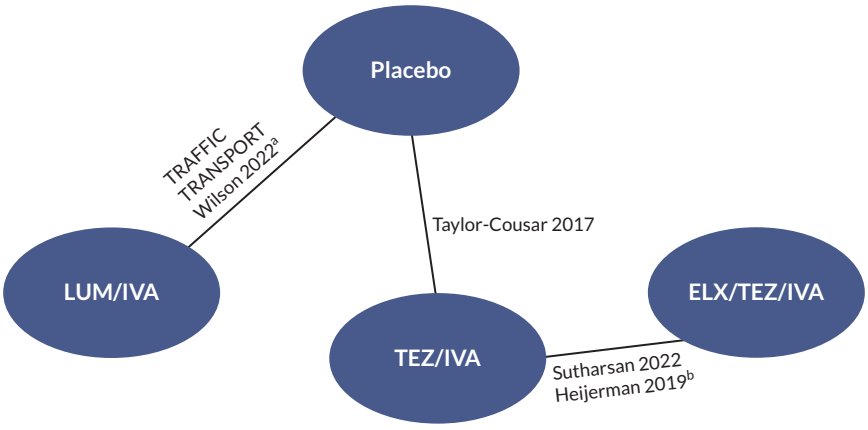

FIGURE 2 Network diagram for the EAG ≥ 12 years F/F NMAs. a, Included in the $ppFEV_1$ NMAs only; b, included in the $ppFEV_1$ sensitivity analysis only.

TABLE 16 Results of the EAG base-case NMA for absolute change from baseline in ppFEV$_1$ through to week 24 in the F/F ≥ 12 years population

ppFEV1: F/F ≥ 12 years: EAG base case	ELX/TEZ/IVA	LUM/IVA	Placebo	TEZ/IVA
ELX/TEZ/IVA	ELX/TEZ/IVA	–	–	–
LUM/IVA	11.37 (9.03 to 13.70)	LUM/IVA	–	–
Placebo	14.20 (12.07 to 16.31)	2.83 (1.84 to 3.81)	Placebo	–
TEZ/IVA	10.20 (8.25 to 12.16)	−1.17 (−2.46 to 0.13)	−4.00 (−3.15 to −4.85)	TEZ/IVA

The results of the EAG's NMA for the absolute change in weight-for-age *z*-score at week 24 contained confidential data. For all ELX/TEZ/IVA contrasts, the treatment effect was positive, and the 95% CrIs excluded 0. The LUM/IVA versus placebo contrast was the only other contrast to have a 95% CrIs excluding 0, but the magnitude of the difference was small. The EAG's results for weight-for-age *z*-scores were the same as the Company's estimates.

Neither the EAG nor the Company conducted indirect comparisons for pulmonary exacerbations requiring IV antibiotics. Of the seven studies included in the EAG's 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 *et al.*[122] No study of ELX/TEZ/IVA reported pulmonary exacerbations requiring IV antibiotics as an outcome. For the economic model, the EAG agreed with the Company that the most appropriate method of modelling the rate pulmonary exacerbations requiring IV antibiotics for ELX/TEZ/IVA treated patients with an F/F genotype was to apply the observed rate ratio from F/MF patients treated with ELX/TEZ/IVA in Middleton *et al.*[60] The number of pulmonary exacerbations requiring IV antibiotics, and the number of participants experiencing serious pulmonary exacerbation AEs for the F/F ≥ 12 years group, along with the F/MF ≥ 12 years ELX/TEZ/IVA data, are presented in *Table 17*.

TABLE 17 Rate ratio of pulmonary exacerbations of CFTR modulators compared with placebo, and percentage of participants with serious pulmonary exacerbations in the F/F genotype, aged ≥ 12 years

Study	Intervention	Comparator	Rate ratio of participants with PEs requiring IV antibiotics (intervention vs. placebo)	Percentage of participants with serious PE AEs, % of SAS at week 28		
				Intervention	Comparator	Odds ratio (95% CI)[b]
TRAFFIC	LUM/IVA	Placebo	Confidential information has been removed	9.34	22.28	0.36 (0.19 to 0.66)
TRANSPORT	LUM/IVA	Placebo		12.83	25.81	0.43 (0.24 to 0.72)
Wilson 2021[124]	LUM/IVA	Placebo	NR	23.53	16.67	1.52 (0.46 to 5.29)
Taylor-Cousar 2017[122]	TEZ/IVA	Placebo	0.53 (95% CI 0.34 to 0.82)	9.16	12.4	0.71 (0.40 to 1.25)
Sutharsan 2022[116]	ELX/TEZ/IVA	TEZ/IVA	NR	1.15	10.23	0.12 (0.005 to 0.65)
Heijerman 2019[118]	ELX/TEZ/IVA	TEZ/IVA	NR	1.82[a]	1.92[a]	0.94 (0.02 to 37.52)
Middleton 2019[60]	ELX/TEZ/IVA F/MF genotype	Placebo	0.22 (95% CI 0.11 to 0.43)	5.45	16.42	0.30 (0.14 to 0.59)

NR, not reported; PE, pulmonary exacerbation; SAS, safety analysis set.
a Reported at week 4.
b Calculated by EAG.

F/RF ≥ 12 years

In the F/RF ≥ 12 years population, only two studies were included in the EAG's NMA: Rowe *et al.*[123] (F/RF subgroup: TEZ/IVA vs. placebo) and Barry *et al.*[117] (F/RF subgroup: ELX/TEZ/IVA vs. placebo). In both studies, patients had similar non-CFTR modulator prior medications (see *Report Supplementary Material 1*). Participants in Barry *et al.*[117] had a slightly higher baseline ppFEV$_1$ (mean ELX/TEZ/IVA 68.10, mean placebo 67.80) than participants in Rowe *et al.*[123] (mean TEZ/IVA 61.80, mean placebo 62.10); however, this is likely in part due to the TEZ/IVA run-in period in Barry *et al.*,[117] which is accounted for in the indirect comparison. The EAG therefore considers the participants to be similar in Barry *et al.*[117] and Rowe *et al.*[123] The key ppFEV$_1$ eligibility criterion was the same, 40–90%, across both studies, and study discontinuation was infrequent (see *Report Supplementary Material 1*). Both studies were assessed to be at low risk of bias at the study level and at the ppFEV$_1$ outcome level. Although Rowe *et al*. was a crossover trial, the EAG considers the washout period of 8 weeks between treatments to be adequate to remove any biasing effects of the previous treatment. A network diagram for the F/RF ≥ 12 years population is presented in *Figure 3*.

The EAG's indirect estimate of the absolute change from baseline in ppFEV$_1$ through to 8 weeks between ELX/TEZ/IVA and placebo was 8.80 (95% CrI 7.01 to 10.61), which was similar to the results of a Bucher analysis supplied by the Company.

For the change in weight-for-age *z*-score at week 8, the EAG's estimate was directly in line with the Company estimate.

For pulmonary exacerbations, the EAG agreed with the Company that the most appropriate method of modelling the rate pulmonary exacerbations requiring IV antibiotics for ELX/TEZ/IVA treated patients with an F/RF genotype was to use the observed rate ratio from F/MF ELX/TEZ/IVA treated patients in Middleton *et al.*[60]

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 *et al.*[117] (F/Gating subgroup: ELX/TEZ/IVA vs. placebo); Ramsey *et al*. (post hoc F/*G551D* subgroup IVA vs. placebo); De Boeck *et al*. (post hoc F/*non-G551D* ≥ 12 years subgroup IVA vs. placebo); and Moss *et al*. (post hoc F/*R117H* ≥ 12 years subgroup IVA vs. placebo). Compared with the NMAs of the F/F ≥ 12 years population and the F/RF ≥ 12 years population, the EAG considers the transitivity assumption likely to be violated in the F/Gating NMA. This is because the prevalence of specific gating or *R117H* mutations, and concomitant best supportive care medications, differed across studies and may be treatment effect modifiers. Specifically:

- The *R117H* mutation is associated with a milder CF phenotype than gating mutations, which may limit the acute increase in ppFEV$_1$ possible for a participant with preserved lung function.[151] The distribution of non-*F508del* CF mutations in Barry *et al.*[117] (F/Gating subgroup), Ramsey *et al*. (post hoc F/*G551D*), De Boeck *et al*. (post hoc F/*non-G551D* ≥ 12 years subgroup) and Moss *et al*. (post hoc F/*R117H* ≥ 12 years subgroup) are presented in *Table 18*.
- Inhaled hypertonic saline was not an approved therapy during Ramsey *et al*. and De Boeck *et al*. and is known to reduce the rate of pulmonary exacerbations in CF.[129,130] The exclusion of inhaled hypertonic saline from Ramsey *et al*.

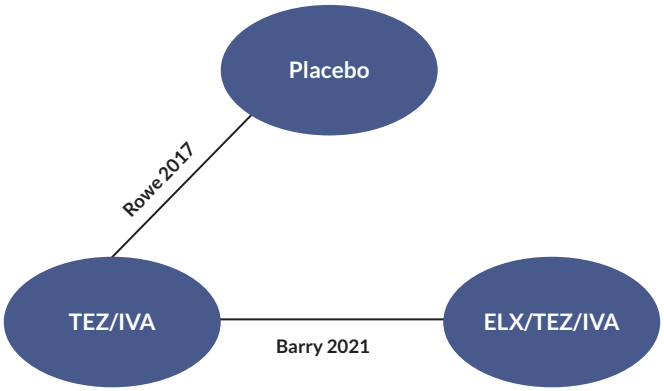

FIGURE 3 Network diagram for the EAG ≥ 12 years F/RF NMA.

TABLE 18 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[117]	ELX/TEZ/IVA	50	35	70	8	16	7	14
	IVA	45	26	58	8	18	11	24
Ramsey 2011[129]	IVA	64	64	100	0	0	0	0
	Placebo	58	58	100	0	0	0	0
De Boeck 2014[130]	IVA	17	0	0	0	0	17	100
	Placebo	17	0	0	0	0	17	100
Moss 2015[131]	IVA	20	0	0	20	100	0	0
	Placebo	19	0	0	19	100	0	0
Total IVA vs. placebo	IVA	101	64	63	20	20	17	17
	Placebo	94	58	62	19	20	17	18

and De Boeck *et al*. may have been offset by a higher use of dornase alfa (73.1% in the placebo arm and 65.1% of the ivacaftor arm across Ramsey *et al*., compared with 52% across both arms in Barry *et al.*[117]), but it is likely that ECM was less optimised in earlier ivacaftor trials, which could have overestimated the treatment effect of the ivacaftor, relative to ECM today.

The EAG notes that while the distribution of F/Gating mutations differs across Ramsey *et al.*[129], De Boeck *et al.*[130] and Moss *et al.*[131], the pooled distribution of mutations is similar to that in Barry *et al.*[117] Nevertheless, those with the F/*R117H* genotype constitute only 19% of participants across the studies considered for inclusion in the NMA, whereas in England in 2021 those with the F/*R117H* genotype constituted 4.6% of genotyped individuals.[152] A network diagram for the F/Gating ≥ 12 years population is presented in *Figure 4*.

The EAG presents the results of both fixed-effect and random-effects NMAs for the F/Gating population. The point estimates of the fixed-effect and random-effect estimates were similar, and no meaningful difference in DIC was observed: random-effect NMA (DIC = 8.1) and the fixed-effect NMAs (DIC = 9.0). The EAG considered the 95% CrIs of the random-effect ppFEV$_1$ model to be implausibly wide and hence the EAG preferred the fixed-effect NMA for the absolute change in ppFEV$_1$. For the weight-for-age *z*-score analysis, the EAG did not consider the 95% CrIs to be implausibly wide, and so preferred the results of the random-effects NMA model, which had a lower DIC (8.5) than the fixed-effect NMAs (13.5).

The EAG and Company analyses contained confidential data and so the exact results could not be reported.

In both the fixed-effect and random-effects ppFEV$_1$ analysis, ELX/TEZ/IVA was associated with a larger increase in ppFEV$_1$ through to week 8 than IVA and placebo, and IVA was associated with a larger increase in ppFEV$_1$ through to week 8 than placebo. In the NMAs of the change from baseline in weight-for-age *z*-score at week 8, ELX/TEZ/IVA was associated with a similar change from baseline to that of IVA monotherapy. This was numerically larger than placebo, but the 95% CrIs crossed 0. The EAG analysis was directly in line with the Company analysis.

Confidence in Network Meta-Analysis

Confidence in Network Meta-Analysis (CINeMA) is a framework used to evaluate confidence in the results of NMAs.[153] Following the assessment protocol, the EAG comments on each of the CINeMA domains across the NMAs performed by the EAG in *Report Supplementary Material 1*. 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 notes that:

- The results of the NMAs are uncertain due to small number of studies within each network, which also precluded a robust assessment of heterogeneity.
- There are no defined minimum clinically important differences for ppFEV$_1$ and weight-for-age *z*-score to aid interpretation of the results. While the magnitude of response to ELX/TEZ/IVA is clinically important, this is less clear for TEZ/IVA and LUM/IVA.

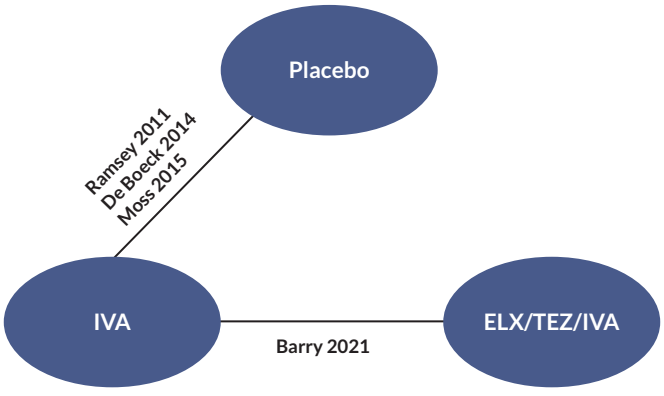

FIGURE 4 Network diagram for the EAG ≥ 12 years F/Gating (including F/*R117H*) NMA.

Efficacy data for evidence gaps

In the 6–11 years age group, no RCT data were available that could provide direct evidence or form a connected evidence network for ELX/TEZ/IVA in the F/F, F/RF and F/Gating genotypes, and for TEZ/IVA in the F/F and F/RF genotypes. For these evidence gaps, the EAG considered three approaches to estimating missing data for ELX/TEZ/IVA or TEZ/IVA versus placebo:

1. applying the observed change from baseline following CFTR modulator therapy from single-arm trials, under the conservative assumption of no worsening for ECM-treated patients during the trial period
2. applying observed RCT data from other genotypes to genotypes where data were missing, under the assumption that the effectiveness of CFTR modulators should be similar between genotypes
3. scaling the acute effects observed in RCTs for people with CF aged ≥ 12 years down, based on the observed difference in treatment response between those ≥ 12 years and those 6–11 years where data are available.

Following these criteria, the EAG's preferred assumptions for the clinical efficacy of ELX/TEZ/IVA and TEZ/IVA in the 6–11 years genotypes where no RCT data were available are presented in *Table 19*. Assumptions were not required for treatment effects on the frequency of pulmonary exacerbations requiring IV antibiotics, as neither the EAG nor the Company modelled an additional treatment effect of CFTR modulators on pulmonary exacerbations requiring IV antibiotics above that predicted by $ppFEV_1$ for the 6–11 years age group. The EAG notes this is a conservative assumption.

Annual rate of $ppFEV_1$ decline

In addition to causing an acute increase in $ppFEV_1$, CFTR modulators affect the long-term rate of $ppFEV_1$ decline in people with CF, which is a key predictor of survival.[154,155] However, few long-term or comparative data are available comparing the impact of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the annual rate of $ppFEV_1$ decline with that of ECM because:

TABLE 19 The EAG's assumptions and sources used for gaps in clinical evidence for people aged between 6 and 11 years

Genotype	Outcome	EAG assumption	Comment
TEZ/IVA			
F/F and F/RF	$ppFEV_1$	2.8 (95% CI 1.0 to 4.6)	Taken from the single-arm estimate of Davies *et al.* 2021,[124] under the conservative assumption of no decrease in $ppFEV_1$ during the acute trial period for ECM
	Weight-for-age *z*-score	0	Assumption. The single arm of Davies *et al.* 2021[124] suggested a reduction in weight-for-age *z*-score following TEZ/IVA treatment (−0.04, SD 0.17), but the EAG considered a reduction in weight-for-age *z*-score for a CFTR modulator compared with ECM to be implausible at the population level
ELX/TEZ/IVA			
F/F	$ppFEV_1$	11.2 (95% CI 7.2 to 15.2)	Taken from the single-arm estimate of Zemanick *et al.* 2022[120]
	Weight-for-age *z*-score	0.28 (95% CI 0.18 to 0.39)	Taken from the single-arm estimate of Zemanick *et al.* 2022[120]
F/Gating	$ppFEV_1$	11.0 (95% CI 6.9 to 15.1)	Applying the treatment effect observed in F/MF patient in Mall *et al.* 2022[119] (ELX/TEZ/IVA vs. placebo, 6–11 years, F/MF genotype)
	Weight-for-age *z*-score	Confidential information has been removed	Applying the treatment effect observed in F/MF patient in Mall *et al.* 2022[119] (ELX/TEZ/IVA vs. placebo, 6–11 years, F/MF genotype)
F/RF	$ppFEV_1$	6.776	Scaled-down treatment effect observed in F/RF ≥ 12 clinical trial
	Weight-for-age *z*-score	Confidential information has been removed	Scaled-down treatment effect observed in F/RF ≥ 12 clinical trial

SD, standard deviation.

- The open-label extension studies of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA are single arm and had 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, meaning that synthetic control cohorts are limited to historical controls or contemporaneous controls who are ineligible for or did not take up CFTR modulator therapy
  - limited follow-up is available for LUM/IVA and TEZ/IVA because most people with CF switched to ELX/TEZ/IVA once it became available.

COVID-19-pandemic-related confounding

Where uncontrolled data are available concerning the long-term clinical outcomes of people with CF treated with CFTR modulator combination therapy, the COVID-19 pandemic introduced a host of confounding factors from March 2020 onwards. 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 have reduced the rate of lung function decline of people with CF.[141]

Early data suggest that the rate of respiratory infections and lung-function decline in people with CF may have slowed in 2020 and 2021. A US single-centre study of children between 2 and 11 years who were ineligible for ELX/TEZ/IVA at the time reported a markedly lower rate of pulmonary exacerbations from 16 March to 15 May 2020 (18% of patients having exacerbations) compared with the same period in 2019 (44% of patients having exacerbations).[156] In the UK, similar data were reported for people with chronic obstructive pulmonary disease (COPD): compared with 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.[157] Such a reduction in acute exacerbations following the onset of the COVID-19 pandemic is consistent with confidential data reported in the DCA.

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).[141] 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 the index, the annual slope was 1.76 (95% CI 1.46 to 2.05), that is an average increase in ppFEV$_1$ during COVID-19. The majority of the Doumit cohort were CFTR modulator-naive, 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 the 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 the index date.

Long-term rate of ppFEV$_1$ decline for 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:

- open-label extension studies Griese *et al.* and Study 445–110, the two Phase III open-label extension studies of ELX/TEZ/IVA with data available at the time of analysis[132,158]
- the Vertex final analysis of UK CF Registry data for ELX/TEZ/IVA, performed as part of the DCA[87]
- Newsome *et al.*, an independent estimation using UK CF Registry data of the rate of ppFEV$_1$ decline for people with CF and gating mutations treated with IVA monotherapy.[159]

Open-label extension studies Griese *et al.*[132] (VX17-445-105) is a 192-week Phase III open-label extension study of Heijerman *et al.*[118] and Middleton *et al.*[60] At the time of the appraisal, an analysis was available at week 192 after 356 participants (70.4%) had completed treatment. F/F or F/MF participants received ELX/TEZ/IVA for 192 weeks, with an annual rate of change in ppFEV$_1$ reported as 0.02 (95% CI −0.14 to 0.19) across all participants.[160–162] In an analysis using data from Griese *et al.*[132] up to year 2 (Lee *et al.*[163] analysis), historical matched-controls from the US CF Registry were estimated to have a mean annual rate of change in ppFEV$_1$ of −1.92 (95% CI −2.16 to −1.69), compared with ELX/TEZ/IVA treated patients' mean annual rate of change in ppFEV$_1$ of 0.39 (95% CI −0.06 to 0.85).[163]

Study 445–110, the open-label extension of Barry *et al.*,[117] F/Gating and F/RF genotypes, reported a similar absence of lung-function decline in people treated with ELX/TEZ/IVA, with data collection during the COVID-19 pandemic. In Study 445–110, an overall change from baseline in $ppFEV_1$ at week 96 of 3.7 (95% CI 2.2 to 5.2, participants who received ELX/TEZ/IVA in both parent and follow-up study) and 4.1 (95% CI 2.5 to 5.7, participants who received IVA or TEZ/IVA in the parent study and then ELX/TEZ/IVA for the follow-up study) was reported.[164] This is consistent with no decline from the change from baseline reported at week 8: 3.7 (95% CI 2.8 to 4.6).

The EAG noted the following risks of bias and limitations in the results of the open-label extension studies:

- The open-label extension studies were single arm and overlapped with the COVID-19 pandemic, meaning that any COVID-19-pandemic-related preservation of lung function, which may be sizeable, for example through reduced viral transmission and pulmonary exacerbations, could confound these analyses.
- Details of exactly how the annualised rate of change analyses were performed were not reported in the Griese *et al.*[132] analyses, and it was unclear if the analyses adequately excluded the acute period of $ppFEV_1$ increase following ELX/TEZ/IVA treatment. For example, the acute window excluded in Lee *et al.*[163] was 21 days; however, in the parent study, Middleton *et al.*,[60] $ppFEV_1$ continued to increase from week 4 to week 8.
- The generalisability of 96 or 144 weeks of follow-up to a person's lifetime is unclear.

The EAG therefore considered the analyses of the Phase III ELX/TEZ/IVA open-label extension studies to be at risk of underestimating the rate of $ppFEV_1$ decline that would be experienced following ELX/TEZ/IVA treatment across a patient's lifetime.

UK CF Registry analysis 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 DCA of UK CF Registry Data.[87] This analysis calculated the rate of $ppFEV_1$ for people treated with ELX/TEZ/IVA in the UK CF Registry from 21 August 2020 to 31 December 2022, compared with matched historical controls. The results of this analysis were considered confidential by the Company, but estimated a larger rate of $ppFEV_1$ decline than did the open-label extension studies of ELX/TEZ/IVA. The EAG considers these data to demonstrate that $ppFEV_1$ can decline in the long term in people treated with ELX/TEZ/IVA. The EAG further notes:

- The time window of the final analysis, August 2020 to 31 December 2022, still overlaps considerably with the COVID-19 pandemic.
- It is uncertain whether the full acute period of increase following ELX/TEZ/IVA was excluded from the analyses.

As such, the EAG considers the confidential Vertex analysis of the UK CF Registry to also be at risk of underestimating the rate of $ppFEV_1$ decline in people treated with ELX/TEZ/IVA.

Assumption-based approach As the available estimates of the rate of $ppFEV_1$ decline directly measured in people treated with ELX/TEZ/IVA were considered to be at high risk of bias, the EAG sought an alternative assumption-based approach. Based on the mechanism of CFTR modulator therapies, discussion with clinical experts and data from clinical trials, the EAG noted the expectation that ELX/TEZ/IVA treatment for people with at least one *F508del* copy would be at least as effective as IVA monotherapy for people with at least one gating mutation. In clinical trials, the sweat chloride response to IVA in people with a gating mutation is of a similar magnitude to the response to ELX/TEZ/IVA in people with at least one *F508del* mutation, but the acute increase in $ppFEV_1$ is smaller with IVA than with ELX/TEZ/IVA. These data suggest at least a similar effect on overall CFTR activity of ELX/TEZ/IVA in people with at least one *F508del* mutation to that of IVA in people with a gating mutation.[60,118,129] As IVA monotherapy has been available for people with certain gating mutations in the UK since late 2012, independent estimates of long-term follow-up of the rate of decline of $ppFEV_1$ for these patients are available from before the COVID-19 pandemic.[159] Such an estimate could provide a lower-bound estimate for ELX/TEZ/IVA with a low associated decision risk.

Newsome *et al.* 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 (2008–12), and a contemporaneous control cohort of people ineligible for IVA but in the post-IVA period (2013–6). 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 to 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 to 1.13).

In the EAG base case a relative reduction, rather than an absolute reduction, is applied to a person's change in $ppFEV_1$ decline following CFTR modulator treatment across their lifetime. To apply the transformed Newsome *et al*. estimate as a relative reduction, the overall rate of $ppFEV_1$ decline of patients in the UK CF Registry prior to IVA treatment was required, but this was not reported in Newsome *et al*. Through bibliography searching of a relevant SLR,[165] the EAG identified Newsome *et al*.[166] Newsome *et al*.[166] reported the absolute rate of $ppFEV_1$ decline in patients who were later treated with IVA in the UK CF Registry, that is a cohort similar to the Newsome *et al*. 2022 cohort: 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 *et al*. 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. From this, the EAG estimated a relative reduction in $ppFEV_1$ decline for Newsome *et al*. 2022 of 37.7% (0.49 divided by 1.3) for people treated with IVA.

The EAG considers applying a long-term rate of decline of 37.7% for people treated with ELX/TEZ/IVA, that is assuming that the long-term effectiveness of ELX/TEZ/IVA for people with at least one *F508del* mutation is similar to that of IVA monotherapy for people with a gating mutation, would be a reasonable, albeit conservative, estimate of the long-term effectiveness of ELX/TEZ/IVA that confers low decision risk.

Following engagement with the Company and patient and professional bodies, the EAG also considered it reasonable to adjust the Newsome *et al*. estimate of the long-term rate of $ppFEV_1$ decline upwards – based on the ratio of the ELX/TEZ/IVA to IVA acute treatment effect – to provide an estimate for the long-term rate of $ppFEV_1$ decline for ELX/TEZ/IVA. To do this, the EAG scaled the 37.7% estimate of the IVA treatment effect by the ratio of the IVA to the ELX/TEZ/IVA acute treatment effect from the EAG's preferred NMA. This produced an estimate reduction in the long-term rate of $ppFEV_1$ decline of 61.0% [37.7 × (15.18/9.38)] for ELX/TEZ/IVA compared with ECM. The EAG does not consider this value to be conservative, and notes that, as the long-term treatment effect of CFTR modulators on $ppFEV_1$ is applied for a person's lifetime in the economic model, there is a high degree of uncertainty around the most appropriate value. The EAG further notes that this estimate of 61.0% is closer to the confidential rates estimated in the primary and sensitivity analyses of the UK CF Registry analysis performed as part of the DCA[87] than both (1) the 37.7% rate of IVA monotherapy calculated based on Newsome 2018 and Newsome 2022 and (2) the Company's preferred assumption of no $ppFEV_1$ decline following treatment with ELX/TEZ/IVA.

Unresolvable uncertainty The EAG highlights that there is 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,[167] and also by the Company in a response to the clarification questions:

> *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 2-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.*

Letter on behalf of the UK CF Registry Research Committee and clinical members of the UK CF Registry Steering Committee

> *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).*
>
> *Vertex response to clarification questions*

As a result, the EAG highlights further research into the long-term rate of lung function decline following ELX/TEZ/IVA as a key recommendation.

LUM/IVA and TEZ/IVA

For LUM/IVA and TEZ/IVA, the Phase III 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 to be −1.33 (95% CI −1.80 to −0.85) for LUM/IVA, and −2.29 (95% CI −2.56 to −2.03) in matched controls, a 42% relative reduction.[138]
- The annual rate of ppFEV$_1$ decline to be −0.80 (95% CI −1.31 to −0.30) for TEZ/IVA, and −2.08 (95% CI −2.34 to −1.82) in matched controls. 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).[135]

Although unaffected by COVID-19-related confounding, the EAG considers each analysis to be at high risk of underestimating the annual rate of ppFEV$_1$ decline for LUM/IVA and TEZ/IVA compared with ECM, because:

- The Company excluded data from the first 21 days (LUM/IVA) or 22 days (TEZ/IVA) of active treatment in order 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.

The EAG therefore considers the Company matched-control analyses to be at high risk of underestimating the annual rate of ppFEV$_1$; instead it prefers the use of an assumption-based approach.

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 with ECM, because:

- In the placebo-controlled TRAFFIC and TRANSPORT,[39] the rate of decline of ppFEV$_1$ between week 8 and the end of study at week 24 was steeper for people receiving LUM/IVA than for those receiving placebo.
- Throughout the open-label extension study, the calculated rate of annual decline was −1.33 (95% CI −1.80 to −0.85), not substantially different from the assumed rate of decline in ECM.[16]

As a result, the EAG prefers to implement no reduction in the rate of ppFEV$_1$ decline for patients treated with LUM/IVA. By contrast, the EAG considers there to be some evidence of a reduction in decline in ppFEV$_1$ for TEZ/IVA, but considers the Company estimate of a 61.5% relative reduction to be an overestimate. The EAG notes that:

- In the 24-week treatment period of Taylor-Cousar *et al.*,[122] 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 with 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 (28.2%: 4/14.2 = 0.282). This leads to the EAG's preferred assumption of the rate of ppFEV$_1$ decline for TEZ/IVA to be a relative reduction in ppFEV$_1$ decline compared with ECM of 17.2% (calculated as 0.282 × 61.0%).

Co-adherence to inhaled therapies

The long-term ppFEV$_1$ decline rate 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.[28] In line with this suggestion, among people with CF and eligible gating mutations in the UK, dornase alfa, hypertonic saline and inhaled antibiotic use decreased in those taking IVA monotherapy in the years following its introduction, relative to those who were ineligible for IVA.[145] 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 long-term ppFEV$_1$ decline rate with ELX/TEZ/IVA and TEZ/IVA, the effects of a reduction in co-adherence to preventative inhaled therapies are implicitly modelled in the EAG base case. The EAG notes that there currently are no robust data on co-adherence to ECM therapies with ELX/TEZ/IVA, but notes that the effect of ECM medications on ppFEV$_1$ is small in comparison with effective CFTR modulator therapy.[168,169] The EAG therefore considers the effects of co-adherence to ECM medications in patients taking CFTR modulator therapies to introduce uncertainty into the long-term effectiveness of CFTR modulator 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, is an active area of current research.[170,171]

Discussion

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 its marketing authorisations for treating people with CF who have at least one *F508del* mutation. Each CFTR modulator combination therapy was compared with each of the others and with ECM. The EAG prioritised 19 clinical trials from the SLR, which included 16 RCTs. All included studies were sponsored by the Company. Twelve 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 being at high risk of bias.

Overall, the EAG considers there to be strong evidence that treatment with 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 considerably greater for ELX/TEZ/IVA than for TEZ/IVA and LUM/IVA.

The EAG also considers there to be good evidence that treatment with 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 for LUM/IVA or TEZ/IVA. The EAG notes that, despite a lack of comparative data, this effect on pulmonary exacerbations in people aged ≥ 12 years should be generalisable to those in the 6–11 years age group and younger.

Treatment with ELX/TEZ/IVA led to an increased weight-for-age *z*-score relative to ECM in people with CF aged ≥ 6 years of all genotypes, albeit with a smaller magnitude for the F/RF genotype. For LUM/IVA the point estimate of the increase in weight-for-age *z*-score was closer to 0 in the in ≥ 12 years F/F genotype than was the ELX/TEZ/IVA estimate, but the 95% CIs still excluded 0. By contrast, there was no significant acute increase compared with placebo for TEZ/IVA in the ≥ 12 years group or for LUM/IVA or TEZ/IVA in the 6–11 years populations.

For people with CF aged < 6 years, (2–5 years for ELX/TEZ/IVA and 1–5 years for LUM/IVA), the EAG considers the acute 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[127,172] or were powered to detect a primary safety outcome, only.[141]
- ppFEV$_1$ measurements were not conducted in these trials, as these measurements are not reliable at this age.[56]
- Many people with CF aged < 6 years may have near-ceiling lung function.

Generalisability

The EAG considers the clinical efficacy data from the CFTR modulator clinical trial programme likely to generalise to clinical practice in England, and notes that the acute effects of CFTR modulator therapy observed in clinical trials are consistent with those reported in the UK CF Registry.

The EAG's clinical experts noted that if ELX/TEZ/IVA is initiated very early, that is before substantial lung or pancreatic damage has 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 years initiating ELX/TEZ/IVA due to:

- the current absence of long-term data for this population
- the likelihood that some damage may have occurred by the age of 2 years in this population, especially to the pancreas.

Key issues and uncertainties

The EAG considers the lifetime effects of CFTR modulators on the rate of ppFEV$_1$ decline and pulmonary exacerbations to be the major outstanding uncertainty in the clinical effectiveness of CFTR modulator therapy. No head-to-head comparative effectiveness data are available for these outcomes in the long term for any CFTR combination modulator therapy. Where uncontrolled long-term data are available, follow-up is often limited to 2–3 years and does not cover the patient's lifetime. The EAG considers this uncertainty to be heightened in the case of ELX/TEZ/IVA, for 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 the COVID-19 pandemic between 2020 and 2022, viral shielding and social distancing may have meaningfully impacted lung function in people with CF, including a direct reduction in exacerbations due to lower rates of infection, and an associated reduction in lung-function decline due to fewer respiratory infections and pulmonary exacerbations.[141,156]

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:

- EuroQol-5 Dimensions (EQ-5D) data were only collected in two CFTR modulator clinical trials, both of LUM/IVA, meaning that the impact of CFTR modulator therapy on EQ-5D, the NICE-preferred HRQoL 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. This leads to uncertainty around the clinical meaningfulness of the response to LUM/IVA and TEZ/IVA, which often had lower bounds of CIs close to, or overlapping, 0.
- The AE 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 AE data on cataracts, lens opacities and hypertension that may be related to CFTR modulator therapy.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Methods

A SLR was undertaken in February 2023 to identify published economic evaluations of ELX/TEZ/IVA, LUM/IVA and TEZ/IVA for the treatment of CF. A separate search was conducted to identify studies reporting HRQoL data in patients with CF.

Multiple electronic databases were searched including MEDLINE, EMBASE, the International Network of Agencies for Health Technology Assessment (INAHTA) and the Cost-Effectiveness Analysis Registry. Further to the database searches, health technology appraisal (HTA) websites including 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 were searched to identify relevant publications. In addition, reference lists of key identified studies were 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 HTA database in March 2018 and the Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluations Database (NHS EED) in March 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 (CF) and the validated CADTH economic evaluations search filter.[173] 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.*[174]). No language (to assess the 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 the search to full-text UK studies. The EAG does not consider this likely to introduce substantial bias, as UK studies were required for the economic model to align with the NICE reference case.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using predefined eligibility criteria. The inclusion and exclusion criteria for each review are outlined in *Table 20*. Additionally, for both searches the EAG reviewed the Company's submission (including results of their SLRs) for additional references.

Results: economic evaluations

The electronic database searches identified 681 records. After duplicates were removed, 618 records remained to be assessed against the inclusion criteria by two independent reviewers. An additional 25 records were identified through 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,[175] an additional erratum[176] and earlier versions of PBAC summary reports being combined. A PRISMA diagram of the included studies is shown in *Figure 5*.

Of the 18 unique studies, 15 were from HTA organisations. Only 2 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.[177,178] The remaining three studies were independent evaluations of LUM/IVA, all conducted from the US payer perspective.[179–181] Seventeen of the included 18 studies conducted cost–utility analyses, reporting results as incremental cost per quality-adjusted life-year (QALY) (ICER), with the exception of Dilokthornsakul *et al.*,[179] who reported incremental costs, QALYs and life-years but did not report the corresponding ICER. Vadagam *et al.*[181] reported outcomes in terms of cost per absolute ppFEV$_1$.

TABLE 20 Cost-effectiveness SLR inclusion criteria

Criteria	Inclusion	Exclusion	Inclusion	Exclusion
Economic evaluations			HRQoL	
Population	Patients with CF	None	Patients with CF	None
Interventions	The interventions below will be considered: • Elexacaftor/tezacaftor/ivacaftor (Trikafta® [Vertex Pharmaceuticals Incorporated. Boston, Massachusetts, USA] or Kaftrio®) • Lumacaftor/ivacaftor (Orkambi®) • Tezacaftor/ivacaftor (Symkevi or Symdeko®)	Ivacaftor monotherapy	None	None
Comparators	Specified interventions vs. each other or ECM	None	None	None
Outcomes	• Costs per unit of outcome (e.g. ICERs) • QALYs • LYG	None.	• Preference-based multiattribute utility values (e.g. EQ-5D, HUI-3, SF-6D) • Direct utility elicitation tools (TTO, standard gamble, rating scale) • Generic health-related quality of life questionnaires (e.g. SF-36, SF-12) • CFQ	Outcomes not listed
Study design	Economic evaluations: • Cost–utility analyses • Cost-effectiveness analyses • Cost-minimisation analyses • Cost–benefit analyses • Cost–consequences analyses	• Budget impact analysis • Cost-analysis only • Commentaries and letters • Reviews (systematic and non-systematic) • Study protocols with no results	• 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
Report type	• Full-text articles • English	• Abstracts with insufficient methodological details	• English	• Non-English studies (numbers of relevant non-English studies will be reported)

CFQ, Cystic Fibrosis Questionnaire; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year; SF-6D, Short-Form 6-Dimension; SF-12, 12-Item Short-Form Health Survey; SF-36, 36-Item Short-Form Health Survey; TTO, time trade-off.

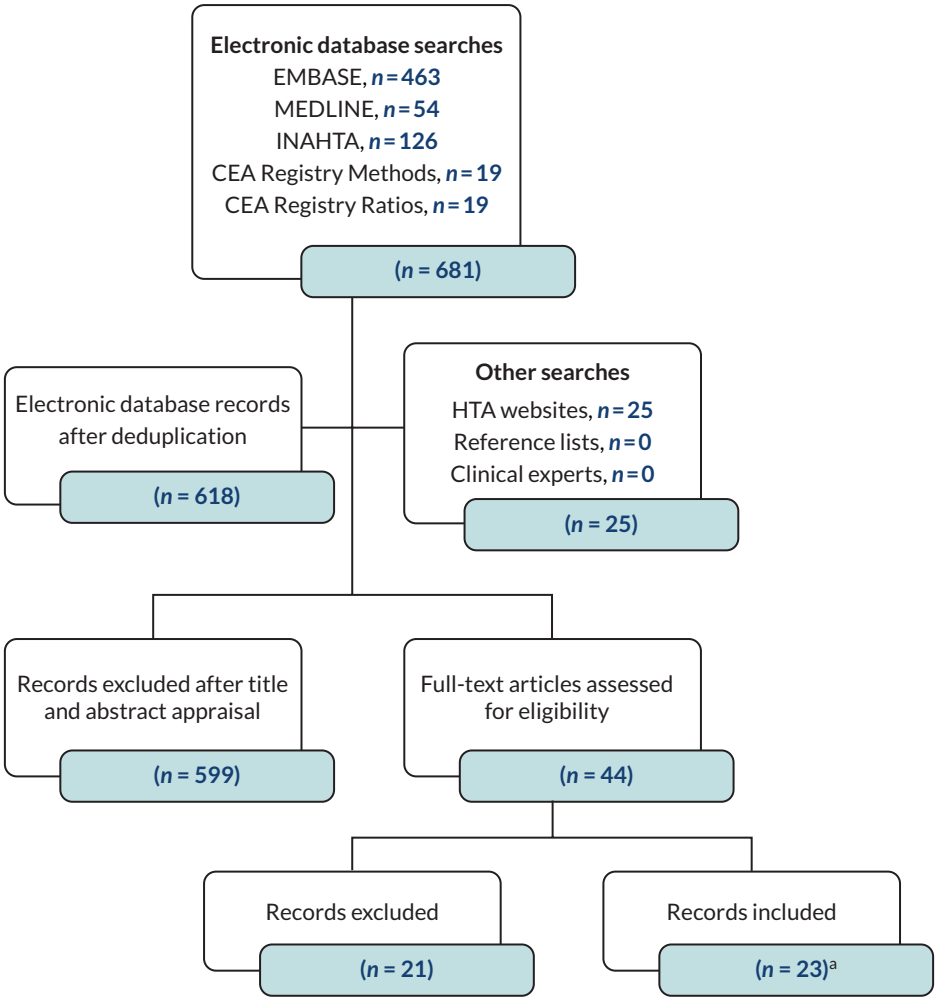

FIGURE 5 The PRISMA diagram of economic evaluations searches. a, Extracted as 18 studies due to studies being combined.

Interventions and comparators

Of the 18 studies included, the majority (11/18) assessed the cost-effectiveness of LUM/IVA,[179–189] while only 2 assessed TEZ/IVA[190,191] and 3 included ELX/TEZ/IVA.[96,192,193] The remaining two studies[177,178] included all three interventions of interest to this research and compared all of ELX/TEZ/IVA, TEZ/IVA and LUM/IVA against ECM for specified genotypes. The interventions were not compared with each other in these two studies but, because the recommended start age varied between drugs, they were modelled sequentially in the relevant genotype populations, with patients switching to the 'best available' therapy available for their age. ECM was used as a comparator in all studies but varied in its definition, with many studies not describing it at all. PBAC 2021[193] also compared ELX/TEZ/IVA with TEZ/IVA in F/F and F/RF genotype populations, while CADTH[96] compared ELX/TEZ/IVA with 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 those based on HTA organisation submissions or reports. All of these studies used the same general structure; applying a Cox proportional hazards (CPH) model by Liou *et al.*[155] 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, CFRD, 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 4 weeks for the first 2 years and annual thereafter. Institute for Clinical and Economic Review 2018[177] used an annual cycle length, whereas Institute for Clinical and Economic Review 2020[178] did not report the cycle length used. Two studies used a Markov state transition model with an annual cycle length,[179,180] each with five health states

[mild lung disease (%FEV_1 predicted ≥ 70%), moderate lung disease (40 ≤ %FEV_1 predicted < 70%), severe lung disease (%FEV_1 predicted < 40%), post lung transplantation and death]. Sharma *et al.*[180] also included transition health states to represent pulmonary exacerbations and lung transplant. Vadagam *et al.*[181] was 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 and CADTH 2022) all reported conducting indirect treatment comparisons 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. Alternative assumptions were implemented in re-analyses produced by CADTH 2021[192] and 2022[96] for ELX/TEZ/IVA, CADTH 2016[182] and 2018[183] for LUM/IVA, and PBAC 2019[190] for TEZ/IVA, in which the rate of decline of ppFEV_1 was equal to that of ECM (see *Report Supplementary Material 1*). In the NICE appraisal for LUM/IVA, the committee noted how it had not been sufficiently justified why USA/Canada data were 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 discussed in only six of the included studies. The two assessments conducted by the Institute for Clinical and Economic Review (in 2018[177] and 2020[178]) stated that AEs were not explicitly modelled in terms of additional costs or disutilities as they were found to be generally comparable across trial arms. Both CADTH reports for LUM/IVA (in 2016[182] and 2018[183]) state that AEs from the TRAFFIC[194] and TRANSPORT[195] trials were included in the model and applied as a cost of a general practitioner visit. This method was also used in NICE TA786.[184] The independent study by Vadagam *et al.*[181] included AEs that occurred in at least 10% of patients in any treatment group in the TRAFFIC[194] and TRANSPORT[195] 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,[184] SMC 2016[188] and SMC 2019[189] for LUM/IVA, and SMC 2019[191] for TEZ/IVA. None of the included ICERs in any of these four assessments was below £200,000.

A summary of the included studies is provided in *Table 21*, with further details in *Report Supplementary Material 1*. All studies were assessed using the Drummond checklist,[196] reported in in *Report Supplementary Material 1*. 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.

In addition to the cost-effectiveness studies identified during the systematic review, the EAG reviewed the economic models submitted as part of the Company submission and reviewed any changes made by HTA organisations to previous Company submissions' base-case assumptions. Further details of this are provided in *Report Supplementary Material 1*.

Results: health-related quality-of-life searches

The electronic database searches identified 1386 potential publications. After duplicates were removed, 1029 publications were screened against the eligibility criteria at the title and abstract stage. After title and abstract assessment, 927 records were excluded, leaving 103 remaining records to be assessed at the full-text stage. As

TABLE 21 Summary of included economic evaluations

Author, year, country	Perspective, discounting and cost year	Model type	Patient population	Intervention/comparator
Multiple CFTR modulators				
Institute for Clinical and Economic Review 2018, USA[177]	Perspective: Healthcare Discount rate: 3% for costs and QALYs Cost year: 2017	Discrete time microsimulation model [developed in TreeAge (TreeAge Software, Inc., Williamstown, MA, USA)] 1-year time cycle	Patients with CF in both homozygous and heterozygous (gating mutation or RF)	Interventions: LUM/IVA, TEZ/IVA and IVA. All are combined with ECM. CFTR modulators were compared with ECM and not directly with each other Comparator: ECM
Institute for Clinical and Economic Review 2020, USA[178]	Perspective: Healthcare 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: 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 Comparator: ECM
ELX/TEZ/IVA				
CADTH Common Drug Review 2021, Canada[192]	Perspective: Canadian public healthcare payer Discount rate: 1.5% for costs and QALYs Cost year: NR	Patient-level simulation model with a lifetime horizon (approximately 65 years) Model cycle = 4 weeks for the first 2 years and annual thereafter	Target population is patients with CF aged ≥ 12 years who have at least one *F508del* mutation in the CFTR gene. Four 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
CADTH Common Drug Review 2022, Canada[96]	Perspective: Canadian public healthcare payer Discount rate: 1.5% for costs and QALYs Cost year: NR	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; (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
PBAC 2021, Australia[193]	Perspective: NR Discount rate: 5% for costs and QALYs Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 years	CF patients aged ≥ 12 years who have at least one *F508del* mutation in the *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

continued

TABLE 21 Summary of included economic evaluations (*continued*)

Author, year, country	Perspective, discounting and cost year	Model type	Patient population	Intervention/comparator
LUM/IVA				
NICE TA786, 2016[184]	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	CF patients homozygous for the *F508del* mutation (age ≥ 12 years)	Intervention: LUM/IVA plus ECM Comparator: ECM
SMC 2016, Scotland[188]	Perspective: Scottish NHS Discount rate: 3.5% for costs and QALYs Cost year: NR	Individual patient state-transition microsimulation model Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients aged ≥ 12 years who are homozygous for the *F508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM
SMC 2019, Scotland[189]	Perspective: Scottish NHS health system Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients aged ≥ 6 years and aged 2–5 years who are homozygous for the *F508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM
CADTH Common Drug Review 2016, Canada[182]	Perspective: Canadian public healthcare 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 = 4 weeks for the first 2 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
CADTH Common Drug Review 2018, Canada[183]	Perspective: Canadian public healthcare 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 = 4 weeks for the first 2 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
PBAC 2018, Australia[185]	Perspective: NR Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients aged ≥ 12 years homozygous for the *F508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM
PBAC 2018, Australia[186]	Perspective: NR Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients aged 6–11 years homozygous for the *F508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM

TABLE 21 Summary of included economic evaluations (*continued*)

Author, year, country	Perspective, discounting and cost year	Model type	Patient population	Intervention/comparator
PBAC 2019, Australia[187]	Perspective: NR Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients aged 2–5 years who are homozygous for the *F508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM
Dilokthornsakul *et al.* 2017, USA[179]	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. Model cycle = 1 year Time horizon = lifetime	CF patients (25 +) with homozygous *phe508del* mutation	Intervention: LUM/IVA plus ECM Comparator: ECM
Sharma *et al.* 2018, USA[180]	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
Vadagam *et al.* 2018, USA[181]	Perspective: USA health-care payer Discount rate: 3% for costs and QALYs Cost year: 2016	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
Tezacaftor/Ivacaftor (TEZ/IVA)				
SMC 2019, Scotland[191]	Perspective: Scottish NHS health system Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 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
PBAC 2019, Australia[190]	Perspective: NR Discount rate: NR Cost year: NR	Individual patient state-transition microsimulation model – lifetime time horizon Model cycle = 4 weeks for the first 2 years and annual thereafter	CF patients ≥ 12 years heterozygous for the *F508del* mutation with residual function	Intervention: TEZ/IVA plus ECM Comparator: ECM

CFFPR, Cystic Fibrosis Foundation Patient Registry; NR, not reported.

previously noted, following the title and abstract review, as the number of full texts to be examined exceeded 100 publications, the pragmatic decision was taken to limit the search to full-text UK studies to identify the most relevant papers for this assessment. Among 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.

Of the 14 included publications:

- Three were based on HTA submissions, 10 were full-text publications and 1 was an abstract that detailed all the required information. The HTA submissions included alternative utility values from previous publications and therefore details are also given in *Table 22*.
- Twelve reported EQ-5D data, of which four additionally reported CRQ-R or SF-36 (36-Item Short-Form Health Survey) data. The remaining studies reported only CFQ-R or SF-36 data.
- Ten reported heath state utility values 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 heath state utility values assigned to each health state varied considerably between publications; for example, those reported by Acaster *et al.*[197] describe a steady decline from a mild health state with a utility of 0.74 to a severe health state with a utility of 0.54, while those in the ivacaftor monotherapy and LUM/IVA clinical trials recorded utility from mild to severe of approximately 0.94–0.89, respectfully. Three of the studies devised health states according to the occurrence and severity of pulmonary exacerbations.[41,201,202] On further investigation by Tappenden *et al.*[203] in 2013 into the relationship between ppFEV$_1$ and utility, it was suggested that

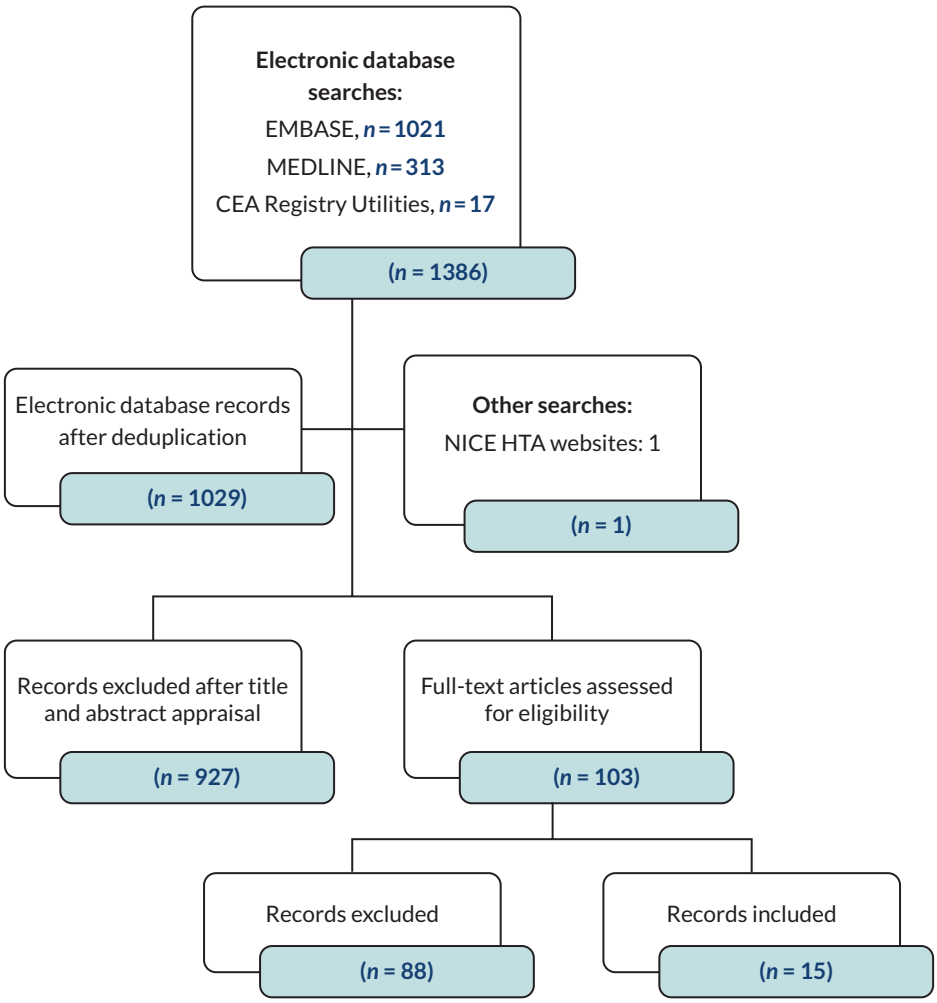

FIGURE 6 PRISMA diagram for HRQoL search.

TABLE 22 Publications identified in the HRQoL literature review

Study	Author, year	HSUVs used from	Country	Measure	HSUVs according to
1	Acaster 2015[197]	Own study	UK	EQ-5D, CFQ-R	$ppFEV_1$ severity
2	Acaster 2019/22[198,199]	Own study	UK	CFQ-R	Physical functioning, role functioning, emotion, vitality, breathing difficulty, cough, abdominal pain, body image
3	Angelis 2015[31]	Own study	UK	EQ-5D-5L, VAS	N/A
4	Bell 2013[200]	Own study	France, UK, Germany, Australia and Ireland	EQ-5D-5L	CF responsible mutation
5	Bradley 2013[201]	Own study	UK	EQ-5D, CFQ-R	Pulmonary exacerbations
6	Cameron 2021[202] (abstract only)	Own study	UK	EQ-5D-5L, TTO	Pulmonary exacerbations
7	Solem 2016[41]	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)[184]	TRAFFIC and TRANSPORT clinical trials	North America, Australia, European Union	EQ-5D-3L, CFQ-R	$ppFEV_1$
9	Tappenden 2013 (HTA)[203]	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[204]	Bradley 2013	UK	EQ-5D	$ppFEV_1$
11	Tappenden 2017[205]	Bradley 2013	UK	EQ-5D	$ppFEV_1$
12	Tappenden 2023[206]	Wildman 2021	UK	EQ-5D-5L mapped to EQ-5D-3L	$ppFEV_1$
13	Whiting 2014 (HTA)[40]	Ivacaftor clinical trial	UK	EQ-5D	$ppFEV_1$
		Gee 2002	UK	SF-36	Disease severity
14	Wildman 2021[207]	Own study	UK	EQ-5D-5L	$ppFEV_1$

HSUV, heath state utility value; HUI, Health Utilities Index; SF-6D, Short-Form 6-Dimensions; SF-36, 36-item short-form health survey; TTO, time trade-off; VAS, visual analogue scale.

only one paper by Johnson *et al.*[208] 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) is provided in *Table 22*, and detailed data extractions can be found in *Report Supplementary Material 1*.

Independent economic assessment

Methods

The systematic review of previously published cost-effectiveness analyses and the Company submission identified no studies that compare all three interventions included within the scope of this appraisal (ELX/TEZ/IVA, LUM/IVA and TEZ/IVA) for the treatment of people with CF with at least one *F508del* mutation. Therefore, the EAG developed a de novo model that incorporated all three interventions included in the NICE final scope,[78] detailed below.

Population(s)

As described in *Decision problem*, the population relevant to this MTA is people with CF with at least one *F508del* mutation. The analyses conducted are based on the genotype eligibility criteria specified in the current and expected marketing authorisation for each CFTR modulator combination therapy.[209–211]

Hence, the populations considered for this appraisal are:

- People with CF who are homozygous for the *F508del* mutation.[209–211]
  - This population is relevant for all three combination therapies and 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,[210] ELX/TEZ/IVA[211] 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.[211]

The age at which patients are eligible to start treatment differs among the three modulator treatments and between genotypes, based on the current and expected marketing authorisation. *Interventions and comparators* provides further details of the interventions and the proposed analyses based on age for the cost-effectiveness analyses.

Model structure

The EAG developed a patient-level microsimulation model that largely followed the structure of the models in the Company submission and used in the previous NICE appraisal for LUM/IVA (TA786),[184] 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 Institute for Clinical and Economic Review in its independent assessments of CFTR modulators[177,178] and re-analyses of the Company submissions produced by CADTH[96,182,184,192] and PBAC,[190] as described earlier in *Results: economic evaluations*. 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 treatments included in this appraisal:

- The model population, consisting of both adults and children, includes patients with heterogeneous characteristics, such as age, 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 years) 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 to incorporate patient history, which may become inefficient.
- A patient simulation model is able to incorporate the correlation between baseline characteristics over time (for example $ppFEV_1$ and exacerbations are not independent of each other) and the joint distribution changing over time. This correlation would be challenging to implement in a Markov model and would result in a much more complex structure than modelling individual patients.

For the reasons described above, the EAG considered that, to most accurately capture the heterogeneous population being modelled and incorporate patient history, an individual simulation model was most appropriate.

A CPH model developed by Liou *et al.*[155] is used to predict patient survival based on nine individual characteristics (age, sex, weight-for-age *z*-score, $ppFEV_1$, number of pulmonary exacerbations, *S. aureus* infection, *B. cepacia* infection,

pancreatic sufficiency status and CFRD status). A patient's mortality hazard is updated in each model cycle to reflect changes in the following risk factors in the CPH function: age, weight-for-age *z*-score, $ppFEV_1$, number of pulmonary exacerbations, and development of CFRD. The remaining four characteristics do not change through the model lifetime and are set at baseline.

The Liou *et al.*[155] model was developed based on a US cohort and the Company does not appear to have searched for any alternative models relevant to the UK. To identify if a more UK-specific model was available, the EAG ran a targeted search for survival prediction models for the UK and identified Keogh *et al.*[154] This paper used a dynamic prediction model for survival in CF patients based on UK CF Registry data from 2005 to 2015 of patients aged ≥ 18 years. 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.*[154] prediction model has not been validated in younger age groups. Despite the Liou *et al.*[155] model being based on a USA data set, clinical experts to the EAG suggested that they do not expect to see large differences between the patient populations. Therefore, despite the limitations of the Liou *et al.*[155] model, which are discussed further in *Report Supplementary Material 1*, the EAG deemed it the best available approach at the time of this appraisal for modelling CF survival based on individual patient characteristics.

The CPH model is applied to a reference survival curve in the first model cycle to represent the mortality rate of CF patients in the UK when modulator treatments are not used, reflective of ECM. 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.*,[212] which used UK CF Registry data from 2011 to 2015 to estimate survival rates among CF patients. This study includes survival predictions for both patients who are homozygous and those who are heterozygous for the *F508del* mutation. The EAG notes that these survival estimates will not be impacted by the introduction of ivacaftor monotherapy in the UK, as this treatment was not available for patients with the genotypes included in this appraisal at the time of the analyses. As a result, the EAG considers this to be the most up to date and relevant representation of average survival for CF patients in the UK receiving ECM without modulator treatment.

The steps below detail the flow of patients in the simulation model, as shown in *Figure 7*, for each comparator. The model uses a monthly cycle length for the first 2 years and an annual cycle thereafter.

1. Based on the relevant trial data, patient characteristics are defined for each individual.
2. An age-specific mortality hazard is assigned to the patient, taken from the reference population survival curves from Keogh *et al.*[212] in the first model cycle and based on the patient's starting age.
3. Patient age, $ppFEV_1$, pulmonary exacerbations, 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 pulmonary exacerbations.
4. Changes in patient characteristics since the previous model cycle are incorporated into the Liou *et al.*[155] CPH model, which is used to update the hazard of death.
5. Costs and utilities are assigned to each patient in each cycle.
6. This process is repeated in each model cycle 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 dies, whereby the next patient is then simulated. The total costs and QALYs per patient are calculated.
7. Each individual simulated patient is duplicated across every treatment arm of the model and steps 1–6 are repeated.
8. The average total costs and QALYs are calculated for each treatment arm.

As discussed, patient-level models have the advantage over cohort-based models of being able to easily incorporate patient heterogeneity. However, they commonly have significantly longer run times, which is particularly evident in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). Therefore, in line with ISPOR (International Society for Pharmacoeconomics and Outcomes Research) good research practice for simulation models,[213] to reduce variance and the number of model runs required, the EAG ensured that each population modelled for each treatment was identical

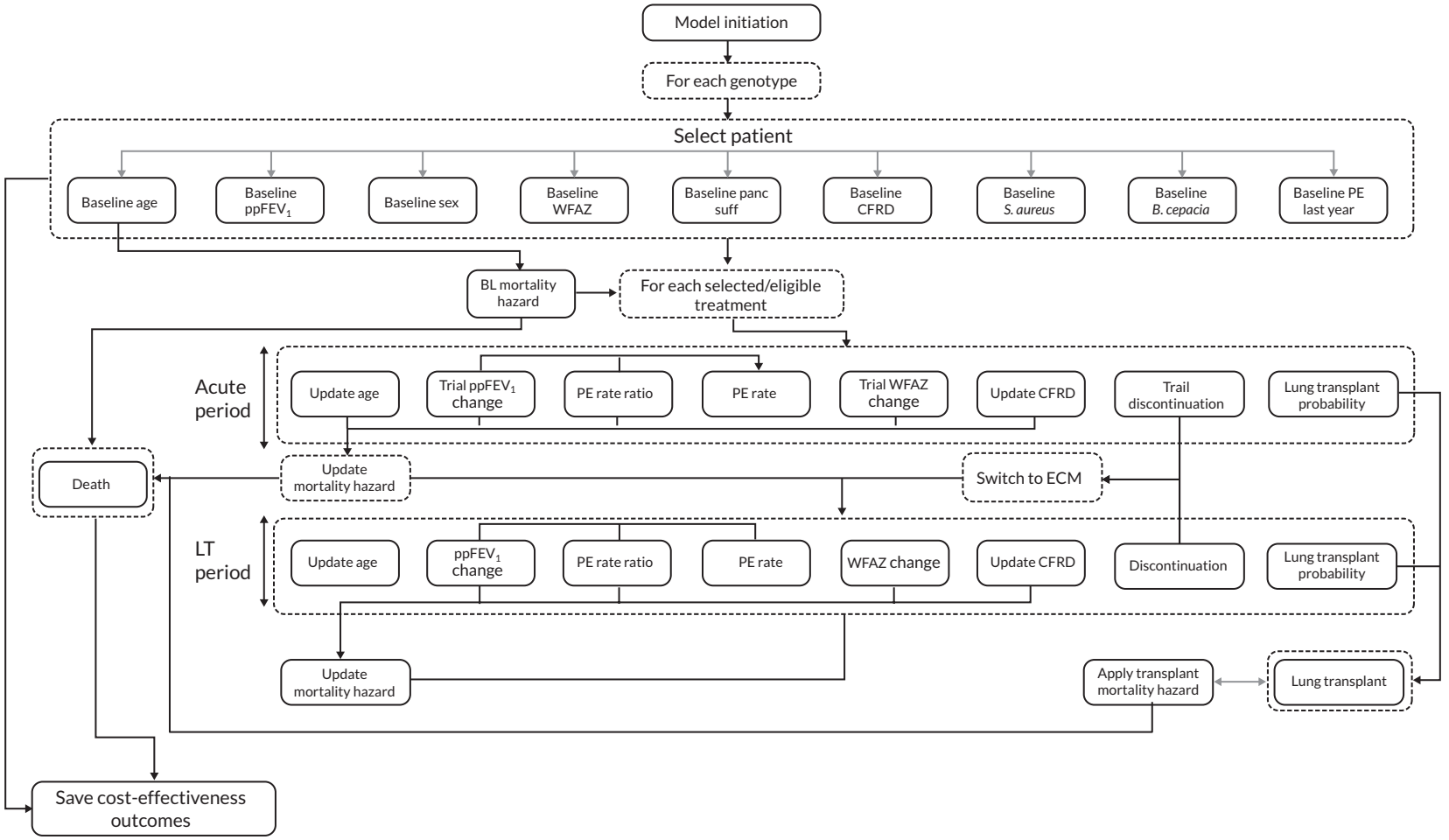

FIGURE 7 Individual simulation model diagram. BL, baseline; LT, long term; panc suff, pancreatic sufficiency status; WFAZ, weight-for-age *z*-score.

through the use of common random numbers. The EAG tested the stability of results by comparing the average cumulative ICERs for each treatment with those of ECM when the model was run with different numbers of patients.

Stability for ELX/TEZ/IVA and TEZ/IVA was considered achieved with smaller numbers of patients (≈1000 and 1500, respectively) than LUM/IVA (2000). This was because the EAG's efficacy estimates for LUM/IVA were similar to those for 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, patients receiving LUM/IVA have the same long-term ppFEV$_1$ decline as patients receiving ECM, resulting in LUM/IVA and ECM having similar model outputs over a lifetime (see *Long-term change in ppFEV$_1$*). 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 Technical Support Document 15,[214] a greater number of patients may be required if similar treatments are compared. Two thousand patients were run in the base-case model.

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 Services in England. Costs and QALYs have been discounted at 3.5%, as per the NICE reference case.[215]

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 *Population(s)*, the three interventions have marketing authorisation for different CF genotypes and age groups.

As outlined in Drummond *et al.*,[196] when there are subgroups of patients with the same condition, the relevant alternative treatments to compare are the mutually exclusive alternatives within each subgroup. Each subgroup can then be considered separately, and cost-effective treatments can be identified by comparing the ICERs of non-dominated treatments. Therefore, the EAG analyses are separated based on genotype, detailed below and shown in *Figure 8*.

1. F/F population: ECM versus LUM/IVA versus ELX/TEZ/IVA versus TEZ/IVA. Patients will receive LUM/IVA from the age of 1 year, in line with the most recent marketing authorisation. In the ELX/TEZ/IVA treatment arm, patients aged 1–2 years will receive ECM before switching to ELX/TEZ/IVA aged 2 years, based on expected marketing authorisation. In the TEZ/IVA treatment arm, patients aged 1–5 years will receive ECM before switching to TEZ/IVA at the age of 6 years.
2. F/MF population: ECM versus ELX/TEZ/IVA for all patients aged ≥ 2 years. Patients aged 1–2 years are not included in this analysis.
3. F/Gating population: ECM versus ELX/TEZ/IVA for all patients aged ≥ 2 years. Patients aged 1–2 years are not included in this analysis.

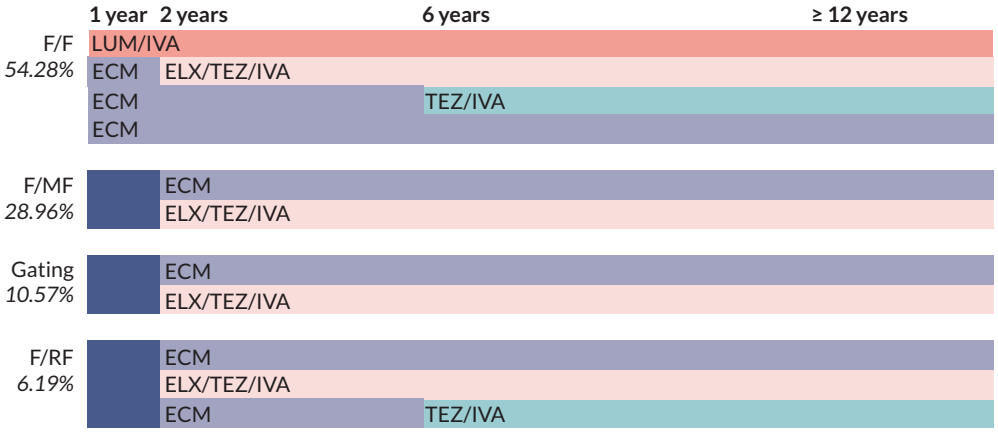

FIGURE 8 Main EAG analyses based on genotype. F/F, *F508del* homozygous.

4. F/RF population: ECM versus ELX/TEZ/IVA versus TEZ/IVA. In the TEZ/IVA treatment arm, patients aged 2–5 years will receive ECM before switching to TEZ/IVA at the age of 6 years.

Established clinical management consists of a range of different therapies to treat CF symptoms and symptoms associated with CF treatments, co-ordinated by a multidisciplinary team. The treatments used as part of ECM can differ depending on patients' lung function and comorbidities, as described in *Management of disease*.

Patient characteristics

The individual simulation model requires patient profiles that include data on the characteristics used in the CPH model to estimate mortality, as described in *Model structure*. 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 receiving ECM, only 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 given below, excluding age, as this is updated in line with each model cycle.

Baseline characteristics

Patients' pancreatic sufficiency status is included only from the trials of patients with a F/RF or F/Gating mutation, as patients who are F/F or F/MF are assumed to be pancreatic insufficient. Data were not available on changes in pancreatic sufficiency status over time and so this 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 to be a conservative assumption. Respiratory infections are also assumed not to change over the model duration as incidence data were not available to inform these changes and therefore do not impact on the mortality hazard equation. Assuming respiratory infections do not change over a patient's lifetime could be considered a conservative approach, as CFTR modulators have been shown to reduce respiratory infections in CF patients.

Patient CFRD status at baseline was assumed equal to the age-specific prevalence rate in the UK CF Registry Report 2021.[1] Data are only reported for patients aged 10–15 years and ≥ 16 years, and therefore the rates for those aged 10–15 years were applied for patients aged 6–15 years. At baseline, 8.3% of patients in the model aged 6–15 years are randomly assigned as having CFRD, while 35.2% of patients aged ≥ 16 years are assigned as having CFRD. As this parameter is randomly assigned to patients, it assumes that CFRD is not related to other patient characteristics that are included in the model. All patients aged < 6 years are assumed not to have CFRD. Clinical advisers to the EAG noted that it is possible for patients aged < 6 years 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 years Baseline data for patients aged ≥ 6 years on age, sex, weight-for-age *z*-score and ppFEV$_1$ were sourced from the various genotype-specific CFTR modulator trials, using the same approach and patient data as that employed by the Company. Patient data were used from only trials where patients had not previously been treated with a CFTR modulator or had undergone a washout period prior to 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 naive, 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 the UK population, based on data from the UK CF Registry Report 2018,[216] a weighted population was created by the Company and used by the EAG. Data used to inform this are shown in *Report Supplementary Material 1*. This involved either oversampling or undersampling patients in particular age groups to ensure that the patient profiles included in the model were representative of the UK population. Details of patients used in the economic model from key CFTR modulator trials can also be found in *Report Supplementary Material 1*.

Patients aged < 6 years As ppFEV$_1$ is not obtained in clinical practice for patients aged < 6 years, because spirometry is not used in this age group, clinical trial data were not available. Therefore, patient profiles of those aged 6–9 years from

each genotype were sampled to create a cohort of patients aged < 6 years. Further details of the approach used for sampling patients are provided in *Report Supplementary Material 1*.

ppFEV$_1$

Once the model has reached the time point equal to the length of trial from which treatment effectiveness data were taken (see *Treatment effectiveness*), 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 vs. all remaining) and stratified by four age groups (6–12, 13–17, 18–24 and ≥ 25 years) taken from Sawicki *et al.*[3] This assumes that the same annual rate of decline for patients aged ≥ 25 years, equal to −1.06 for the F/RF genotype and −1.86 for all remaining genotypes, is applied for the rest of a patient's lifetime. In the Company's model, this means that patients receiving ECM reach a ppFEV$_1$ of 15% at around 40–50 years old, if they remain alive and have not received a lung transplant. Clinical experts to the EAG noted how the rate of decline in ppFEV$_1$ slows over time, and the linear decline after 30 years old may be slower than that suggested by the Company's approach. The EAG ran a targeted literature search for studies reporting a ppFEV$_1$ decline in CF patients over time. A study[16] was identified that reported 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 US Cystic Fibrosis Foundation Patient Registry between the years 2003 and 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 (see figure 2 in Szczesniak *et al.*[16]) and for the homozygous genotype only (see figure 5 in Szczesniak *et al.*[16]), which the EAG digitised using Engauge Digistizer[217] to produce an estimate of annual ppFEV$_1$ rate of change for ages 6–75 years to apply in its model. The EAG notes that any analysis based on observed lung function data alone is subject to survivor bias, which may represent a challenge in using survival models in CF following acute increases in lung function, and has highlighted this as an area for future research in *Suggested research priorities*. 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 patients in the F/RF group have a slower rate of decline because they have a milder form of disease, the digitised values from the overall CF population were applied rather than the homozygous for the F/RF population.

Pulmonary exacerbations

The CPH model includes pulmonary exacerbations that require hospitalisation or IV antibiotics. Pulmonary exacerbations are included in the model as a function of age and ppFEV$_1$. This is based on the formula derived by Whiting *et al.*[40] in the ivacaftor monotherapy HTA, which estimated the association between average annual pulmonary exacerbation rate and average ppFEV$_1$ for patients aged < 18 and aged ≥ 18 years, as shown below. This was based on data from the US Cystic Fibrosis Foundation Patient Registry 2004 published in Goss *et al.*[218] The equation for < 18 seconds is applied to patients aged 6–18 years only. Pulmonary exacerbations are assumed not to occur in patients aged < 6 years. Although clinical experts to the EAG considered that all patients are at risk of pulmonary exacerbations, the EAG did not include pulmonary exacerbations in patients aged < 6 years because the formula for estimating pulmonary exacerbation is based on ppFEV$_1$ and age, and in clinical practice ppFEV$_1$ is not measured in younger patients (i.e. those < 6 years). A similar assumption is used in the Company's model.

Average annual pulmonary exacerbation rate in patients aged 6 to < 18 years = $8.5938 \times \exp(-0.035 \times \text{ppFEV}_1)$

Average annual pulmonary exacerbation rate in patients aged ≥ 18 years = $3.7885 \times \exp(-0.026 \times \text{ppFEV}_1)$

Cystic fibrosis-related diabetes status

Patients aged ≥ 6 years who do not have CFRD at baseline are at risk of developing it over the model lifetime. 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 to 2005,[219] as shown in *Table 23*. The EAG notes that this is historical data and the incidence of CFRD may have changed since that time. UK CF Registry data from 2009 showed that 3.3% of patients aged < 16 years and 26.8% of patients ≥ 16 years were receiving treatment for CFRD compared with 8.3% and 35.5%, respectively, in 2021. This suggests that the incidence of CFRD may have increased from 2009 to 2021; however, as the EAG identified a lack of incidence data by age group for the UK, the older data were used. The EAG does not expect that using older data will have a large impact on the ICER.

TABLE 23 Annual incidence of CFRD by age group and sex

Age group (years)	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

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 pulmonary exacerbations and weight-for-age *z*-score. This may be considered a conservative assumption as some evidence has shown that, if initiated at an early age, CFTR modulators can also reduce the number of respiratory infections and development of CFRD or pancreatic insufficiency. The initial treatment effect is applied for the duration of the trial period from which the efficacy data were sourced, referred to as the acute period. When relevant head-to-head data from RCT data were available, the EAG used effectiveness data sourced from the relevant trial. When these were not available, the results from the EAG's NMAs, described in *Indirect treatment comparisons*, were used, along with assumptions when required. The treatment effects applied in the model for the key clinical inputs are detailed below.

Acute change in ppFEV$_1$

Age 1–5 years As previously noted, patients aged < 6 years do not have measures of ppFEV$_1$ available as this is not measured in clinical practice. Therefore, patients in the model aged 1–5 years have had patient profiles assigned that are sampled from patients aged 6–9 years, including a measure of ppFEV$_1$ at baseline. An acute increase in ppFEV$_1$ for patients aged 1–5 years is applied as soon as patients initiate treatment. This increase is assumed to be equal to that in patients aged 6–11 years, sourced from the clinical trials or NMA data for the relevant genotype (see *Age 6–11 years* for details). Although in clinical practice ppFEV$_1$ would not be measured 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 the age of 6 years and the impact of any changes in ppFEV$_1$ is not implemented in the CPH model for mortality until patients are 6 years old.

Age 6–11 years The EAG model inputs for the acute increase in ppFEV$_1$ due to CFTR modulator treatment are shown in *Table 24*. These are in line with the EAG's preferred data sources of clinical effectiveness, as discussed in detail in *Efficacy data for evidence gaps*.

Age ≥ 12 years For patients aged ≥ 12 years, direct trial estimates of the acute increase in ppFEV$_1$ were used when available. No randomised controlled data for ELX/TEZ/IVA were available for patients aged ≥ 12 years in F/F, F/Gating or F/RF populations. Therefore, the EAG conducted its own NMAs to obtain estimates of the acute increase in ppFEV$_1$ in these populations, as described in *Indirect treatment comparisons*. 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.

Long-term change in ppFEV$_1$

The long-term effectiveness of CFTR modulator treatments on change in ppFEV$_1$ is subject to a high degree of uncertainty. Therefore, the EAG made assumptions based on the best data available to inform the long-term change in ppFEV$_1$ for the three CFTR modulator treatments.

As discussed in *Long-term rate of ppFEV$_1$ decline for ELX/TEZ/IVA*, the EAG considers a reduction in the long-term rate of ppFEV$_1$ decline of 61.0% for ELX/TEZ/IVA compared with ECM to be the most appropriate estimate and applies this in the EAG base case.

TABLE 24 The EAG preferred inputs for acute increase in ppFEV1 for patients aged 6–11 years and aged ≥ 12 years

CFTR modulator treatment	Acute increase in ppFEV1 (95% CI)	Acute period duration (weeks)	Data source
Patients aged 6–11 years; values also applied to patients aged < 6 years			
F/F genotype			
LUM/IVA	2.4 (0.4 to 4.4)	24	Ratjen *et al.* 2017[126] (VX14-809-109): placebo-controlled, Phase III RCT of LUM/IVA
ELX/TEZ/IVA	11.2 (7.2 to 15.2)	24	Taken from single-arm estimate of Zemanick *et al.* 2022[120]
TEZ/IVA	2.8 (1.0 to 4.6)	24[a]	Taken from single-arm estimate of Davies *et al.* 2021[124]
F/MF genotype			
ELX/TEZ/IVA	11.0 (6.9 to 15.1)	24	Mall *et al.* 2022[119] (VX19-445-116): placebo-controlled, Phase III RCT of ELX/TEZ/IVA
F/Gating genotype			
ELX/TEZ/IVA	11.0 (6.9 to 15.1)	24	Assumed equal to value for F/MF genotype
F/RF genotype			
ELX/TEZ/IVA	6.78 (4.99 to 8.57)[b]	8	EAG analysis
TEZ/IVA	2.8 (1.0 to 4.6)	8	Single-arm estimate of Davies *et al.* 2021[124]
Patients aged ≥ 12			
F/F genotype			
LUM/IVA	2.83 (1.84 to 3.82)	24	Ratjen *et al.* 2017[126] (VX14-809-109): placebo-controlled, Phase III RCT of LUM/IVA
ELX/TEZ/IVA	14.20 (12.07 to 16.31)	24	EAG NMA
TEZ/IVA	4.0 (3.1 to 4.8)	24	Taylor-Cousar *et al.* 2017[122] (VX14-661-106): Phase III, placebo-controlled RCT
F/MF genotype			
ELX/TEZ/IVA	14.3 (12.7 to 15.8)	24	Middleton *et al.* 2019[60] (VX17-445-102): placebo-controlled, Phase III RCT of ELX/TEZ/IVA
F/Gating genotype			
ELX/TEZ/IVA	15.18 (12.16 to 18.22)	8	EAG NMA
F/RF genotype			
ELX/TEZ/IVA	8.80 (7.01 to 10.61)	8	EAG NMA
TEZ/IVA	6.8 (5.7 to 7.8)	8	Rowe *et al.* 2017[123] (VX14-661-108): Phase III, placebo-controlled crossover RCT of TEZ/IVA

F/F, *F508del* homozygous.
a This trial period was a duration of 8 weeks. To allow comparison across treatments, the EAG assumed that this treatment effect also applied for 24 weeks.
b This CI was inputted by the EAG by applying the same width as that observed in the ≥ 12 years population.

As noted in *LUM/IVA and TEZ/IVA*, 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. 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 with ECM. Therefore, the EAG applied a 0% relative reduction in decline compared with 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 with TEZ/IVA, based on the data observed in the acute period, it is expected that TEZ/IVA would have a greater impact than LUM/IVA but a smaller impact than ELX/TEZ/IVA. Therefore, the EAG applied the ratio of the acute effects observed in the aged ≥ 12 years 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 with ECM of 17.2% for TEZ/IVA (see *LUM/IVA and TEZ/IVA*).

The EAG preferred to implement a relative reduction in the rate of $ppFEV_1$ decline, rather than the absolute reduction reported in Newsome *et al.*[159] (see *Assumption-based approach*), as relative effect measures are less affected by baseline risk than absolute measures, and are therefore usually more transportable and consistent between studies.[220–222] However, to test the sensitivity of the EAG base case to applying an absolute versus relative reduction in $ppFEV_1$, the EAG performed a scenario analysis applying a scaled Newsome *et al.* 2022 estimate of IVA for ELX/TEZ/IVA (0.79 per year slower decline than ECM) and scaled this estimate for TEZ/IVA (0.22 per year slower decline than ECM). Further details of the methods used are available in *Report Supplementary Material 1*.

Change in pulmonary exacerbations

As trials in younger age groups either were not powered to detect a difference in pulmonary exacerbations or did not collect data on pulmonary exacerbations, the EAG applied a treatment effect for the impact of CFTR modulators on the rate of pulmonary exacerbations (requiring antibiotics or hospitalisation) only for patients aged ≥ 12 years. This is considered a conservative assumption and similar to that applied in the Company model.

The treatment effect for patients aged ≥ 12 years is applied as a rate ratio in the model. In NICE TA786 for LUM/IVA, the EAG noted that as the annual rate of pulmonary exacerbations is a function of a patient's $ppFEV_1$ value, which has a separate treatment effect applied, the observed change in pulmonary exacerbations 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 separate treatment effects are applied to both $ppFEV_1$ and pulmonary exacerbations. To adjust for this risk of double counting in the Company's MTA submission, calibration techniques were used to derive a rate ratio for pulmonary exacerbations when receiving CFTR modulators compared with ECM to account for the acute $ppFEV_1$ increase. The EAG applied the same calibration approach; however, unlike in 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 time frame to that of the trial. The data sources used to inform the initial rate ratio values are described in *Table 25*; calibrated values are redacted due to confidentiality agreements. The EAG does not consider that any robust evidence was provided to show that the effects of CFTR modulators on the rate of pulmonary exacerbations, independent of the $ppFEV_1$ effect, exist beyond the acute period. For both LUM/IVA and TEZ/IVA, the estimated pulmonary exacerbation event rates from the initial placebo-controlled trials appeared to increase when compared with the observational extension studies, whereas the event rates in ELX/TEZ/IVA long-term extension studies and final analysis of the managed access agreement may 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 pulmonary exacerbations in the acute period. No further separate treatment effect on pulmonary exacerbations beyond that applied through the effect on $ppFEV_1$ is applied in the long term.

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 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 patients may also potentially gain excessive weight in the long term as a result of following advice to observe a high-calorie diet that was given 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 of the treatment effectiveness on weight-for-age *z*-score are provided below.

TABLE 25 Change in the rate of pulmonary exacerbations for patients aged ≥ 12 years

CFTR modulator treatment	PE rate ratio (uncalibrated)	Data source for uncalibrated rate ratio
F/F genotype		
LUM/IVA	0.44	Wainwright 2015 (VX12-809-103) and (VX12-809-104): Phase III placebo-controlled RCTs of LUM/IVA in participants aged ≥ 12 years
ELX/TEZ/IVA	0.22	Assumed equivalent to patients with F/MF genotype
TEZ/IVA	0.53	Taylor-Cousar 2017[122] (VX14-661-106): Phase III placebo-controlled RCT in people with CF aged ≥ 12 years with F/F genotype
F/MF genotype		
ELX/TEZ/IVA	0.22	Middleton 2019[60] (VX17-445-102): placebo-controlled Phase III RCT of ELX/TEZ/IVA, F/MF patients
F/Gating genotype		
ELX/TEZ/IVA	0.22	Assumed equivalent to patients with F/MF genotype
F/RF genotype		
ELX/TEZ/IVA	0.22	Assumed equivalent to patients with F/MF genotype
TEZ/IVA	0.54	Rowe 2017[123] (VX14-661-108): Phase III placebo-controlled crossover RCT in people with CF aged ≥ 12 years with F/RF genotype

F/F, *F508del* homozygous; PE, pulmonary exacerbation.

Age 1–5 years As described in *Acute change in ppFEV$_1$, Age 1–5 years*, trial data for LUM/IVA were available for F/F genotype patients aged 1–2 and aged 2–5 years. In patients aged 1–2 years, an increase in weight-for-age *z*-score of 0.06 was observed. A higher increase was observed in patients aged 2–5 years, 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 in patients aged 2–5 years with either F/F or F/MF genotype that was substantially smaller than that observed with LUM/IVA, with an absolute increase of 0.02. As in the model no change beyond the acute increase is assumed over the patient's lifetime, only applying an acute increase of 0.02 for ELX/TEZ/IVA patients starting aged 2–5 years was considered overly conservative by the EAG as this would not capture the long-term benefits expected from that treatment. Therefore, the EAG applied the values observed in patients aged 6–11 years for patients aged 1–5 years for both LUM/IVA and ELX/TEZ/IVA. These are described in the following section.

Age 6–11 years Model inputs for the acute increase in weight-for-age *z*-score due to CFTR modulator treatment are in line with the EAG's preferred data sources on clinical effectiveness, discussed in detail in *Critical review and synthesis of information*, and clinically plausible assumptions when required. An overview of the data used for different genotypes and treatments is described below. Owing to confidentiality, inputs are unable to be shown.

- 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 it applied a value of 0.
- For the F/MF genotype, the EAG applied the values observed in the placebo-controlled, Phase III RCT of ELX/TEZ/IVA.[119]
- Direct trial evidence for ELX/TEZ/IVA was not available in the F/Gating population. The EAG assumed an equivalent treatment effect to that observed in the F/MF population, which the EAG's clinical experts considered reasonable.
- Owing to a lack of direct trial evidence for the ELX/TEZ/IVA F/RF population, as described in *Efficacy data for evidence gaps*, the EAG took the mid-point of the treatment effect observed in the ≥ 12 years F/RF population when multiplied by the observed reduction in weight-for-age *z*-score treatment effect between the ≥ 12 years and 6–11 years groups in the F/MF and F/F genotypes, respectively. 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.

Age ≥ 12 years 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 *Indirect treatment comparisons*. Owing to confidentiality, these data are unable to be presented.

Treatment discontinuation

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 details of the rates and data sources used for each of the three CFTR modulator treatments are shown in *Table 26*.

On discontinuing CFTR modulator treatments, patients receive ECM only, with the associated costs and annual ppFEV$_1$ decline. Clinical experts to the EAG noted that on 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 on discontinuation.

Long-term discontinuations

Data from modulator treatments extension studies were used to inform the discontinuation rates beyond the acute period. No long-term data are available for ELX/TEZ/IVA for patients aged 2–5 years; therefore, the EAG assumed that long-term discontinuation rates for this age group are equal to those observed in patients aged 6–11 years.

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 from 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 27*.

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 of and assumptions about acute period compliance rates are the same as those applied for discontinuation rates, as previously described in *Acute period discontinuations*. These data are confidential and, therefore, unable to be reported. As no data on both long-term compliance and treatment effectiveness were available for the three included CFTR modulators, the EAG assumed 100% compliance following the acute period. As the impact of compliance in the model is only through a reduction in costs, applying a lower compliance rate beyond the trial period would not account for any differences in efficacy that result from lower compliance. The EAG is aware that compliance in the real world may be lower than 100%, but, based on clinical expert opinion to the EAG, it is expected to remain high due to the quick decline in health experienced by patients when they discontinue. The EAG has conducted a scenario analysis (see *Scenario analysis*) that uses an alternative long-term compliance rate based on the Company's latest estimate from the data collection agreement.[87]

Lung transplantation

In line with the Company's models, and based on UK clinical guidance for transplantation, patients in the model are eligible for lung transplant once their ppFEV$_1$ falls below 30%. Clinical experts to the EAG noted that 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 a patient's ppFEV$_1$ will be around ≤ 30% by the time of the transplant. The Company applies a probability of lung transplant based on data from the UK CF Registry 2021 report,[1] in which 5 patients out of the 78 evaluated received a lung transplant (6.4%). The EAG notes that this proportion is much lower than in 2019, and there is a possibility that this value had been impacted by the COVID-19 pandemic. In response to clarification questions, the Company also stated that the smaller number of transplants in 2021 may have

TABLE 26 Acute period discontinuation rates applied in the economic model

Genotype	Acute period (weeks)	Annual rate of discontinuations	Source
ELX/TEZ/IVA			
Age 2–5 years			
F/F	24	Confidential information has been removed	Study 445–111, Phase III non-randomised trial of F/F and F/MF genotype patients aged 2–5 years
F/MF	24	Confidential information has been removed	Study 445–111, Phase III non-randomised trial of F/F and F/MF genotype patients aged 2–5 years
F/Gating	24	Confidential information has been removed	Assumed equal to F/F and F/MF
F/RF	24	Confidential information has been removed	Assumed equal to F/F and F/MF
Age 6–11 years			
F/F	24	0.067	Zemanick *et al.* 2021[120] (VX18-445-106): Phase III non-randomised trial of ELX/TEZ/IVA
F/MF	24	0.036	Mall *et al.* 2022[119] (VX19-445-116): placebo-controlled Phase III 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 years			
F/F	24	0.025	Sutharsan *et al.* 2022[116] (VX18-445-109): TEZ/IVA-controlled Phase III RCT of ELX/TEZ/IVA in people with CF aged ≥ 12 years
F/MF	24	0.033	Middleton *et al.* 2019[60] (VX17-445-102): placebo-controlled Phase III RCT of ELX/TEZ/IVA aged ≥ 12 years with an F/MF CF genotype
F/Gating	8	0.049	Barry *et al.* 2021:[117] active controlled Phase III RCT. F/RF or F/Gating
F/RF	8	0.049	Barry *et al.* 2021:[117] active controlled Phase III RCT. F/RF or F/Gating
TEZ/IVA			
Age 6–11 years			
F/F	8	0.121	Davies *et al.* 2021:[124] Phase III RCT for patients aged 6–11 years
F/RF	8	0.121	Davies *et al.* 2021:[124] Phase III RCT for patients aged 6–11 years
Age ≥ 12 years			
F/F	24	0.143	Taylor-Cousar *et al.* 2017:[122] Phase III RCT for patients aged ≥ 12 years, F/F
F/RF	24	0.081	Rowe *et al.* 2017:[123] Phase III RCT for patients aged ≥ 12 years, F/RF
LUM/IVA			
1–5 years	24	0.149	McNamara *et al.* 2019 (VX15-809-115): Phase III non-randomised. Data from patients aged 2–5 years assumed applicable for patients aged 1–2 years
6–11 years	24	0.13	Ratjen *et al.* 2017[126] (VX14-809-109): placebo-controlled Phase III RCT of LUM/IVA
≥ 12 years	24	0.152	Wainwright *et al.* 2015[39]

TABLE 27 Long-term annual discontinuation rates

Genotype/age group	Study period (weeks)	Annual rate of discontinuations	Source
ELX/TEZ/IVA			
Age 2–11 years			
F/F	96	0.026	Ratjen *et al.* 2021[133]
F/MF	96	0.026	Ratjen *et al.* 2021[133]
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 years			
F/F	144	Confidential information has been removed	Griese *et al.* 2022[132]
F/MF	144	Confidential information has been removed	Griese *et al.* 2022[132]
F/Gating	96	Confidential information has been removed	Study 445–110[134]
F/RF	96	Confidential information has been removed	Study 445–110[134]
TEZ/IVA			
Age 6–11 years			
F/F	96	Confidential information has been removed	Sawicki *et al.* 2022[136]
F/RF	96	Confidential information has been removed	Sawicki *et al.* 2022[136]
Age ≥ 12 years			
F/F	96	Confidential information has been removed	Flume *et al.* 2021[135]
F/RF	96	Confidential information has been removed	Flume *et al.* 2021[135]
LUM/IVA			
1–5 years	96	0.06	McNamara 2019
6–11 years	96	0.035	Chilvers *et al.* 2021[139]
≥ 12 years	96	0.152	Konstan *et al.* 2017[138]

F/F, *F508del* homozygous.

been a result of CFTR modulators. As the model requires a value for lung transplant that represents the impact without CFTR modulators, the EAG applied the values from the UK CF Registry 2019 report. The exact number of patients aged < 16 years who received a bilateral lung transplant in 2019 was not available, and this information was reported for patients aged < 5 years only. As a result of this, the probability of transplant in the EAG model included only patients aged > 16 years. 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 patient's ppFEV$_1$ reaches < 30%.

Following lung transplant, the CPH model for mortality is no longer implemented and a separate mortality post lung transplant is applied. The Company used international data collected between 1992 and 2017 on survival post lung transplant among CF patients. Survival post lung transplant may differ across countries and healthcare systems and therefore the EAG considered a UK-specific source to be more appropriate. The NHS annual report on Cardiothoracic Organ Transplantation 2021–2[223] provides post-lung-transplant 1- and 5-year survival rates for CF 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.

Adverse events

The EAG included the AEs that were either highlighted by the EAG's clinical experts as problematic for patients or reported as AEs of special interest across the clinical trials, namely rash events and liver AEs. In terms of liver AEs, the EAG identified increased alanine aminotransferase and increased aspartate aminotransferase as those that were reported consistently between clinical trials noted in *Adverse effects of treatment*, and therefore these 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 were low, and most events occurred in patients aged ≥ 12 years. 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.

Because three different treatments were included in the model, there was no common ECM arm in the clinical trials that could be used to assess AEs. As the model requires a common ECM arm with which to compare all three CFTR modulator treatments, the difference between the placebo arm and the 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 be either positive or negative. In cases where the rate of AEs in the treatment arm was negative, that is the AE 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 were 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 years, although placebo-controlled comparative data were available in Davies *et al*.,[124] the control arm of the study consisted of 10 patients only. Therefore, the EAG compared the treatment arm of Davies *et al*.[124] with the placebo arm of Mall *et al*.,[119] the placebo-controlled trial of patients aged 6–11 years for ELX/TEZ/IVA. Owing to confidentiality agreements, the AE data used in the model are unable to be reported.

Health-related quality of life

Utility values were required in the economic model based on $ppFEV_1$ and disutility of pulmonary exacerbations and following lung transplant. The EAG applied a reduction in HRQoL with age, as per the general population, based on the Health Survey for England EQ-5D-3L general population value set. This value set provides general population utility values only for individuals aged ≥ 16 years. Therefore, the EAG applied a conservative assumption, assuming no decline in HRQoL due to age prior to age 16 years in the model.

The Company's models also applied a treatment-specific utility increment for patients treated with ELX/TEZ/TEZ (all CFTR genotypes) and TEZ/IVA (F/RF only) based on CFQ-R 8D data. This was not applied in the EAG base case based on limitations and uncertainties in the methods used to derive the values. An additional increment of 0.03 in the ELX/TEZ/IVA model only for carers of children aged 6–11 years was also applied in the Company's model. This was based on a study of 25 carers using the Care-related Quality of Life (CarerQoL) measure. Based on the small sample size, it is unclear if all carers have the same experience and for how long the carer impact should apply. Owing to a lack of reliable estimates, carer HRQoL was not included in the EAG base-case analyses, but this was explored in a scenario analysis (see *Scenario analysis*). The EAG considers that further research is required into the impact of CF on carers and how the use of new treatments may improve their quality of life.

Health-related quality of life stratified by $ppFEV_1$ value

The economic model was constructed to capture the main benefits of treatment for CF and, as a result, utility values that reflect changing $ppFEV_1$ were required. The SLR undertaken by the EAG, described in *Results: health-related quality-of-life searches*, identified five individual studies (reported in 10 separate studies) that reported HRQoL values stratified by $ppFEV_1$ grouping, all of which used the EQ-5D. One of these studies was the NICE TA786 for LUM/IVA,

which reported that 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 reflect patients' adaptation to life with a chronic disease and limit the detection of treatment benefit. During TA786, the committee stated that there was no evidence to suggest that the EQ-5D was inappropriate and that this measure 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 pulmonary exacerbations. A utility decrement for pulmonary exacerbations 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 be supported by 'qualitative empirical evidence on the lack of content validity for the EQ-5D' that 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%, and < 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 in terms of lung function. The UK CF Registry report provides only the median age of the population, which in 2021 was 21 years. This is largely in line with the mean age of all patients in the modelled cohort (21.9 years). The general population utility value for male and female patients (weighted according to the UK CF Registry sex split, 53.2% male) was sourced from Health Survey for England 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 × 0.981 = 0.907). A similar stepwise process was used for the subsequent $ppFEV_1$ categories, shown in *Table 28*. In the EAG's model, the utility value for the group 70% to < 90% was applied for all patients with a $ppFEV_1$ of ≥ 70%.

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 *et al.*,[197] who reported EQ-5D values classified by $ppFEV_1$ grouping. This study was also identified in the EAG's SLR. The EAG notes that the Acaster *et al.* study included adult patients who had a self-reported CF diagnosis and $ppFEV_1$ value and so may potentially suffer from selection bias. However, these values show the greatest differences in utility values between the best ($ppFEV_1$ ≥ 70% = 0.74) and the worst ($ppFEV_1$ < 40% = 0.54) health states, which patient experts noted best reflected the HRQoL of CF patients. Therefore, the EAG used the values reported in this study in a scenario analysis to explore the impact on the ICER. A separate scenario analysis is also included using utility values from the Company's model. The EAG notes that, although the values for each $ppFEV_1$ group are lower than the EQ-5D values applied in the EAG base case, the reduction in utility when moving from $ppFEV_1$ 70–40% to ≤ 40% is the same between the Company's and the EAG's utility values. It is also noteworthy that the EAG model applies an age adjustment to utility values over the lifetime of the model, whereas this was not included in the Company's model.

TABLE 28 The EAG-applied EQ-5D value

ppFEV1 grouping (%)	LUM/IVA trial value	Relative difference compared with ≥ 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

Disutility of pulmonary exacerbations

The EAG identified two UK-based studies in the review of utility values (see *Results: health-related quality-of-life searches*) that also reported on the disutility of pulmonary exacerbations. Bradley *et al.*[201] reported disutility values for major exacerbation (0.174) and minor exacerbation (0.015). This study was conducted in adult CF patients with *P. 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.*[206] 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 antibiotics day was 0.12. Additionally, the Company applied disutility associated with a pulmonary exacerbation based on a study assessing the impact of pulmonary exacerbations on HRQoL using data from the ivacaftor monotherapy clinical trial. This collected EQ-5D-3L data from patients aged ≥ 12 years with a *G551D* mutation. Based on data reported in this study, a disutility of 0.07 was applied for 30 days for each pulmonary exacerbation.

In line with using the trial data from LUM/IVA for utility values stratified by $ppFEV_1$, the EAG used the disutility associated with pulmonary exacerbations from the ivacaftor monotherapy clinical trial, as applied by the Company. This included patients from the age of 12 years, unlike the other sources available for UK data.

Post lung transplant

Numerous studies identified in the EAG's SLR 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 are sourced from a study by Anyanwu *et al.*[224] This study collected data from patients post lung transplant in UK lung transplant centres during 1998. In the ivacaftor monotherapy HTA, Whiting *et al.*[40] used the data from bilateral lung transplant patients (n = 79 patients) from the Anyanwu *et al.*[224] study as these were said to most likely reflect CF transplant patients. The authors 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 post lung transplant is similar to the value used by the Company (0.8) and by Tappenden *et al.*[206] (0.83) for $ppFEV_1$ ≥ 70%. A recently published SLR[225] of HRQoL for CF patients post lung transplant found that patients' HRQoL up to 5 years post lung transplant is equal to that of general population and the HRQoL of CF patients following transplant is greater than or equal to that of patients with other indications requiring lung transplant. For these reasons, the EAG applies the same utility value post lung transplant as that used for patients with $ppFEV_1$ ≥ 70% (0.908).

Resource use and costs

The economic model includes costs related to drug acquisition, ECM, pulmonary exacerbations, monitoring related to CFTR modulators and lung transplantation. Further details of each of these costs are provided in the following section.

CFTR modulator acquisition costs

The drug acquisition costs included in the model based on list price are given in *Table 29* and were obtained from the *British National Formulary*.[226] Treatment regimens based on age group and weight for each of the CFTR-modulator combinations are described in *Summary of intervention*. The annual cost of each CFTR-modulator combination therapy by age group is presented in *Table 30*. Patient access scheme prices were provided by NICE to the EAG and used in the final model results presented in this report. Patient access scheme discounts were subject to change following further commercial arrangements. Owing to confidentiality, only list prices are presented below.

The EAG notes that although 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 30*).

Established clinical management costs

Drug costs Because the nature of CF causes a wide range of symptoms and associated illnesses (e.g. respiratory infections, pancreatic insufficiency, CFRD), its management is multidisciplinary and so no one standard treatment is

TABLE 29 Cystic fibrosis transmembrane conductance regulator-modulator acquisition costs

Treatment	Strength[a]	Pack size	List price (£)	
			Pack price (£)	Cost per unit (£)
LUM/IVA	75 mg/94 mg sachet	56	8000.00	142.86
	100 mg/125 mg sachet			
	150 mg/188 mg sachet			
	100 mg/125 mg tablets	112	8000.00	71.43
	200 mg/125 mg tablet			
TEZ/IVA	50 mg/75 mg tablets	28	6293.91	224.76
	100 mg/150 mg tablets			
ELX/TEZ/IVA	80 mg/40 mg/60 mg sachet	28	8346.30	298.08
	100 mg/50 mg/75 mg sachet			
	37.5 mg/25 mg/50 mg tablets	56	8346.30	149.04
	75 mg/50 mg/100 mg tablets			
Ivacaftor	59.5 mg sachet	28	7000.00	250.00
	75 mg sachet			
	75 mg tablets	28	7000.00	250.00
	150 mg tablets			

a The order of the strength of the tablets reflects the order of the associated combination therapy. For example, for LUM/IVA, strength of 100 mg/125 mg represents 100 mg of lumacaftor and 125 mg of ivacaftor.
Source: *British National Formulary*.[226]

TABLE 30 Cystic fibrosis transmembrane conductance regulator-modulator acquisition costs per year according to dose

Treatment	Age group (years)	Units per day	Annual cost (£)
LUM/IVA	1–5	Two sachets per day (one sachet every 12 hours)	104,357.14
	≥ 6	Four tablets per day (two tablets every 12 hours)	104,357.14
TEZ/IVA	≥ 6	One tablet of TEZ/IVA in the morning and one tablet of IVA in the evening	173,414.31
ELX/TEZ/IVA	2–5	One sachet of ELX/TEZ/IVA in the morning and one sachet of IVA in the evening	200,187.00
	≥ 6	Two tablets of ELX/TEZ/IVA in the morning and one tablet of IVA in the evening	200,187.00

applied to all patients. However, as described in *Management of disease* (see *Table 2*), a set of therapies is 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 *et al.*[145] that used UK CF Registry data to explore treatment use 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%), as shown in *Table 31*.

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 use. The treatments included were inhaled antibiotics, dornase alfa,

TABLE 31 Annual ECM costs by $ppFEV_1$ group

Treatment	Cost per year (£)	Proportions taking treatment			Total cost (£)			Source/assumptions
		$ppFEV_1$ > 80%	$ppFEV_1$ > 60–80%	$ppFEV_1$ < 60%	$ppFEV_1$ > 80%	$ppFEV_1$ > 60–80%	$ppFEV_1$ < 60%	
Inhaled antibiotics	12,086.13	0.49	0.59	0.7	5922.20	7130.82	8460.29	CF Registry report 2018; see *Report Supplementary Material 1* for further details
Dornase alfa	6043.84	0.73	0.8	0.8	4412.01	4835.08	4835.08	Tappenden *et al.* 2023,[206] pulmozyme 2.5 mg; daily dose 2.5 mg
Hypertonic saline solution	173.75	0.37	0.4	0.42	64.29	69.50	72.98	Tappenden *et al.* 2023,[206] 6% or 7% inhalation solution; daily dose 8 ml
Azithromycin	99.53	0.4	0.59	0.71	39.81	58.72	70.67	Tappenden *et al.* 2023,[206] azithromycin 250 mg tablets; daily dose 250 mg
Flucloxacillin	48.29	0.31	0.27	0.22	14.97	13.04	10.62	Tappenden *et al.* 2023,[206] flucloxacillin 250 mg or 500 mg capsules; daily dose1 g
					10,453.28	12,107.15	13,449.63	

hypertonic saline solution, azithromycin, flucloxacillin and supplementary feeding (both oral and gastrostomic). One of the EAG's clinical experts (a senior dietitian) advised that the costs and dosages associated with supplementary feeding are extremely variable between both patients and centres in the UK. Because of 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 UK CF Registry 2018 report[227] on the proportion of each inhaled antibiotic used to calculate an overall weighted cost of inhaled antibiotics (see *Report Supplementary Material 1*). 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 patient's $ppFEV_1$. The EAG notes that the three $ppFEV_1$ groups used for ECM drug costs differ from 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 details of the costs and resource use applied are provided in *Table 31*.

The dosage of each drug was informed by Tappenden *et al.*,[206] which was identified during the EAG's HRQoL SLR (see *Results: health-related quality-of-life searches*). The EAG assumed that the dosage of 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 available dosage details differ between adults and children, the cost was very low and therefore the EAG does not expect this to have a large impact on the overall costs. The costs of treatment assume full adherence and that treatment is prescribed as per the recommended guidelines.

The EAG notes that a confidential comparator price is available for colistimethate dry powder, which makes up a proportion of the inhaled antibiotics drug costs. As the impact on the ICERs was negligible, publicly available eMIT and list prices (sourced from the *British National Formulary*[226]) have been used. The study used to inform ECM resource use by $ppFEV_1$ grouping also explored the difference in use between patients eligible for ivacaftor and those not eligible. Clinical experts to the EAG noted that it is currently unknown if other treatments can be reduced while patients are taking CFTR modulators, as data are not currently available on the impact on CFTR modulator efficacy when it is not taken in combination with ECM. Therefore, the EAG base case assumed equal ECM drug costs between patients receiving ECM alone and those receiving CFTR modulators. During the appraisal, various stakeholders commented that the need for, and cost of, non-CFTR modulator therapies may be lower in patients treated with ELX/TEZ/IVA. A scenario analysis is included in which the EAG calculated the weighted average reduction of resource use between patients eligible for ivacaftor and those not eligible from 2018 (reported by Granger *et al.*)[145] . This results in a 23% reduction in ECM drug costs for patients on CFTR modulator treatments. An additional scenario applies a reduction of 40%, based on the maximum reduction observed across any single resource use component within Granger *et al.*[145] (hypertonic saline). The EAG notes that an ongoing study (CF STORM)[170] is being conducted to estimate the impact of reducing or stopping treatment with nebulised mucoactive therapies, while receiving treatment of ELX/TEZ/IVA, on decline in lung function. This will hopefully provide evidence in place of the current assumption in any future modelling. The EAG also notes that the Cystic Fibrosis Dietitians Specialist Group of the British Dietetic Association (CF BDA) reported that treatment with CFTR modulators has led to a reduction in prescribing of oral nutritional supplements and the removal of gastronomy feeding tubes in some patients. While, as noted above, these costs could not be incorporated into the ECM costs, the EAG's scenario analyses represent a reduction in all ECM costs.

Healthcare costs In addition to drug costs, patients with CF will regularly come into contact with numerous healthcare professionals as part of the multidisciplinary approach to disease management. Costs of healthcare were taken from Tappenden *et al.*,[206] who reported CF disease management costs split by $ppFEV_1$ group and inflated to 2021–2 prices using the NHS Cost Inflation Index (CII) for pay and prices ($ppFEV_1$ > 70% = £3460; $ppFEV_1$ 40–69% = £3877; $ppFEV_1$ < 40% = £3411). Tappenden *et al.* 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 pulmonary exacerbations requiring IV antibiotics, GP visits, hospital-based consultant visits, nurses, physiotherapists, psychologists, dietitians, occupational therapists, radiographers, social workers and visits to accident and emergency.

Costs of pulmonary exacerbations

In the economic model, as pulmonary exacerbations occur as a function of age and ppFEV$_1$, patients with a lower ppFEV$_1$ are more likely to have a greater number of pulmonary exacerbations each year and, therefore, incur greater costs. Clinical experts to the EAG noted that although the cost of pulmonary exacerbations may differ between ppFEV$_1$ groups (> 70%, 40–70%, < 40%), this is largely due to the greater number of pulmonary exacerbation 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 3-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 a 14-day inpatient stay in hospital, receiving IV antibiotics. Clinical experts during the NICE committee meeting highlighted that there may be a reduced requirement for IV antibiotics for patients experiencing a pulmonary exacerbation while being treated with CFTR modulators. Therefore, the EAG also provided an illustrative scenario involving a 50% reduction in pulmonary exacerbation costs to reflect reduced use of IV antibiotics or days in hospital.

The unit cost of inpatient stay and IV drugs used in hospital to treat pulmonary exacerbations, shown in *Table 32*, was taken from Tappenden *et al.*[206] and inflated to 2021/22 prices using the NHS CII for pay and prices.

Monitoring costs

Monitoring costs of liver function tests (bilirubin, aspartate transaminase and alanine transaminase) and ophthalmologist visits are applied to all patents on CFTR modulator treatments, in line with guidance in the SmPC. Clinical experts to the EAG noted that 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 years. This differed from the Company's models in which costs are applied only 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 a follow-up ophthalmology visit are included. Clinical experts also stated that monitoring for liver function is applied every 3 months in the first year of initiating treatment, and annually thereafter. Costs were sourced from NHS Reference Costs 2021/22.[215] Further details can be found in *Report Supplementary Material 1*.

Cost of lung transplantation

The cost of lung transplant is taken from NHS Reference Costs 2021/22[215] 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 in the model have had a lung transplant, they no longer receive the treatment costs and disease management costs associated with CF. Instead, costs associated with post lung transplant were taken from the study by Anyanwu *et al.*,[228] which reported post-lung-transplant follow-up costs up to 15 years. The EAG used the reported costs associated with bilateral lung transplant. The reported costs had been discounted at 6%; therefore, the EAG reversed the discounting and inflated costs to 2022 prices using the NHS Cost Inflation Index (NHSCII),[229] as shown in *Table 33*.

TABLE 32 Cost per pulmonary exacerbation event

Resource	Unit cost (£)	Resource use (days)	Total cost (£)	Source
Inpatient stay (per day)	421.92	14	5906.91	Tappenden *et al.*, 2023.[206] Cost per non-elective bed-day, weighted by FCEs and average length of stay, assumed interventions for bronchiectasis (codes DZ12C to DZ12F). Inflated to 2021/22 costs
IV drugs in hospital	28.58	14	400.07	Tappenden *et al.*, 2023.[206] Costs consists of 3 g of ceftazidime, 481–560 mg of tobramycin, sodium chloride 0.9% and heparin 50 units in 5 ml. Inflated to 2021/22 costs
Total cost per pulmonary exacerbation event			6139.98	Calculated

FCE, finished consultant episode.

TABLE 33 Lung transplant and follow-up costs

Resource	Cost (£)	Source
Lung transplant	73,388	NHS Reference Costs 2021/22. 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)	28,935.71	Anyanwu *et al.* 2002,[228] inflated to 2022
Post-lung-transplant annual follow-up cost (second year)	12,055.13	
Post-lung-transplant annual follow-up cost (third year)	11,755.98	
Post-lung-transplant annual follow-up cost (years 4–10)	10,392.64	
Post-lung-transplant annual follow-up cost (years 11 +)	8501.43	

List of key assumptions

The EAG's economic model employs a number of assumptions, with the main ones detailed below. A comparison of the key differences between the EAG and Company model assumptions/data sources can also be found in *Report Supplementary Material 1*.

- An individual's baseline mortality is equal to the marginal population mortality. This assumes that any given patient characteristics at baseline are the same as those of the general CF population.
- Baseline characteristics are based on patients combined from the main CFTR modulator trials for each specific genotype.
- Patients' pancreatic sufficient status and respiratory infections do not change over time and therefore do not contribute to the risk of mortality.
- No pulmonary exacerbations in patients aged < 6 years.
- No CFRD in patients aged < 6 years.
- No decline in a patient's weight-for-age *z*-score.
- No treatment effect on the rate of pulmonary exacerbations for patients aged < 12 years.
- The relative reduction in the rate of $ppFEV_1$ decline compared with ECM is equal to 61.0% per year for patients on ELX/TEZ/IVA following the acute period, applied for the lifetime.
- The relative reduction in the rate of $ppFEV_1$ decline compared with ECM is equal to 17.2% per year for patients on TEZ/IVA following the acute period, applied for the lifetime.
- Same rate of decline in $ppFEV_1$ as ECM following the acute period for patients on LUM/IVA.
- No independent treatment effect of pulmonary exacerbations beyond the acute period.
- No further discontinuations beyond 5 years on treatment with CFTR modulators.
- CFTR modulator compliance rates from the key trials of efficacy data are applied in the acute period. Assumed 100% after this point.
- 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.
- Patients are eligible for lung transplant once their $ppFEV_1$ reaches 30%.
- Treatments included in ECM costs are inhaled antibiotics, dornase alfa, hypertonic saline solution, azithromycin and flucloxacillin only.
- All ECM and pulmonary exacerbation treatment costs are the same for adults and children.
- Treatment costs for pulmonary exacerbations do not differ by $ppFEV_1$ value.
- Utility values are based on $ppFEV_1$ taken from LUM/IVA trial of patients aged ≥ 12 years and are assumed to apply to all treatment arms.
- Disutility due to pulmonary exacerbations is applied for 30 days.
- Utility value post lung transplant is equal to utility of patients with $ppFEV_1$ 70–90%.

Results

Base-case analysis

As described in *Interventions and comparators*, the three CFTR modulator treatments included in this MTA have marketing authorisation in different genotype populations and age groups. As the three modulators must be analysed within common populations so that mutually exclusive alternatives can be compared appropriately, the EAG analyses are separated based on genotype. For both the F/MF and F/Gating genotypes, ELX/TEZ/IVA is the only modulator treatment available and therefore the analysis is equivalent to a pairwise comparison against ECM. For both F/F and F/RF, more than one modulator option is available. As stated in the NICE methods guide, '…when comparing multiple mutually exclusive options, a fully incremental approach should be adopted that compares the treatments sequentially in rank order of effectiveness (or cost)'.[230] 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 strongly dominated and are therefore removed from consideration in the final ICER calculations.[196] When interventions have both higher costs and QALYs than their predecessor, the ICER is calculated between those two treatments. If the calculated ICER is higher than that of the next most expensive alternative treatment, then the lower-cost treatment is considered extendedly dominated and removed from consideration.[196]

The EAG conducted both deterministic and probabilistic analyses. The probabilistic sensitivity analysis was based on 1000 iterations of the model. Although some of the probabilistic ICERs are higher than the deterministic, these do not differ substantially.

Severity modifier

As outlined in the NICE methods guide,[230] '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 QALY weightings for severity are shown in *Table 34*.

The EAG calculated the absolute and proportional QALY shortfall using a published calculator by the University of York.[231] 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 the Heath Survey for England 2014 and uses the model for estimating general population HRQoL norms by Hernández Alava *et al*.,[232] as recommended by the NICE Decision Support Unit.

Table 35 shows the mean age and sex distribution of each genotype in the EAG model and the lifetime QALYs for patients without CF. The corresponding QALY weight for each population is also shown.

As shown in *Table 35*, a severity modifier of 1 is applied to all genotypes. 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 genotype patients and 9 for F/RF genotype patients.

Results

All results calculated by the EAG included patient access scheme prices for all CFTR modulator treatments, which were subject to change following ongoing commercial arrangements. Owing to confidentiality agreements, the results of all cost-effectiveness analyses are unable to be presented. However, in both the deterministic and the probabilistic base-case fully incremental analysis, both LUM/IVA and TEZ/IVA were extendedly dominated in the F/F population (i.e. the

TABLE 34 Quality-adjusted life-year weightings for severity modifier

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	< 0.85	< 12
× 1.2	0.85–0.95	12–18
× 1.7	At least 0.95	At least 18

TABLE 35 Quality-adjusted life-year 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	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
QALYs without CF	22.67	22.52	22.51	21.10
QALY weight	1	1	1	1

ICERs were higher than a more effective treatment, namely ELX/TEZ/IVA). In the F/RF population, TEZ/IVA was also extendedly dominated by ELX/TEZ/IVA.

In both comparisons against ECM alone and fully incremental analysis, all ICERs were substantially higher than the NICE recommended willingness-to-pay (WTP) threshold of £20,000–30,000.

The highest severity modifier of 1.7 is the equivalent of an ICER threshold of £34,000–51,000. All ICERs in the EAG base-case analysis were also substantially higher than this threshold.

One-way sensitivity analysis

A deterministic sensitivity analysis was conducted by varying key model parameters between the upper and lower values of the expected value used in the deterministic base case. The key model parameters include:

- CFRD prevalence/incidence for age and sex subgroups
- baseline CF mortality by sex
- the $ppFEV_1$ limit required for a patient to be eligible for lung transplant
- probability of death from lung transplant in years 1 and 2
- change in $ppFEV_1$ for ECM patients by age
- lowest possible $ppFEV_1$ limit for patients
- parameters determining rates of pulmonary exacerbation in ECM patients
- acute and long-term change in $ppFEV_1$ for CFTRm (cystic fibrosis transmembrane conductance regulator modulator) treatments for age subgroups
- acute changes in pulmonary exacerbation rate for CFTRm treatments for age subgroups
- acute changes in weight-for-age *z*-score for CFTRm treatments for age subgroups
- acute and post-acute changes in discontinuation rate for CFTRm treatments for age subgroups
- health state, concomitant medication and pulmonary exacerbation costs
- health state utility.

Inputs affecting individual subgroups across genotypes were varied separately. Inputs separate across genotypes were varied concomitantly.

Cystic fibrosis-related diabetes prevalence/incidence, baseline mortality, risk of death in the years following transplant, change in $ppFEV_1$ for ECM patients, CFTRm efficacy inputs, health state costs and health state utilities were varied individually for each treatment by their 95% CIs. No estimates of precision were available for the $ppFEV_1$ limit required for transplant eligibility, the lowest possible $ppFEV_1$ limit for patients or parameters determining rates of pulmonary exacerbation in ECM patients (which uses a formula based on age and $ppFEV_1$); therefore, the standard error was assumed to equal ± 20% of the mean value or was varied at an individually determined fixed interval.

The EAG presented the results of the deterministic sensitivity analysis in tornado diagrams displaying the top 10 parameters for the total CF population (all ages) for each genotype. Owing to confidentiality arrangements, these are

unable to be reported. All lower- and upper-bound ICERs produced from the deterministic sensitivity analysis fell in the north-east quadrant of the cost-effectiveness plane.

The key drivers of changes in the ICER versus ECM in all genotype populations were inputs for health state utility and $ppFEV_1$ change. This is because the long time horizon and high survival rate ensures that health state utility remains relevant and change in $ppFEV_1$ is a significant driver of mortality risk for patients in the model. Inputs affecting baseline mortality or the coefficients to derive the annual rate of pulmonary exacerbation also had a notable impact on the ICER, albeit substantially less so than the other key drivers. Costs are noticeably absent, largely because the highest cost items (drug acquisition costs) were not varied owing to certainty in the price.

Scenario analysis

The EAG ran a number of scenarios to test alternative assumptions made in the model. These are described in *Table 36*.

The scenario analyses were conducted separately for each genotype and the results are presented as full incremental ICERs. Across all genotypes, none of the implemented scenario analyses resulted in an ICER below the WTP threshold of £20,000–30,000. The conclusions of all scenario analyses did not change, and both LUM/IVA and TEZ/IVA remained extendedly dominated in all analyses.

Additional exploratory analysis

As noted in *Identification of important subgroups*, clinical experts suggested that ELX/TEZ/IVA may prevent any further lung decline from occurring if it is initiated in the youngest population treatable (those < 2 years old). The EAG wanted to run an incident population of 2-year-old patients through the model to explore the effect of assuming no lung decline for patients on ELX/TEZ/IVA when all patients start treatment at the age of 2 years (potentially prior to any irreversible lung or pancreatic damage), although clinicians suggested that treatment may need to be initiated at a younger age to prevent any damage. However, owing to limitations of the model (see *Strengths and limitations of the analysis*), 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 experienced no further decline. In addition, the direct treatment effect of ELX/TEZ/IVA on pulmonary exacerbations is assumed to apply for a patient's lifetime. The ongoing CF-STORM study is currently exploring whether reducing the use of nebuliser treatments, when taken alongside ELX/TEZ/IVA, results in any significant decline in lung function. As this additional scenario applies optimistic assumptions regarding the impact of ELX/TEZ/IVA, it also implements a 40% reduction in the costs of ECM medication costs for patients on CFTR modulator treatments.

As this exploratory scenario essentially assumes that a patient's lung function is restored to normal, a 1.5% discount rate for both costs and benefits is applied. Although the EAG considers the 1.5% discount rate to be applicable in this exploratory scenario, this is the case only 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 would be higher if this did not apply.

The EAG notes that due to the use of the 1.5% discount rate in this scenario, a severity modifier of 1.2 is applicable. The EAG notes that despite applying liberal assumptions about the effectiveness of ELX/TEZ/IVA in the long term for all patients in the prevalent population, and applying a severity weighting of 1.2, the ICERs are still considerably higher than the acceptable NICE WTP threshold.

In addition to the EAG's presented scenario analyses, a number of additional analyses were run based on the preferences of the NICE committee, following discussions about their preferred assumptions. While the results of these are not presented in this report, a summary of the committee's preferred assumptions is presented below:[233]

- Long-term relative reduction in $ppFEV_1$ decline for ECM using a non-linear decline based on Szczesniak *et al.*[16]
- Long-term relative reduction in $ppFEV_1$ decline for ELX/TEZ/IVA greater than the estimate from the UK CF Registry final analysis but < 100%.
- Long-term relative reduction in $ppFEV_1$ decline with TEZ/IVA of 61.5%.
- Long-term relative reduction in $ppFEV_1$ decline with LUM/IVA of 42%.

TABLE 36 The EAG's scenario analyses

	Base case	Scenario analysis
Clinical parameters		
1	Long-term decline in ppFEV$_1$ modelled as a relative reduction in decline compared with ECM	Long-term decline in ppFEV$_1$ modelled as an absolute reduction compared with ECM
2	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e. same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline for each CFTR modulator based on the Company estimates. This would apply the value for ELX/TEZ/IVA based on the UK CF Registry final analysis [(confidential information has been removed) (AR data only)], and reported rates for TEZ/IVA (61.5%) and LUM/IVA (42%) from the Company models
3	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e. same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline for ELX/TEZ/IVA based on the UK CF Registry final analysis [(confidential information has been removed) (AR data only)], EAG base-case assumptions for TEZ/IVA and LUM/IVA
4	Long-term decline in ppFEV$_1$ for patients on ELX/TEZ/IVA equal to relative reduction of 61%, scaled for TEZ/IVA (17.2% per year slower decline than ECM). No reduction in decline relative to ECM for patients on LUM/IVA (i.e. same long-term decline as ECM patients)	Apply relative reduction in the rate of ppFEV$_1$ decline based on lower-bound estimates calculated by the EAG of 37.7% for ELX/TEZ/IVA and 10.63% for TEZ/IVA
5	Both an indirect effect (through ppFEV$_1$) and a direct treatment effect on pulmonary exacerbations applied	No separate treatment effect on pulmonary exacerbations applied. The effect on pulmonary exacerbations is therefore only due to the treatment effect on ppFEV$_1$ (indirect treatment effect)
6	Direct treatment effect on pulmonary exacerbations applied for the trial period only	Direct treatment effect on pulmonary exacerbations applied for the observed period equal to the long-term extension studies
7	No discontinuations beyond 5 years on treatment	No discontinuations beyond the observed extension study period (96 weeks or 144 weeks) as applied in the Company's model
8	100% long-term compliance with CFTR modulators after the acute period	93% long-term compliance with CFTR modulators after the acute period
HRQoL		
9	Health state utility values (EQ-5D-3L) sourced from the LUM/IVA clinical trial	Health state utility values taken from Acaster *et al.* 2015[195] (EQ-5D). Same as those applied in the Company scenario analysis
10	Pulmonary exacerbation disutility applied for 30 days	Pulmonary exacerbation disutility applied for 14 days
11	Health state utility values (EQ-5D-3L) sourced from the LUM/IVA clinical trial	Company model utility values based on CFQ-R utility values
12	No carer QoL utility values included	Inclusion of utility increment for carers of patients aged < 12 years on ELX/TEZ/IVA
Costs		
13	No difference in ECM medication costs between patients on CFTR modulators and ECM alone	Reduction in ECM medication costs for patients on CFTR modulator treatments of 23%
14	No difference in ECM medication costs between patients on CFTR modulators and ECM alone	Reduction in ECM medication costs for patients on CFTR modulator treatments of 40%

QoL, quality of life.

- Applying the treatment effect of CFTR modulators on pulmonary exacerbations for a lifetime.
- Applying a rate of adherence based on the data collection agreement for CFTR modulators.
- Health-state utility values based on EQ-5D from Acaster *et al.*[197]
- A treatment-specific utility benefit applied for ELX/TEZ/IVA in all genotypes, and for TEZ/IVA in the F/RF genotype only.
- A carer utility benefit applied for carers of children on ELX/TEZ/IVA from treatment initiation to 18 years of age.
- Disease-management costs for people on CFTR modulators reduced, including a 40% reduction in ECM drug costs and healthcare costs based on Granger *et al*. and a 50% reduction in pulmonary exacerbation costs.
- 1.2 severity modifier is applied using these assumptions.

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 detailed quality assurance of the MTA model. A health economist not involved in the MTA project independently reviewed the MTA model, including carrying out 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. The EAG also compared key model outputs such as median survival with published sources.

As an additional quality assurance step, the EAG used the Company's preferred parameter estimates and assumptions for ELX/TEZ/IVA within the EAG model, for patients aged ≥ 6 years only, as this was the population used in the Company model. As the EAG model was not built to be a replica of the Company's model, it would be expected that there would be some differences that cannot be accounted for by the model set-up. Although there were some differences in costs in both the ECM and the ELX/TEZ/IVA arms between the two models, the results were largely similar and the resulting ICERs were broadly comparable.

Discussion

Summary of key results

The purpose of this MTA was to assess the cost-effectiveness of ELX/TEZ/IVA, LUM/IVA and TEZ/IVA for the treatment of people with CF with at least one *F508del* mutation. All results shown in this report are based on patient access scheme prices for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA.

All three CFTR modulator treatments have marketing authorisation for F/F patients, but the age at which these treatments are available to patients differs. LUM/IVA has marketing authorisation for patients aged ≥ 1 year, TEZ/IVA for those aged ≥ 6 years and ELX/TEZ/IVA for those aged ≥ 2 years. Therefore, in the economic model, any patient who starts 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 was below the NICE-recommend 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. LUM/IVA was the least cost-effective. 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 for patients 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 with ECM.

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 more cost-effective of the two treatments, producing both higher costs and higher QALYs than TEZ/IVA.

ELX/TEZ/IVA had the greatest impact on the annual rate of pulmonary exacerbations, $ppFEV_1$ decline, improvement in median survival and rate of lung transplants in every genotype. This translated into greater improvements in both life-years and QALYs than with 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 WTP threshold of £20,000–30,000.

Scenario 1 examined the consequences of applying an absolute rather than a relative reduction in the rate of $ppFEV_1$ decline with ELX/TEZ/IVA. This reduced the ICERs; however, the EAG does not consider applying an absolute reduction of 0.79 (ELX/TEZ/IVA) to older patients to be clinically plausible. This is because the assumed rate of decline for older patients using the non-linear model of Szczesniak *et al*. is already close to 0.79 (≤ 0.70 for F/F, F/MF and F/Gating individuals from age 40 years, and ≤ 0.61 for F/RF individuals from age 40 years). 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; that is, the EAG considers the estimated relative reduction (61.0% of the ECM reduction) to be more transportable to these individuals than the absolute reduction (ECM reduction 0.79).

Across all populations, the assumptions about the long-term effectiveness of CFTR modulator treatments on $ppFEV_1$ decline had one of the greatest impacts. The EAG considers the two scenarios changing the long-term effectiveness assumptions further in line with the Company's estimates (scenarios 2 and 3) to be optimistic and likely to overestimate the effect of CFTR modulators, as previously discussed. Scenario 2 applied the relative reduction in the long-term rate of $ppFEV_1$ decline based on the Company's analyses. This applied a rate of 42% for LUM/IVA, 61.5% for TEZ/IVA, both taken from the Company models, and (confidential information has been removed) 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, both LUM/IVA and TEZ/IVA remained extendedly dominated in the F/F population. In the F/RF genotype population, TEZ/IVA also remained extendedly dominated. Owing to more optimistic assumptions applied for the long-term effect, the ICERs for ELX/TEZ/IVA reduced, as expected.

Scenario 3 changed the assumptions made about the long-term effectiveness of ELX/TEZ/IVA only, applying the relative rate of decline calculated from the final analysis of the data collection agreement of UK CF Registry data,[87] while keeping the rates for LUM/IVA and TEZ/IVA the same as in the EAG base case. The calculated rate of decline is based on the mixed-effects model that 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 these were 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, which was not provided by the Company, would have included all available data and appropriately modelled the impact of review type on $ppFEV_1$, rather than analysing subsets of the data. Scenario 4 used a long-term rate of decline for ELX/TEZ/IVA of 37.7% and TEZ/IVA of 10.63%. These were derived by applying the relative rate of decline calculated for IVA from Newsome *et al*. 2022 as the relative rate of decline for ELX/TEZ/IVA, which was then scaled by the ELX/TEZ/IVA:TEZ/IVA acute treatment effect in the F/F population (37.7×4/14.2). The EAG notes that these estimates are likely to be conservative in the short term, but as the estimates are applied for a person's lifetime in the economic model, it offers estimates that confer a lower decision risk given the uncertainty with applying relative rates of decline for time periods much longer than the currently available data include.

In both scenarios 5 and 6, the assumptions about the direct treatment effect of CFTR modulators on pulmonary exacerbations were changed. Scenario 5 assumed no separate direct treatment effect on pulmonary exacerbations, and therefore the effect on pulmonary exacerbations is only due to the treatment effect on $ppFEV_1$. This had a minimal impact on the ICERs across all genotypes. Scenario 6 extended the time for which the direct treatment effect on pulmonary exacerbations was applied from the acute trial period to the period of the long-term extension studies. This also had a minimal impact on the ICERs.

Clinical experts stated that CFTR modulators are generally well tolerated, yet they do see patients discontinue treatment for various reasons after the first few years. Therefore, the EAG's base case assumed no further discontinuations after 5 years on treatment. Scenario 7 explored the impact of changing this time period to the observed extension study period only (96 weeks or 144 weeks), as applied in the Company's models. This reduced the ICERs across all genotypes.

Scenario 8 applied a 93% compliance rate for all CFTR modulator treatments after the trial period. The ICERs for ELX/TEZ/IVA reduced in the range of ≈£30,000–40,000 across the different genotypes. The EAG notes that, although compliance rates may be lower outside clinical trials, any reduction in efficacy may not be fully accounted for. In addition, clinical experts to the EAG noted that when patients stop taking modulator treatments, particularly ELX/TEZ/IVA, they may quickly feel the loss in benefits and therefore resume treatment quickly. As a result, clinical experts expect high treatment adherence.

Scenario 9 applied alternative EQ-5D values from Acaster *et al*.[197] These values were lower than those applied in the EAG base case. This resulted in lower incremental QALYs across all comparisons, and therefore higher ICERs. However, the EAG notes that the total QALYs on ECM in this scenario are lower and therefore a severity modifier of 1.2 applies to genotypes F/F, F/MF and F/Gating. Owing to the higher average age in the F/RF population, the severity modifier did not apply to this age group. The inclusion of a severity modifier therefore results in lower overall ICERs. The utility values applied in this scenario are based on 401 UK participants aged ≥ 18 years with a self-reported clinical diagnosis of CF; therefore, there is potential selection bias in study recruitment. However, patient experts noted that the Acaster values were most representative of the HRQoL for patients with CF, as they could reflect the large differences in utility values between the best and worst health states. The EAG therefore considers the Acaster values to also be a plausible option. 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 or conclusions from the results.

Reducing the duration of the disutility value applied for pulmonary exacerbations to 14 days from 30 days (scenario 10) did not have a substantial impact on any of the ICERs.

Scenario 11 applied the utility values from the Company's model based on the CFQ-R data. The EAG notes that, as with scenario 9, this resulted in in lower incremental QALYs across all comparisons, and therefore higher ICERs, with this being one of the most influential scenarios. In contrast to scenario 9 using the Acaster utility values, however, the use of the Company's CFQ-R values did cause the severity modifier to apply and therefore resulted in higher ICERs than the EAG base case.

The EAG is aware of the large impact on the life of carers of patients with CF. The EAG was unable to source appropriate EQ-5D data that measured the decrement on carers' quality of life as a result of CF. The Company applied an increment of 0.03 to patients aged 6–11 years receiving ELX/TEZ/IVA based on data collected from 25 carers. In scenario 12, the Company's increment of 0.03 was applied to patients aged < 12 years receiving ELX/TEZ/IVA. Owing to the resulting increase in QALYs for patients on ELX/TEZ/IVA, this resulted in lower ELX/TEZ/IVA ICERs for all genotypes.

Scenarios 13 and 14 explored the impact of reduced costs of ECM medications due to CFTR modulator use. It was highlighted to the EAG by clinical experts that the impact of a reduction in the use of concomitant medications due to CFTR modulators is currently unknown and being explored in ongoing studies. The impact was greatest on the F/MF and F/Gating populations but was not a significant factor.

The EAG also implemented an additional exploratory scenario to investigate the impact of ELX/TEZ/IVA preventing any long-term lung decline post treatment initiation. This exploratory scenario also assumes that the direct treatment effect of ELX/TEZ/IVA on the rate of pulmonary exacerbations lasts for a lifetime. Although this scenario resulted in lower ICERs for ELX/TEZ/IVA than 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.

Generalisability of results

The perspective of the analysis reflects NHS England and therefore the 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 utilise CF trust data, the 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 < 40%. Therefore, the modelled population excludes those patients with the worst lung function and the 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 years. Clinical experts to the EAG noted that if ELX/TEZ/IVA is initiated in very young patients, such as those aged 1–2 years, this may avoid long-term lung damage and could potentially 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.

Strengths and limitations of the analysis

As noted in Drummond *et al.*,[194] failure to consider all available treatment options in an economic evaluation may result in the cost-effectiveness of an intervention being overestimated. A key strength of the EAG's analysis is that all three interventions in the final NICE scope are included in 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.

The EAG's base-case cost-effectiveness results differ largely from the results from the Company's models. However, as the EAG separated its analyses based on genotype and included younger age groups to reflect recent marketing authorisation, the results are not directly comparable. Because the EAG compared 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 before they are able to start TEZ/IVA and ELX/TEZ/IVA, in line with the marketing authorisation for these treatments. As the Company submitted separate models for each modulator therapy, compared only with ECM, this was not a feature of the Company's models.

Nonetheless, there are other fundamental differences between the EAG's approach and the Company's models that drive the differences in cost-effectiveness. The EAG used a more recent baseline mortality hazard based on UK CF Registry data from 2011 to 2015,[212] which included survival estimates for male and female patients either *F508del* homozygous or *F508del* 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 years than had been applied in the Company's models using a linear decline. This was in line with the opinion of the EAG's clinical experts, who suggested that one would expect to see a slower rate of decline for patients after the age of 30 years than had been suggested in the Company's approach.

The EAG's model predicts a median age at death of patients on ECM ranging from 45 to 50 years, depending on genotype. The EAG's clinical experts stated that they expect the median survival age for patients on ECM to be in the mid-40s, and 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, conditional on being alive until the age of 20 years, based on UK CF Registry data, as reported by Keogh *et al.* 2018[212] (age 46.8 years for male patients who are *F508del* heterozygous). As the average age of patients in the model is 21 years, this comparison also provides further validation that the EAG's model can predict survival with ECM. The median survival age of ECM patients from the Company's model for ELX/TEZ/IVA was 38 years, which the EAG deemed too low based on recent advances in treatment and care for CF patients before the use of CFTR modulators and in comparison with the recent median survival estimate in the UK CF Registry. The Company's baseline mortality hazard is based on UK CF Registry data from 1985 to 2008, and clinical experts to the EAG noted how care, and in turn survival, has improved since that time. Therefore, the EAG's 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's and the Company's median predicted survival ages.

Despite the strengths of the EAG's approach, a number of limitations required assumptions to be made in the analyses. A key uncertainty in the model, due to a lack of long-term data, is the treatment effectiveness of each CFTR modulator over a patient's lifetime, as discussed in *Key issues and uncertainties*. Therefore, the EAG made assumptions using the best available evidence. As previously discussed in the *Summary of key results*, the ICERs were most sensitive to the assumptions regarding long-term effectiveness.

The model structure uses an individual microsimulation model in which a CPH model developed by Liou *et al.*[153] is used to predict patient survival based on nine baseline characteristics and demographic variables. The CPH model was based on a historical US data set and has not been validated in the UK population. However, clinical experts advising the EAG stated that they would not expect significant differences between the two populations. The CPH model was not developed or validated to assess the impact on mortality of changes in an individual's characteristics over time, such as an acute increase in ppFEV$_1$. Therefore, it is unknown what impact using the model in this way would have 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 years, and it is likely that a small number of patients aged > 50 years were included in the sample. As ppFEV$_1$ is not a clinical outcome measured in patients aged < 6 years, these patients were also not included in the data set used to develop the CPH model. If the prediction of mortality is substantially different for patients of younger or older ages, then the current model used may inaccurately predict survival ages for these patients. When the EAG attempted to model an incident population (all starting at age 2 years) to explore the effect of ELX/TEZ/IVA providing a lifetime benefit and preventing any future decline in lung health if initiated 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 model's median predicted survival age with ECM in the EAG's base case is in line with clinical experts' opinion and recent data from the UK CF Registry.

Data on changes in infection rates over time could not be included in the model because there was a lack of available data on prevalence rates and, therefore, on how these rates may change over time with age or following treatment with CFTR modulators. Clinical experts noted that respiratory infections are associated with a decline in lung function and that there is some evidence of CFTR modulators reducing *Pseudomonas* prevalence. The impact of changes in infections over time on the cost-effectiveness results is unknown, but the benefits of CFTR modulator treatments may have been underestimated.

As a necessary model simplification, there are also a range of other symptoms and diseases that are not explicitly tracked in the economic model, including, but not limited to, gastrointestinal symptoms; changes in CF-related liver disease; sinus disease; bronchiectasis; bowel and bladder control; changes in chronic infection status; and depression and mental health. The EAG agrees that treatment with ELX/TEZ/IVA will have large and clinically meaningful effects on most of these features of CF, and for others not in this list. Although it was not included in the EAG base case because of uncertainty in the analysis and the use of the CFQ-R-8D to measure HRQoL rather than the EQ-5D, the EAG notes that should a treatment-specific utility increment be included for ELX/TEZ/IVA, this could capture further increases in quality of life experienced by a patient receiving that treatment, if these benefits do not already correlate with ppFEV$_1$.

When data were not available, assumptions were made regarding the best available evidence to apply. For patients in the model aged < 6 years, when evidence was not available from clinical trials or lacked face validity, the EAG assumed the same efficacy as for patients aged 6–11 years. This is likely to be a conservative assumption, as younger patients may receive greater benefits long term as less lung damage has occurred by the time they start treatment, and treatment may also prevent infections developing in very young patients. In addition, patient-level data were not available for patients aged < 6 years. Therefore, a subset of patients with the same characteristics as individuals aged 6–8 years was created so that the latter group of patients could be modelled. Although this involved resampling patients already in the patient population, using individuals aged 6–8 years ensured that patients as similar in age as possible to the cohort being created were used, without overly reducing the number of patients available for sampling and the resulting heterogeneity in characteristics.

The NICE reference case states that HRQoL should be measured using the EQ-5D, with data taken directly from the trials being preferred. Unfortunately, EQ-5D data were collected in only one of the CFTR modulator trials (LUM/IVA).[39] CFQ-R data were collected in the ELX/TEZ/IVA trial, yet the Company did not map these to the EQ-5D, despite a published algorithm being available. Therefore, the EAG applied the EQ-5D values obtained from patients in the LUM/IVA study to all treatment arms in the model, following some adjustments. This was based on *F508del* homozygous patients aged ≥ 12 years and so these values were assumed to also be representative of *F508del* heterozygous patients aged < 12 years. Alternative EQ-5D values from Acaster *et al.*[197] were also used in a scenario analysis. During the NICE committee meetings, patient experts stated that these values were a more accurate representation of the large difference in utility between the best and worst health states. Therefore, the NICE committee preferred the Acaster *et al.* values for decision-making.

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, some variation remained in the ICER for LUM/IVA; however, the EAG did not deem this to change the overall conclusions. In addition, owing to the significant run time of the model and the requirements of deterministic and probabilistic sensitivity analyses to be completed, running a greater number of patients was not possible. This is a common limitation of patient-level simulation models,[214] 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 win the MTA was treatment sequencing. In the EAG model, patients are treated with ECM until they are eligible to start each CFTR modulator, based on age. In clinical practice, patients may start a CFTR modulator, such as LUM/IVA, at the youngest age possible, 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 is available in routine clinical practice, patients may be started on another on discontinuation.

Chapter 5 Assessment of factors relevant to the NHS and other parties

The EAG considers that all factors relevant to the NHS and other parties are captured in the clinical effectiveness 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 years. Clinical experts to the EAG noted that if ELX/TEZ/IVA is initiated in very young patients, such as those aged 1–2 years, this may avoid long-term lung damage and could potentially provide 'near normal' lifetime lung function. Therefore, the incident CF population may experience greater benefits from treatment with ELX/TEZ/IVA.

Chapter 6 Discussion

Statement of principal findings

This MTA evaluated the clinical effectiveness and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA for treating CF compared with each other and with ECM in England. 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 year 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 receive this. 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 $ppFEV_1$; 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 weight-for-age *z*-score, and reductions in pulmonary exacerbations, where these outcomes were reported. In the EAG's microsimulation, this translated into a predicted large survival benefit for the prevalent population of CF individuals recruited in clinical trials in comparison with ECM, LUM/IVA and TEZ/IVA in the relevant CF genotypes. Effect sizes were attenuated in the F/RF population, which is likely to be because the F/RF genotype is associated with a milder CF phenotype at baseline.

Compared with ELX/TEZ/IVA, LUM/IVA and TEZ/IVA had smaller but still statistically significant increases in $ppFEV_1$ and reductions in pulmonary exacerbations compared with ECM, when reported. While LUM/IVA was associated with a statistically significant, but small, acute increase in weight-for-age *z*-score compared with ECM, TEZ/IVA was not associated with a statistically significant increase in weight-for-age *z*-score compared with ECM during the acute phase of the clinical trials.

Although no validated minimum clinically important differences were available 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. 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 that the magnitude of the effects are considerably smaller than for ELX/TEZ/IVA. This is observed in the results of the EAG's patient simulation model, in which the incremental life-years gained compared with ECM were considerably smaller for LUM/IVA than for ELX/TEZ/IVA in the F/F genotype, and considerably smaller for TEZ/IVA than for ELX/TEZ/IVA in the F/F and F/RF genotypes.

The EAG considers the key clinical trials of CFTR modulators to have good generalisability to clinical practice in England, and notes that acute effects similar to those seen in clinical trials were also observed in the UK CF Registry 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 the following:

- 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 advanced 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 in 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, then they will be initiated before an individual's $ppFEV_1$ declines to < 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 2–4 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, for which the majority of long-term data are from uncontrolled clinical trial extension studies and real-world data, where data collection windows overlapped substantially with the COVID-19 pandemic. In the absence of robust data on 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 that could approximate the long-term $ppFEV_1$ decline rate among people treated with ELX/TEZ/IVA compared with ECM, namely a relative reduction of 37.7%, which the EAG scaled up to 61.0% based on the ratio of the ELX/TEZ/IVA:IVA acute treatment effect. For TEZ/IVA, the EAG scaled down the assumed ELX/TEZ/IVA relative reduction based on the ratio of the ELX/TEZ/IVA:TEZ/IVA acute treatment effect, giving a relative reduction in $ppFEV_1$ decline of 17.2% for TEZ/IVA. For LUM/IVA, the EAG did not apply a slowing of the rate of decline of $ppFEV_1$ compared with ECM.

NICE typically considers interventions a cost-effective use of NHS resources if the ICER sits below a £20,000–30,000 threshold. None of the EAG's base-case ICERs (either pairwise vs. ECM alone or full incremental results) would be considered cost-effective.

The differences in clinical effectiveness between the three modulator treatments were observed in the cost-effectiveness results, with ELX/TEZ/IVA having the lowest ICERs when compared with LUM/IVA or TEZ/IVA in the populations in which more than one CFTR modulator is available. The differences 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, the proportion of patients requiring lung transplant, and the change in both $ppFEV_1$ and weight-for-age *z*-score.

For the F/F population, all three modulator treatments have marketing authorisation. The ICERs from the full incremental analysis showed that both LUM/IVA and TEZ/IVA were extendedly dominated.

In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Base-case deterministic results were similar in the two populations when compared with ECM.

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 more cost-effective of the two treatments, producing both higher costs and higher QALYs than TEZ/IVA and extendedly dominating TEZ/IVA due to the resulting lower ICER.

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 compared with ECM, with high incremental costs, resulting in sensitive ICERs. This was seen with changes in the magnitude of the ICERs but not the direction of results, with all scenario analyses resulting in the same conclusions as the base-case analysis.

The key drivers of changes in the ICER versus ECM in all genotype populations were inputs for health state utility and $ppFEV_1$ change. This is because the long time horizon and high survival ensure that health state utility remains relevant and change in $ppFEV_1$ is a significant driver of mortality risk for patients in the model. Costs are noticeably absent from the one-way sensitivity analysis key drivers, largely because the highest cost items (drug acquisition costs) are not varied due to certainty in the price, in the absence of an agreed commercial discount.

Although the scenarios on long-term effectiveness had 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 it considers the rates of $ppFEV_1$ decline applied in these scenarios to be overly optimistic in terms of the long-term effectiveness.

However, owing to the high uncertainty of the long-term effectiveness of the CFTR modulators, the EAG deems these scenarios to potentially provide the lowest estimate of the likely ICERs achieved.

The EAG notes that the use of alternative assumptions about the direct treatment effect of CFTR modulators on pulmonary exacerbations and discontinuations has a minimal impact on the ICERs.

The use of alternative utility values was explored using lower EQ-5D values than those applied in the EAG base case. This resulted in lower incremental QALYs across all comparisons and, therefore, in higher ICERs. However, this also changed the severity modifier calculations, and so a 1.2 severity modifier was applicable in this scenario, which overall resulted in lower ICERs than in the base case.

Strengths and limitations of the assessment

A strength of the EAG's clinical analyses is the combination of the EAG's SLR and unpublished data provided by the Company through study clinical study reports and ad hoc analyses to constitute relatively complete outcome data for the key acute clinical parameters of interest, with consistent outcome definitions between studies. As a result of the availability of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA through managed access agreements in the UK and other countries in the years prior to this MTA, the EAG was able to:

- use real-world data on the use of CFTR modulators to inform the clinical effectiveness and cost-effectiveness modelling
- receive input from clinical experts with years of experience of treating patients with CFTR modulators.

The EAG welcomes 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 uncertain due to the potential impact of the COVID-19 pandemic on clinical outcomes and lung function of people with CF. The EAG notes additional uncertainty due to the rapid serial uptake of CFTR modulators, which meant that the available real-world data were uncontrolled.

The key strength of the EAG's economic assessment is that all three CFTR modulator interventions in the NICE final scope are included in 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. Compared with existing models of CF, and the Company submission:

- The EAG's economic model uses a baseline mortality hazard specific to the *F508del* population, based on a published flexible parametric cubic spline model fit to UK CF Registry data 2011–5. The use of a flexible parametric model can provide a better fit to the data than may be achievable with standard parametric survival models.
- The EAG applied a non-linear decline in ppFEV$_1$ over time for patients receiving ECM, which resulted in a slower rate of decline for patients aged ≥ 25 years, in line with real-world data and clinical expert opinion.
- The EAG's model predicts a median age of death for patients on ECM ranging from 45 to 50 years, depending on genotype, which is in line with the EAG's clinical experts' opinion expecting median survival age for patients on ECM to be in the mid-40s, and higher than in the Company's model.

A key limitation of the EAG's economic analysis, which also applies to the Company's economic models, is the use of a CPH model developed using historical data applied to a population in the USA. This model was not developed or validated to assess the impact on mortality of changes in an individual's characteristics over time but instead was 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 model's median predicted survival age with ECM is in line with clinical experts' opinion and recent data from the UK 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 that EQ-5D data from the LUM/IVA trial were applied to all populations. Patient-level data were not available for patients in the model aged < 6 years, and therefore patients aged 6–8 years were resampled and assumed to represent patients aged < 6 years. 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.

Uncertainties

As noted in *Statement of principal findings*, 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 2–4 years, meaning that the effects of CFTR combination therapies over the lifetime are highly uncertain, and heightened for ELX/TEZ/IVA, for which the majority of long-term data are from uncontrolled clinical trials and real-world data, which 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 AEs on a person's mental health
- long-term probability of developing different lung infections
- the effects of CFTR modulator therapies on key non-pulmonary outcomes, such as the development of CFRD and CF-related liver disease
- co-adherence to ECM medications among 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 for which the effect sizes are small
- impact of CFTR modulator therapy on a person's HRQoL, and their carer's, as EQ-5D was not measured in most clinical trials
- long-term effectiveness of CFTR modulators, in particular ELX/TEZ/IVA, in young children and people with little existing lung damage, a subgroup of patients for whom the long-term clinical outcomes of treatment with ELX/TEZ/IVA might be the most positive.

All of the above clinical evidence-based uncertainties apply to the cost-effectiveness analysis. An additional key uncertainty related to the economic model is the application of the Liou *et al.*[155] CPH model to predict mortality. As the data used to develop this model did not include patients aged < 6 years or > 62 years, it is uncertain how the model performs in predicting survival for these ages. In addition, as previously noted, the CPH model was developed not to predict changes in a patient's characteristics over time but instead to predict a person's mortality hazard based on their current characteristics. Although it may not be incorrect to use the CPH model in this way, further validation of this should be undertaken.

Patient and public involvement

Patient and public involvement was conducted by NICE for the MTA, which impacted the decisions the EAG made during the project. No further additional patient and public involvement occurred for this research.

Impact and learning

This project provided an independent clinical effectiveness and cost-effectiveness assessment of CFTR modulator therapies for CF as part of the NICE MTA, which ultimately resulted in the recommendation of ELX/TEZ/IVA, TEZ/IVA and LUM/IVA for routine commissioning in England, following further commercial arrangements.[233]

Suggested research priorities

- Further long-term data collection and statistical modelling of the effects of CFTR modulators on the key parameters of the current economic model, namely the long-term rate of ppFEV$_1$ decline, the frequency of pulmonary exacerbations requiring IV antibiotics and changes in weight-for-age *z*-score. This should include an assessment of the impact of any changes in co-adherence to non-CFTR modulator therapies for CF and make continued use of clinical trial registry-based data collection.
- 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.
- Expanded long-term data collection of key clinical outcomes not routinely reported by clinical trials and registries, including changes in infection status, development of CFRD and development of CF-related liver disease.
- Further validation of the CPH model used to model the impact of changes in patient characteristics over time on survival in the UK population, or alternative models that could be used to predict changes in survival probability following CFTR modulator therapy. In particular, future research should focus on the prediction of survival for younger patients, in the light of changes to the landscape of CF care with CFTR modulator treatments. This should include research into alternative prediction models to be used in economic models that are able to account for the multisystem nature of CF and the impact of effective modulator treatments such as ELX/TEZ/IVA. As clinical evidence on non-pulmonary outcomes is currently limited, future research should prioritise these areas.
- Further research into the impact of modulator treatments, particularly ELX/TEZ/IVA, on the HRQoL of patients and their carers should be conducted. As the NICE reference case stipulates that the EQ-5D should be used to measure HRQoL in economic evaluations, future research should include the use of the published algorithm for mapping CFQ-R to EQ-5D for use in economic models that meet the NICE reference case, in addition to the collection of EQ-5D data.

Chapter 7 Conclusions

ELX/TEZ/IVA appears very effective at improving clinical outcomes for people with CF with at least one *F508del* mutation. LUM/IVA and TEZ/IVA also improve clinical outcomes for people with CF and two *F508del* mutations (LUM/IVA and TEZ/IVA) or an *F508del* mutation and a residual function mutation (TEZ/IVA), but to a much lesser extent than ELX/TEZ/IVA.

The economic evaluation undertaken as part of the MTA showed that the fully incremental analyses resulted in ICERs that were substantially higher than the £20,000–30,000 threshold. The high drug acquisition costs of CFTR modulators may be a barrier to the availability of these treatments in routine commissioning.

Subsequent to our research being completed, a commercial agreement was reached that allowed NICE to make a positive recommendation for all three modulator treatments included in this appraisal.

Additional information

CRediT contribution statement

Steven J Edwards (https://orcid.org/0000-0002-9049-3421): Conceptualisation, Funding acquisition, Methodology, Project administration, Supervision, Writing – reviewing and editing.

Benjamin G Farrar (https://orcid.org/0000-0001-8912-6133): Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.

Kate Ennis (https://orcid.org/0000-0003-4284-217X): Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.

Nicole Downes (https://orcid.org/0000-0003-0496-9671): Project administration, Supervision.

Victoria Wakefield (https://orcid.org/0000-0002-2058-6411): Investigation, Supervision, Validation.

Isaac Mackenzie (https://orcid.org/0009-0005-1604-7326): Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Visualisation.

Archie Walters (https://orcid.org/0000-0001-6614-8452): Investigation.

Tracey Jhita (https://orcid.org/0000-0002-8041-0346): Conceptualisation, Investigation, Supervision, Validation.

Acknowledgements

The EAG would like to thank Dr Charlotta Karner, Kayleigh Kew and Alexander Allen for their assistance with title, abstract and full-text appraisal, and data extraction. The EAG would like to thank the Newcastle External Assessment Group for their critique of the second interim analysis of the real-world data collected as part of the data collection agreement.

The EAG would like to thank Dr Paul Aurora, Consultant, Great Ormond Street Hospital, for providing clinical advice throughout the project, and Dr Rishi Pabary, Consultant, Royal Brompton and Harefield Hospitals, and Dr Joanna Whitehouse, Consultant and Centre Director, West Midlands Adult Cystic Fibrosis Centre, for providing clinical advice throughout the project and for providing feedback on the clinical sections of the report. The EAG thanks Professor Ruth Keogh, Professor of Biostatistics and Epidemiology, London School of Hygiene and Tropical Medicine, for providing advice on survival modelling during the project. The EAG thanks Professor Paul Tappenden, Professor of Health Economics, University of Sheffield, for providing advice on the health economic model. The EAG would also like to thank Cochrane Cystic Fibrosis for support and discussion during evidence identification, and the UK CF Registry for providing data as part of Data Request 469. We thank people with cystic fibrosis and their families for consenting to their data being used in the UK CF Registry, and NHS teams in CF centres and clinics for the input of data into the Registry. The UK CF Registry is supported and co-ordinated by the UK Cystic Fibrosis Trust.

Data-sharing statement

Shareable data are provided in full in the extraction tables in *Report Supplementary Material 1*. Due to confidentiality agreements, some data cannot be shared. All data requests should be submitted to the corresponding author for consideration.

Ethics statement

No ethical approval was needed as all included data were from secondary published sources.

Information governance statement

This study did not handle any personal information.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/CPLD8546.

Primary conflicts of interest: None. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of the *BMJ* work independently of one another. The views and opinions expressed in this report are those of the BMJ-TAG.

References

1. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry: 2021 Annual Data Report*. London: Cystic Fibrosis Trust; 2022.
2. Schluter DK, Southern KW, Dryden C, Diggle P, Taylor-Robinson D. Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: a UK CF registry-based study. *Thorax* 2020;**75**:123–31.
3. Sawicki GS, Konstan MW, McKone EF, Moss RB, Lubarsky B, Suthoff E, *et al*. Rate of lung function decline in people with cystic fibrosis having a residual function gene mutation. *Pulmonary Ther* 2022;**8**:385–95.
4. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nat Rev Dis Primers* 2015;**1**:15010.
5. Ward CL, Omura S, Kopito RR. Degradation of CFTR by the ubiquitin–proteasome pathway. *Cell* 1995;**83**:121–7.
6. Desai M, Hine C, Whitehouse JL, Brownlee K, Charman SC, Nagakumar P. Who are the 10%? – non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies. *Respir Med* 2022;**199**:106878.
7. Association for Laboratory Medicine. *Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK 2nd Version*. London: Association for Laboratory Medicine; 2014.
8. National Institute for Health and Care Excellence. *Cystic Fibrosis: Diagnosis and Management (NG78)*. 2017. URL: www.nice.org.uk/guidance/ng78 (accessed December 2022).
9. Hoo ZH, Wildman MJ, Curley R, Walters SJ, Campbell MJ. Rescue therapy within the UK Cystic Fibrosis Registry: an exploration of predictors of intravenous antibiotic use amongst adults with CF. *Respirology* 2018;**23**:190–7.
10. Caley L, Smith L, White H, Peckham DG. Average rate of lung function decline in adults with cystic fibrosis in the United Kingdom: data from the UK CF registry. *J Cyst Fibros* 2021;**20**:86–90.
11. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. *J Cyst Fibros* 2017;**16**:S70–8.
12. Norris AW, Ode KL, Merjaneh L, Sanda S, Yi Y, Sun X, *et al*. Survival in a bad neighborhood: pancreatic islets in cystic fibrosis. *J Endocrinol* 2019;**241**:R35–50.
13. Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med* 2013;**3**:a009746.
14. Smith S, Rowbotham N, Davies G, Gathercole K, Collins SJ, Elliott Z, *et al*. How can we relieve gastrointestinal symptoms in people with cystic fibrosis? An international qualitative survey. *BMJ Open Respir Res* 2020;**7**:e000614.
15. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry: 2019 Annual Data Report*. London: Cystic Fibrosis Trust; 2020.
16. Szczesniak R, Andrinopoulou ER, Su W, Afonso PM, Burgel PR, Cromwell E, *et al*. Lung function decline in cystic fibrosis: impact of data availability and modeling strategies on clinical interpretations. *Ann Am Thorac Soc* 2023;**20**:958–68.
17. Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, *et al*.; CF-EpinNet collaboration. Data Resource Profile: the UK Cystic Fibrosis Registry. *Int J Epidemiol* 2018;**47**:9–10e.
18. National Institute for Health and Care Excellence (NICE). *Data Collection Agreement*. 2020. URL: www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement (accessed May 2023). London: NICE; 2020.
19. Vertex Pharmaceuticals Inc. *Vertex Announces Agreement with NHS England for Access to All Licensed Cystic Fibrosis Medicines*. 2019. Press release, 24 October 2019 URL: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-agreement-nhs-england-access-all-licensed (accessed June 2023).

20. Cystic Fibrosis Trust. *Cystic Fibrosis Complications and Symptoms*. n.d. URL: www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/cystic-fibrosis-complications (accessed May 2023).
21. Stalvey MS, Clines GA. Cystic fibrosis-related bone disease: insights into a growing problem. *Curr Opin Endocrinol Diabetes Obes* 2013;**20**:547–52.
22. Kobelska-Dubiel N, Klincewicz B, Cichy W. Liver disease in cystic fibrosis. *Prz Gastroenterol* 2014;**9**:136–41.
23. Cystic Fibrosis Trust. *Fertility and Cystic Fibrosis*. n.d. URL: www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/how-does-cystic-fibrosis-affect-the-body/symptoms-of-cystic-fibrosis/fertility (accessed December 2022).
24. Cystic Fibrosis Trust. *Cystic Fibrosis Insight Survey – Report on the 2017 and 2018 Surveys*. London: Cystic Fibrosis Trust; 2019.
25. National Institute for Health and Care Excellence (NICE). *ID3834 Professional Organisation Submission. ACPCF. Catherine Brown*. London: NICE; 2023.
26. National Institute for Health and Care Excellence (NICE). *ID3834. Professional Organisation Submission. Cystic Fibrosis Trust. Ellie Davies*. London: NICE; 2023.
27. National Institute for Health and Care Excellence (NICE). *ID3834. Professional Organisation Submission. CF Voices. Christina Walker*. London: NICE; 2023.
28. National Institute for Health and Care Excellence (NICE). *ID3834. Professional Organistaion Submission. CFDigicare. Dr Martin Wildman*. London: NICE; 2023.
29. National Institute for Health and Care Excellence (NICE). *ID3834 Professional Organisation Submission. British Paediatric Respiratory Society. Dr Manjith Narayanan*. London: NICE; 2023.
30. National Institute for Health and Care Excellence (NICE). *ID3834. Professional Organisation Submission. UK Psychosocial Professionals in Cystic Fibrosis. Dr Thomas Clarke*. London: NICE; 2023.
31. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Nicod E, Serrano-Aguilar P; BURQOL-RD Research Network. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. *BMC Health Serv Res* 2015;**15**:428.
32. Daly C, Ruane P, O'Reilly K, Longworth L, Vega-Hernandez G. Caregiver burden in cystic fibrosis: a systematic literature review. *Ther Adv Respir Dis* 2022;**16**:17534666221086416.
33. Mowforth OD, Davies BM, Kotter MR. Quality of life among informal caregivers of patients with degenerative cervical myelopathy: cross-sectional questionnaire study. *Interact J Med Res* 2019;**8**:e12381.
34. Cystic Fibrosis Trust. *The Cost of Cystic Fibrosis 2022*. London: Cystic Fibrosis Trust; 2022.
35. Cystic Fibrosis Trust. *Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK*. London: Cystic Fibrosis Trust; 2011.
36. Habib AR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. *Ann Am Thorac Soc* 2015;**12**:420–8.
37. Ancel J, Launois C, Perotin JM, Ravoninjatovo B, Mulette P, Hagenburg J, *et al*. Health-related quality of life in adults with cystic fibrosis: familial, occupational, social, and mental health predictors. *Healthcare* 2022;**10**:1351.
38. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;**121**:64–72.
39. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, *et al*.; TRAFFIC Study Group. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for *Phe508del* CFTR. *N Engl J Med* 2015;**373**:220–31.

40. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, *et al*. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2014;**18**(18).

41. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. *Health Qual Life Outcomes* 2016;**14**:63.

42. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D. Discussion Paper 172*. York: Centre for Health Economics, University of York; 1999.

43. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res* 2003;**12**:63–76.

44. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005;**128**:2347–54.

45. Flume PA, Suthoff ED, Kosinski M, Marigowda G, Quittner AL. Measuring recovery in health-related quality of life during and after pulmonary exacerbations in patients with cystic fibrosis. *J Cyst Fibros* 2019;**18**:737–42.

46. Perrem L, Stanojevic S, Shaw M, Davis S, Retsch-Bogart G, Ratjen F. Changes in the parent Cystic Fibrosis Questionnaire-Revised (CFQ-R) with respiratory symptoms in preschool children with cystic fibrosis. *J Cyst Fibros* 2020;**19**:492–8.

47. Jaudszus A, Zeman E, Jans T, Pfeifer E, Tabori H, Arnold C, *et al*. Validity and reliability of a novel multimodal questionnaire for the assessment of abdominal symptoms in people with cystic fibrosis (CFAbd-Score). *Patient* 2019;**12**:419–28.

48. Evans J, Davies S, Cross K. *The Financial Costs of Cystic Fibrosis*. Bristol: University of Bristol; 2023.

49. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;**127**:725–34.

50. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;**159**:179–87.

51. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;**15**:75–88.

52. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, *et al*. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;**177**:253–60.

53. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, *et al*.; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the Global Lung Function 2012 equations. *Eur Respir J* 2012;**40**:1324–43.

54. Ejiofor LCK, Mathiesen IHM, Jensen-Fangel S, Olesen HV, Skov M, Philipsen LKD, *et al*. Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment. *Pediatr Pulmonol* 2020;**55**:3364–70.

55. Foong RE, Harper AJ, Skoric B, King L, Turkovic L, Davis M, *et al*. The clinical utility of lung clearance index in early cystic fibrosis lung disease is not impacted by the number of multiple-breath washout trials. *ERJ Open Res* 2018;**4**:00094–2017.

56. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, *et al*.; London Cystic Fibrosis Collaboration. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2011;**183**:752–8.

57. Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, Ratjen F. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012;**40**:61–6.

58. Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. *Pediatr Pulmonol* 2011;**46**:393–400.
59. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;**182**:627–32.
60. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, *et al*. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;**381**:1809–19.
61. Keogh RH, Cosgriff R, Andrinopoulou ER, Brownlee KG, Carr SB, Diaz-Ordaz K, *et al*. Projecting the impact of triple CFTR modulator therapy on intravenous antibiotic requirements in cystic fibrosis using patient registry data combined with treatment effects from randomised trials. *Thorax* 2022;**77**:873–81.
62. Scoffone VC, Chiarelli LR, Trespidi G, Mentasti M, Riccardi G, Buroni S. *Burkholderia cenocepacia* infections in cystic fibrosis patients: drug resistance and therapeutic approaches. *Front Microbiol* 2017;**8**:1592.
63. National Institute for Health and Care Excellence. *TA266 Mannitol Dry Powder for Inhalation for Treating Cystic Fibrosis*. 2012. URL: www.nice.org.uk/guidance/ta266 (accessed December 2022).
64. National Institute for Health and Care Excellence. *TA276 Colistimethate Sodium and Tobramycin Dry Powders for Inhalation for Treating Pseudomonas Lung Infection in Cystic Fibrosis*. London: NICE; 2013. URL: www.nice.org.uk/guidance/ta276 (accessed December 2022).
65. Electronic Medicines Compendium. *Kalydeco 25 mg Granules in Sachet*. 2022. URL: www.medicines.org.uk/emc/product/10982/smpc (accessed July 2024).
66. Electronic Medicines Compendium. *Kalydeco 150 mg Film-Coated Tablets*. 2022. URL: www.medicines.org.uk/emc/product/3040/smpc (accessed July 2024).
67. Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, *et al*. VX-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. *Mol Biol Cell* 2013;**24**:3016–24.
68. Okiyoneda T, Veit G, Dekkers JF, Bagdany M, Soya N, Xu H, *et al*. Mechanism-based corrector combination restores DeltaF508-CFTR folding and function. *Nat Chem Biol* 2013;**9**:444–54.
69. Veit G, Roldan A, Hancock MA, Da Fonte DF, Xu H, Hussein M, *et al*. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor–tezacaftor–ivacaftor (Trikafta) combination. *JCI Insight* 2020;**5**:e139983.
70. Veit G, Vaccarin C, Lukacs GL. Elexacaftor co-potentiates the activity of *F508del* and gating mutants of CFTR. *J Cyst Fibros* 2021;**20**:895–8.
71. Fiedorczuk K, Chen J. Mechanism of CFTR correction by type I folding correctors. *Cell* 2022;**185**:158–68.e11.
72. Electronic Medicines Compendium. *Orkambi 100 mg/125 mg Film Coated Tablets*. 2021. URL: www.medicines.org.uk/emc/product/8952/smpc (accessed January 2023).
73. Electronic Medicines Compendium. *Orkambi 100 mg/125 mg Granules in Sachet*. 2021. URL: www.medicines.org.uk/emc/product/9845/smpc (accessed January 2023).
74. National Institute for Health and Care Excellence. *Lumacaftor–Ivacaftor for Treating Cystic Fibrosis Homozygous for the F508del Mutation*. 2016. URL: www.nice.org.uk/guidance/ta398 (accessed December 2022).
75. Electronic Medicines Compendium. *Symkevi 100 mg/150 mg tablets PLGB 22352/0003*. 2021. URL: www.medicines.org.uk/emc/product/9634/smpc (accessed January 2023).
76. Electronic Medicines Compendium. *Kaftrio 75 mg 50 mg 100 mg Film-Coated Tablets*. 2021. URL: www.medicines.org.uk/emc/product/11724/smpc (accessed January 2023).
77. Electronic Medicines Compendium. *Kaftrio 60 mg/40 mg/80 mg Granules in Sachet*. 2023. URL: www.medicines.org.uk/emc/product/15303 (accessed July 2024).

78. National Institute for Health and Care Excellence. *Ivacaftor–Tezacaftor–Elexacaftor, Tezacaftor–Ivacaftor and Lumacaftor–Ivacaftor for Treating Cystic Fibrosis [ID3834]: Final Scope*. 2023. URL: www.nice.org.uk/guidance/indevelopment/gid-ta11187/documents (accessed February 2023).

79. NHS England. *Updated Commissioning Statement: Ivacaftor, Tezacaftor/Ivacaftor, Lumacaftor/Ivacaftor and Elexacaftor/Tezacaftor/Ivacaftor for Licensed and Off-Label Use in Patients with Cystic Fibrosis Who Have Named Mutations*. London: NHS England; 2022.

80. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry: 2022 Annual Data Report*. London: Cystic Fibrosis Trust; 2023.

81. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest* 2009;**135**:1610–18.

82. Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, Diggle P. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax* 2012;**67**:860–6.

83. European Medicines Agency. *Report of the Workshop on Endpoints for Cystic Fibrosis Clinical Trials*. London: European Medicines Agency; 2012.

84. McColley SA, Martiniano SL, Ren CL, Sontag MK, Rychlik K, Balmert L, *et al*. Disparities in first evaluation of infants with cystic fibrosis since implementation of newborn screening. *J Cyst Fibros* 2023;**22**:89–97.

85. Bosch B, Bilton D, Sosnay P, Raraigh KS, Mak DYF, Ishiguro H, *et al*. Ethnicity impacts the cystic fibrosis diagnosis: a note of caution. *J Cyst Fibros* 2017;**16**:488–91.

86. National Institute for Health and Care Excellence. *Public Committee Slides 20 June 2024*. 2024. URL: www.nice.org.uk/guidance/indevelopment/gid-ta11187/documents (accessed July 2024).

87. Vertex Pharmaceuticals Inc. *An Observational Study of Users of Kaftrio, Orkambi and Symkevi in the UK Cystic Fibrosis Registry to Satisfy Data Collection Agreement in the UK (LONGITUDE)*. Final Analysis for Kaftrio (unpublished). London: Vertex Pharmaceuticals (Europe) Limited; 2023.

88. National Institute for Health and Care Excellence (NICE). *Ivacaftor–Tezacaftor–Elexacaftor, Tezacaftor–Ivacaftor and Lumacaftor–Ivacaftor for Treating Cystic Fibrosis [ID3834]. Committee Papers 3 November 2023*. 2023. URL: www.nice.org.uk/guidance/indevelopment/gid-ta11187/documents (accessed July 2024).

89. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.

90. BMJ Technology Assessment Group. *Final Protocol. Elexacaftor–Tezacaftor–Ivacaftor, Lumacaftor–Ivacaftor and Tezacaftor–Ivacaftor for Treating Cystic Fibrosis [ID3834]*. 2023. URL: www.nice.org.uk/guidance/indevelopment/gid-ta11187/documents (accessed Februrary 2023).

91. Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II *CFTR* gene variants (most commonly *F508del*). *Cochrane Database Syst Rev* 2020;**12**:CD010966.

92. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2022.

93. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

94. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

95. Sterne J, Hernán M, McAleenan A, Reeves B, Higgins J. *25.5 Risk of Bias in Uncontrolled Before–After Studies (Including Interrupted Time Series)*. In Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2023.

96. Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review elexacaftor–tezacaftor–ivacaftor and ivacaftor (Trikafta). *Can J Health Technol* 2022;**2**:3546.

97. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials: Report by the Decision Support Unit*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2016.

98. van Valkenhoef G, Kuiper J. *gemtc: Network Meta-Analysis Using Bayesian Methods: R Package Version 1.0-1;* 2021. URL: https://github.com/cran/gemtc.

99. Stan Development Team. *18 Stansummary: MCMC Output Analysis*. n.d. URL: https://mc-stan.org/docs/cmdstan-guide/index.html (accessed May 2023).

100. Chopra R, Paul L, Manickam R, Aronow WS, Maguire GP. Efficacy and adverse effects of drugs used to treat adult cystic fibrosis. *Expert Opin Drug Saf* 2015;**14**:401–11.

101. Naureckas ET, Morgan RL, Oermann CM, Resnick HE, Brady C, Campbell A, *et al*. CFTR modulator guidelines. *Pediatr Pulmonol* 2017;**52**:121–2.

102. Habib A, Kajbafzadeh M, Yang CL, Skolnik K, Quon B. Clinical efficacy and safety of CFTR-directed therapies in cystic fibrosis: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2018;**197**:A6269.

103. Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *Cochrane Database Syst Rev* 2018;**2018**:CD010966.

104. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, *et al*. Cystic fibrosis foundation pulmonary guidelines: use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thoracic Soc* 2018;**15**:271–80.

105. Takyar J, Thapa K, Jain A, Sharma A. Pro8 efficacy of CFTR modulators against pulmonary exacerbation in cystic fibrosis: a systematic review and network meta-analysis. *Value Health* 2019;**22**:S842.

106. Tronzon CJ, Fenn N. Non-respiratory effects of CFTR modulators in pediatric patients with cystic fibrosis: a systematic review. *J Pediatric Pharmacol Therapeutics* 2021;**26**:529–30.

107. Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, *et al*. Effect of CFTR modulators on anthropometric parameters in individuals with cystic fibrosis: an evidence analysis center systematic review. *J Acad Nutr Dietet* 2021;**121**:1364–78.e2.

108. Southern KW, Murphy J, Sinha IP, Nevitt SJ. A systematic Cochrane review of corrector therapies (with or without potentiators) for people with cystic fibrosis with class II gene variants (most commonly F508DEL) [1]. *Paediatr Respir Rev* 2021;**38**:33–6.

109. Koutsovasili A, Gogas K, Souliotis K, Kani C, Markantonis S. POSA273 systematic review, meta-analysis of per OS administered drugs in cystic fibrosis. *Value Health* 2022;**25**:S173.

110. Yousif Hamdan AH, Zakaria F, Lourdes Pormento MK, Lawal OS, Opiegbe A, Zahid S, *et al*. Cystic fibrosis transmembrane conductance regulator protein modulators in children and adolescents with different CF genotypes – systematic review and meta-analysis. *Curr Rev Clin Exp Pharmacol* 2023;**19**:93.

111. Dawood SN, Rabih AM, Niaj A, Raman A, Uprety M, Calero MJ, *et al*. Newly discovered cutting-edge triple combination cystic fibrosis therapy: a systematic review. *Cureus* 2022;**14**:e29359.

112. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev* 2015;**2015**:CD009841.

113. Southern KW, Patel S, Sinha IP, Nevitt SJ. A systematic Cochrane Review of correctors (specific therapies for class II CFTR mutations) for cystic fibrosis [1]. *Paediatr Respir Rev* 2019;**30**:25–6.

114. Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From ivacaftor to triple combination: a systematic review of efficacy and safety of CFTR modulators in people with cystic fibrosis. *Int J Mol Sci* 2020;**21**:5882–23.

115. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ Open* 2019;**9**:e024537.

116. Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, *et al.*; VX18-445-109 Study Group. 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. *Lancet Respir Med* 2022;**10**:267–77.

117. Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, *et al.*; VX18-445-104 Study Group. Triple therapy for cystic fibrosis Phe508del-Gating and -residual function genotypes. *N Engl J Med* 2021;**385**:815–25.

118. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, *et al.*; VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019;**394**:1940–8.

119. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, *et al*. Efficacy and safety of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis heterozygous for *F508del* and a minimal function mutation: a phase 3b, randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2022;**206**:1361–9.

120. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, *et al*. A phase 3 open-label study of ELX/TEZ/IVA in children 6 through 11 years of age with CF and at least one *F508del* allele. *Am J Respir Critical Care Med* 2021;**203**:1522.

121. ClinicalTrials.gov. *Evaluation of ELX/TEZ/IVA in Cystic Fibrosis (CF) Subjects 2 through 5 Years*. 2020. URL: https://clinicaltrials.gov/study/NCT04537793. (accessed: June 2023).

122. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, *et al*. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017;**377**:2013–23.

123. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, *et al*. Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med* 2017;**377**:2024–35.

124. Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, *et al.*; VX16-661-115 Investigator Group. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *J Cyst Fibros* 2021;**20**:68–77.

125. Wilson J, You X, Ellis M, Urquhart DS, Jha L, Duncan M, *et al*. VO_{2max} as an exercise tolerance endpoint in people with cystic fibrosis: lessons from a lumacaftor/ivacaftor trial. *J Cyst Fibros* 2021;**20**:499–505.

126. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, *et al.*; VX14-809-109 investigator group. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2017;**5**:557–67.

127. Stahl M, Roehmel J, Eichinger M, Doellinger F, Naehrlich L, Kopp MV, *et al*. An exploratory study to determine the impact of lumacaftor/ivacaftor (LUM/IVA) on disease progression in children 2 through 5 years of age with cystic fibrosis homozygous for F508del-CFTR (F/F). *J Cyst Fibros* 2021;**20**:S22–3.

128. Rayment JH, Asfour F, Rosenfeld M, Higgins M, Liu L, Mascia M, *et al*. A phase 3, open-label study of lumacaftor/ivacaftor in children 1 to less than 2 years of age with cystic fibrosis homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2022;**206**:1239–47.

129. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, *et al.*; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;**365**:1663–72.

130. De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, Higgins M. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros* 2014;**13**:674–80.

131. Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, *et al*.; VX11-770-110 (KONDUCT) Study Group. Efficacy and safety of ivacaftor treatment: randomized trial in subjects with cystic fibrosis who have an R117H-CFTR mutation. *Lancet Respir Med* 2015;**3**:524–33.

132. Griese M, Tullis E, Chilvers M, Fabrizzi B, Jain R, Legg J, *et al*. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one *F508del* allele: 144-week interim results from an open-label extension study. *J Cyst Fibros* 2022;**21**:S99–100.

133. Ratjen F, Escobar H, Gaffin J, McColley S, Roesch E, Ruiz F, *et al*. Elexacaftor/tezacaftor/ivacaftor in children aged 6 and older with cystic fibrosis and at least 1 *F508del* allele: interim results from a Phase 3 open-label extension study. *J Cyst Fibros* 2021;**20**:S265.

134. ClinicalTrials.gov. *NCT04058366: Study Evaluating the Long-Term Safety and Efficacy of VX-445 Combination Therapy*. 2023. URL: https://clinicaltrials.gov/ct2/show/NCT04058366 (accessed July 2022).

135. Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, *et al*. Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. *Lancet Respir Med* 2021;**9**:733.

136. Sawicki GS, Chilvers M, McNamara J, Naehrlich L, Saunders C, Sermet-Gaudelus I, *et al*. A phase 3, open-label, 96-week trial to study the safety, tolerability, and efficacy of tezacaftor/ivacaftor in children >= 6 years of age homozygous for *F508del* or heterozygous for *F508del* and a residual function CFTR variant. *J Cyst Fibros* 2022;**21**:675–83.

137. Walker S, Flume P, McNamara J, Solomon M, Chilvers M, Chmiel J, *et al*. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *J Cyst Fibros* 2019;**18**:708–13.

138. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, *et al*. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017;**5**:107–18.

139. Chilvers MA, Davies JC, Milla C, Tian S, Han Z, Cornell AG, *et al*. Long-term safety and efficacy of lumacaftor–ivacaftor therapy in children aged 6–11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study. *Lancet Respir Med* 2021;**9**:721–32.

140. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/Ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2017;**195**:912–20.

141. Doumit M, Chuang S, Middleton P, Selvadurai H, Sivam S, Ruseckaite R, *et al*. Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic. *J Cyst Fibros* 2023;**22**:581–6.

142. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravitlles M, *et al*. Reduction in hospitalised COPD exacerbations during COVID-19: a systematic review and meta-analysis. *PLOS ONE* 2021;**16**:e0255659.

143. Vertex Pharmaceuticals Inc. *Clinical Study Report. Protocol VX20-445-111. A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 through 5 Years of Age*. Unpublished. Boston, MA; 2022.

144. Taylor-Cousar JL, Jain M, Barto TL, Haddad T, Atkinson J, Tian S, *et al*.; VX14-809-106 Investigator Group. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. *J Cyst Fibros* 2018;**17**:228–35.

145. Granger E, Davies G, Keogh RH. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? *J Cyst Fibros* 2022;**21**:316–22.

146. NICE. *Lumacaftor–Ivacaftor for Treating Cystic Fibrosis Homozygous for the F508del Mutation [TA398]*. 2016. URL: www.nice.org.uk/guidance/ta398 (accessed December 2022).

147. O'Sullivan BP, Baker D, Leung KG, Reed G, Baker SS, Borowitz D. Evolution of pancreatic function during the first year in infants with cystic fibrosis. *J Pediatr* 2013;**162**:808–12.e1.

148. Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. *J Pathol* 2016;**238**:311–20.

149. Bijvelds MJC, Roos FJM, Meijsen KF, Roest HP, Verstegen MMA, Janssens HM, *et al*. Rescue of chloride and bicarbonate transport by elexacaftor–ivacaftor–tezacaftor in organoid-derived CF intestinal and cholangiocyte monolayers. *J Cyst Fibros* 2022;**21**:537–43.

150. National Institue for Health and Care Excellence. *ID3834. Professional Organisation Submission. UK Psychosocial Professionals in Cystic Fibrosis*. Dr Thomas Clarke; London: NICE; 2023.

151. Wagener JS, Millar SJ, Mayer-Hamblett N, Sawicki GS, McKone EF, Goss CH, *et al*. Lung function decline is delayed but not decreased in patients with cystic fibrosis and the R117H gene mutation. *J Cyst Fibros* 2018;**17**:503–10.

152. UK Cystic Fibrosis Registry. *2021 Annual Data Report*. 2022.

153. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, Salanti G. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLOS Med* 2020;**17**:e1003082.

154. Keogh RH, Seaman SR, Barrett JK, Taylor-Robinson D, Szczesniak R. Dynamic prediction of survival in cystic fibrosis: a landmarking analysis using UK Patient Registry data. *Epidemiology* 2019;**30**:29–37.

155. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;**153**:345–52.

156. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. *Pediatr Pulmonol* 2021;**56**:1271–3.

157. Lawless M, Burgess M, Bourke S. Impact of COVID-19 on hospital admissions for COPD exacerbation: lessons for future care. *Medicina* 2022;**58**:66.

158. Vertex Pharmaceuticals Inc. *AURORA F/RF F/G OLE (Study 110): Clinical Study Report – Part A: A Phase 3, Open-Label Study Evaluating the Long-Term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Version 1.0, Protocol Number: VX18-445-110*. Unpublished. Boston, MA; 2022.

159. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Using negative control outcomes and difference-in-differences analysis to estimate treatment effects in an entirely treated cohort: the effect of ivacaftor in cystic fibrosis. *Am J Epidemiol* 2022;**191**:505–15.

160. Selvadurai H, Polineni D, Daines C, Tullis E, Costa S, Linnemann R, *et al*. TP084. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in people with cystic fibrosis (CF) and at least one *F508del* allele: an open-label, 192-week extension study. *Respirology* 2024;**29**.

161. Polineni D, Daines CL, Tullis E, Costa S, Linnemann RW, Mall MA, *et al*. *Long Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) in People with Cystic Fibrosis (CF) and At Least One F508del Allele: An Open Label, 192 Week Extension Study*. In: *46th European Cystic Fibrosis Conference, Vienna, Austria*, 7–10, June 2023.

162. Vertex Pharmaceuticals Inc. *Clinical Study Report. A Phase 3, Open-Label Study Evaluating the Long-Term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation*. Unpublished. Boston, MA; 2023.

163. Lee T, Sawicki GS, Altenburg J, Millar SJ, Geiger JM, Jennings MT, *et al*. Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis. *J Cyst Fibros* 2023;**22**:402–6.

164. ClinicalTrials.gov. *NCT04058366. Study Evaluating the Long-Term Safety and Efficacy of VX-445 Combination Therapy*. 2024. URL: www.clinicaltrials.gov/study/NCT04058366?term=NCT04058366&rank=1&tab=results (accessed July 2024).

165. Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, De Iorio F. Real-world outcomes of ivacaftor treatment in people with cystic fibrosis: a systematic review. *J Clin Med* 2021;**10**:1527.

166. Newsome SK, Daniel R. CF-EpiNet. IPD2.03: the effects of 3-year ivacaftor use on lung function and intravenous days seen in UK CF Registry data. *J Cyst Fibros* 2018;**17**:68.

167. UK CF Registry. *Data Request Report – 469*. London: Cystic Fibrosis Trust; 2023.

168. Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, *et al.*; SIMPLIFY Study Group. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. *Lancet Respir Med* 2023;**11**:329–40.

169. Newsome SJ, Daniel RM, Carr SB, Bilton D, Keogh RH. Investigating the effects of long-term dornase alfa use on lung function using registry data. *J Cyst Fibros* 2019;**18**:110–7.

170. Southern K. *ISRCTN14081521: A Randomised Open-Label Trial to Assess Change in Respiratory Function for People with Cystic Fibrosis (pwCF) Established on Triple Combination Therapy (Kaftrio™) after Rationalisation of Nebulised Mucoactive Therapies (the CF STORM Trial)*. London: BioMed Central Limited, ISRCTN Registry; 2021.

171. ClinicalTrials.gov. *NCT05519020: Inhaled Therapy Adherence and Outcomes to Kaftrio in Cystic Fibrosis*. 2022. URL: https://classic.clinicaltrials.gov/ct2/show/NCT05519020 (accessed July 2023).

172. Vertex Pharmaceuticals Inc. *Clinical Study Report. Protocol VX16-809-122. A Phase 3, 2-Part, Open-Label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age with Cystic Fibrosis, Homozygous for F508del*. Unpublished. Boston, MA; 2022.

173. Canadian Agency for Drugs and Technologies in Health. *Economic Evaluations and Models – MEDLINE*. CADTH Search Filters Database. 2016. URL: https://searchfilters.cadth.ca/link/16 (accessed February 2023).

174. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. Performance of Ovid MEDLINE search filters to identify health state utility studies. *Int J Technol Assess Health Care* 2017;**33**:472–80.

175. Tice JA, Kuntz KM, Wherry K, Seidner M, Rind DM, Pearson SD. The effectiveness and value of novel treatments for cystic fibrosis. *J Managed Care Specialty Pharm* 2021;**27**:276–80.

176. Vadagam P, Kamal KM, Covvey JR, Giannetti V, Mukherjee KE. Cost-effectiveness and budget impact of lumacaftor/ivacaftor in the treatment of cystic fibrosis. *J Managed Care Specialty Pharm* 2019;**25**:285–6.

177. Institute for Clinical and Economic Review. *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value*. Boston, MA: ICER; 2018.

178. Institute for Clinical and Economic Review. *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value*. Boston, MA: ICER; 2020.

179. Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the long-term clinical and economic outcomes of lumacaftor/ivacaftor in cystic fibrosis patients with homozygous phe508del mutation. *Value Health* 2017;**20**:1329–35.

180. Sharma D, Xing S, Hung YT, Caskey RN, Dowell ML, Touchette DR. Cost-effectiveness analysis of lumacaftor and ivacaftor combination for the treatment of patients with cystic fibrosis in the United States. *Orphanet J Rare Dis* 2018;**13**:172.

181. Vadagam P, Kamal KM, Covvey JR, Giannetti V, Mukherjee K. Cost-effectiveness and budget impact of lumacaftor/ivacaftor in the treatment of cystic fibrosis. *J Managed Care Specialty Pharm* 2018;**24**:987–97.

182. Canadian Agency for Drugs and Technologies in Health. *Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi): (Vertex Pharmaceuticals (Canada) Incorporated): Indication: For the Treatment of Cystic*

Fibrosis in Patients Age 12 Years and Older Who Are Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2016. URL: www.cda-amc.ca/sites/default/files/cdr/pharmacoeconomic/SR0471_Orkambi_PE_Report.pdf (assessed March 2023).

183. Canadian Agency for Drugs and Technologies in Health. *Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi): (Vertex Pharmaceuticals (Canada) Incorporated): Indication: For the Treatment of Cystic Fibrosis in Patients 6 Years of Age and Older Who Are Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2018. URL: www.ncbi.nlm.nih.gov/books/NBK540212/

184. National Institute for Health and Care Excellence (NICE). *Lumacaftor and Ivacaftor Combination Therapy for Treating Cystic Fibrosis Homozygous for the F508del Mutation [TA786]*. London: NICE; 2016. URL: www.nice.org.uk/guidance/ta398 (accessed December 2022).

185. Pharmaceutical Benefits Advisory Committee (PBAC). *Public Summary Document – July 2018 PBAC Meeting. Lumacaftor with Ivacaftor for Treatment of Patients with Cystic Fibrosis (CF) Aged ≥ 12 Years Who Are Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene*. Australian Government: Pharmaceutical Benefits Scheme; 2018. URL: www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Lumacaftor-Orkambi-psd-july-2018 (accessed May 2023).

186. Pharmaceutical Benefits Advisory Committee (PBAC). *Public Summary Document – July 2018 PBAC Meeting. (Lumacaftor/Ivacaftor) for the Treatment of Patients with Cystic Fibrosis (CF) Aged 6–11 Years Who Are Homozygous for the F508del Mutation in the CF Transmembrane Conductance Regulator (CFTR) Gene*. Australian Government: Pharmaceutical Benefits Scheme; 2018. URL:www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Lumacaftor-psd-july-2018 (accessed May 2023).

187. Pharmaceutical Benefits Advisory Committee (PBAC). *Public Summary Document – July 2019 PBAC Meeting. Lumacaftor/Ivacaftor Granules for Treatment of Cystic Fibrosis (CF) Patients Aged 2 Years and Older Who Are Homozygous for the F508del Mutation in the CF Transmembrane Conductance Regulator (CFTR) Gene*. Australian Government: Pharmaceutical Benefits Scheme; 2019. URL www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-07/lumacaftor-with-ivacaftor-sachet-containing-granules (accessed May 2023).

188. Scottish Medicines Consortium (SMC). *Lumacaftor 200 mg, Ivacaftor 125 mg Film-Coated Tablet (Orkambi®)*. [SMC 1136/16]. Glasgow: Scotland; 2016. URL: https://scottishmedicines.org.uk/media/1961/lumacaftor-ivacaftor__orkambi__final_april_2016_for_website.pdf (accessed March 2023).

189. Scottish Medicines Consortium (SMC). *Lumacaftor and Ivacaftor 200 mg/125 mg, 100 mg/125 mg Film-Coated Tablets and 100 mg/125 mg,150 mg/188 mg Granules in Sachets (Orkambi®). [SMC2182]*. Glasgow: Scotland; 2019. URL: https://scottishmedicines.org.uk/media/4652/lumacaftor-ivacaftor-orkambi-revised-final-july-2019-for-website.pdf (accessed March 2023).

190. Pharmaceutical Benefits Advisory Committee (PBAC). *Public Summary Document – March 2019 PBAC Meeting. Tezacaftor/Ivacaftor for Treatment of Cystic Fibrosis (CF) Patients Aged 12 Years and Older Who Have At least One Residual Function (RF) Mutation in the CFTR Gene*. Australian Government: Pharmaceutical Benefits Scheme; 2019. URL: www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-03/tezacaftor-with-ivacaftor-tablet-containing-tezacaftor-100-psd-march-2019 (accessed May 2023).

191. Scottish Medicines Consortium (SMC). *Tezacaftor and Ivacaftor 100 mg/150 mg Film-Coated Tablets (Symkevi®). [SMC2183]*. Glasgow: Scotland; 2019. URL: https://scottishmedicines.org.uk/media/4643/tezacaftor-ivacaftor-symkevi-final-july-2019-for-website.pdf (accessed March 2023).

192. Canadian Agency for Drugs and Technologies in Health. *CADTH Reimbursement Review Elexacaftor–Tezacaftor–Ivacaftor and Ivacaftor (Trikafta). (Vertex Pharmaceuticals (Canada) Incorporated): Indication: Treatment of cystic fibrosis in patients aged ≥ 12 years who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2021. URL: www.cda-amc.ca/sites/default/files/DRR/2021/SR0673-combined-report.pdf (accessed March 2023).

193. Pharmaceutical Benefits Advisory Committee (PBAC). *Public Summary Document – December 2021 PBAC Meeting. Elexacaftor 100 mg/Tezacaftor 50 mg/Ivacaftor 75 mg Film-Coated Tablets Co-Packaged with Ivacaftor 150 mg Film-Coated Tablets*. Australian Government: Pharmaceutical Benefits Scheme; 2021. URL www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/pbac-public-summary-documents-december-2021 (accessed May 2023).

194. Vertex Pharmaceuticals Inc. *TRAFFIC Clinical Study Report: Protocol VX12-809-103. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. V.1. 8 September 2014*. Unpublished. Boston, MA; 2014.

195. Vertex Pharmaceuticals Inc. *TRANSPORT: Clinical Study Report. Protocol VX12-809-104. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation*. Unpublished. Boston, MA; 2014.

196. Drummond M. *Methods for the Economic Evaluation of Health Care Programmes*. 4th edn. Oxford: Oxford University Press; 2015.

197. Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. *Health Qual Life Outcomes* 2015;**13**:33.

198. Acaster S, Mukuria C, Rowen D, Brazier J, Wainwright C, Quon B, *et al*. Development of the Cystic Fibrosis Questionnaire-Revised preference based scoring algorithm. *Pediatr Pulmonol* 2019;**54**:443.

199. Acaster S, Mukuria C, Rowen D, Brazier JE, Wainwright CE, Quon BS, *et al*. Development of the Cystic Fibrosis Questionnaire-Revised-8 Dimensions: estimating utilities from the Cystic Fibrosis Questionnaire-Revised. *Value Health* 2022;**26**:567–78.

200. Bell SC, Mainz JG, MacGregor G, Madge S, MacEy J, Fridman M, *et al*. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. *BMC Pulm Med* 2019;**19**:146.

201. Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J* 2013;**41**:571–7.

202. Cameron R, Matthews J, Office D, Rowley M, Abbott J, Simmonds N, *et al*. Patient valuation of health-related quality of life associated with treatment burden and pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros* 2021;**20**:S158.

203. Tappenden P, Harnan S, Uttley L, Mildred M, Carroll C, Cantrell A. Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis: systematic review and economic model. *Health Technol Assess* 2013;**17**(56).

204. Tappenden P, Harnan S, Uttley L, Mildred M, Walshaw M, Taylor C, Brownlee K. The cost effectiveness of dry powder antibiotics for the treatment of *pseudomonas aeruginosa* in patients with cystic fibrosis. *PharmacoEconomics* 2014;**32**:159–72.

205. Tappenden P, Sadler S, Wildman M. An early health economic analysis of the potential cost effectiveness of an adherence intervention to improve outcomes for patients with cystic fibrosis. *PharmacoEconomics* 2017;**35**:647–59.

206. Tappenden P, Navega Biz A, Hernandez Alava M, Sasso A, Sutton L, Ennis K, *et al*. A model-based economic analysis of the CFHealthHub intervention to support adherence to inhaled medications for people with cystic fibrosis in the UK. *Int J Technol Assess Health Care* 2023;**39**:e6.

207. Wildman MJ, O'Cathain A, Hind D, Maguire C, Arden MA, Hutchings M, *et al*. An intervention to support adherence to inhaled medication in adults with cystic fibrosis: the ACtiF research programme including RCT. *Programme Grants Appl Res* 2021;**9**(11).

208. Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. *Pharmacotherapy* 2000;**20**:1167–74.

209. European Medicines Agency. *Orkambi*. 2015. URL: www.ema.europa.eu/en/medicines/human/EPAR/orkambi#assessment-history-section (accessed December 2022).

210. European Medicines Agency. *Symkevi*. 2018. URL: www.ema.europa.eu/en/medicines/human/EPAR/symkevi#assessment-history-section (accessed December 2022).

211. European Medicines Agency. *Kaftrio*. 2020. URL: www.ema.europa.eu/en/medicines/human/EPAR/kaftrio#assessment-history-section (accessed December 2022).

212. Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: a longitudinal study using UK patient registry data. *J Cyst Fibros* 2018;**17**:218–27.

213. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. *Value Health* 2012;**15**:821–7.

214. Davis S, Stevenson M, Tappenden P, Wailoo AJ. *NICE DSU Technical Support Document 15: Cost-Effectiveness Modelling Using Patient-Level Simulation*. Sheffield: University of Sheffield; 2012.

215. NHS. *National Cost Collection for the NHS 2021/22*. 2023. URL: www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed January 2023).

216. UK CF Registry Trust. *2018 Genotype Data by Nation and Age: Number of Individuals Eligible by Genotype for CFTR Modulating Therapy in Each Nation of the UK, Defined by Centre Attended*. 2020.

217. Mitchell M, Muftakhidinov B, Winchen T. *Engauge Digitizer Software*. 2023. URL: http://markummitchell.github.io/engauge-digitizer (accessed June 2023).

218. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: epidemiology and pathogenesis. *Thorax* 2007;**62**:360–7.

219. Adler AI, Shine BSF, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. *Diabetes Care* 2008;**31**:1789–94.

220. Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002;**21**:1575–600.

221. Engels EA, Schmid CH, Terrin N, Olkin I, Lau J. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med* 2000;**19**:1707–28.

222. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, *et al.*; STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLOS Med* 2007;**4**:e297.

223. NHS England. *Annual Report on Cardiothoracic Organ Transplantation Report for 2021/2022*. London: NHS England; 2022.

224. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. Assessment of quality of life in lung transplantation using a simple generic tool. *Thorax* 2001;**56**:218–22.

225. Raguragavan A, Jayabalan D, Saxena A. Health-related quality of life following lung transplantation for cystic fibrosis: a systematic review. *Clinics* 2023;**78**:100182.

226. Joint Formulary Committee. *British National Formulary*. 2021. URL: https://bnf.nice.org.uk/ (accessed January 2023).

227. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry: 2018 Annual Data Report*. 2019.

228. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. An economic evaluation of lung transplantation. *J Thorac Cardiovasc Surg* 2002;**123**:411–8; discussion 418.

229. Jones KB. *Unit Costs of Health and Social Care 2021*. Canterbury: Personal Social Services Research Unit, University of Kent; 2021.

230. National Institute for Health and Care Excellence (NICE). *NICE Health Technology Evaluations: The Manual. Process and Methods [PMG36]*. 2022. URL: www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (accessed September 2022).

231. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021.

232. Hernández Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by Age and Sex for the UK*. Sheffield: Decision Support Unit, University of Sheffield; 2022.

233. National Institute for Health and Care Excellence. *Ivacaftor–Tezacaftor–Elexacaftor, Tezacaftor–Ivacaftor and Lumacaftor–Ivacaftor for Treating Cystic Fibrosis. TA988 Final Guidance*. 2024. URL: www.nice.org.uk/guidance/ta988 (accessed July 2024).

EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library