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

Slides for public – ACIC information redacted

Multiple Technology Appraisal

Technology appraisal committee D [12 October 2023]

Chair: Stephen Smith

Lead team: Carole Pitkeathley, Guy Makin, Sofia Dias

External assessment group: BMJ

Technical team: Anna Willis, Nigel Gumbleton, Linda Landells

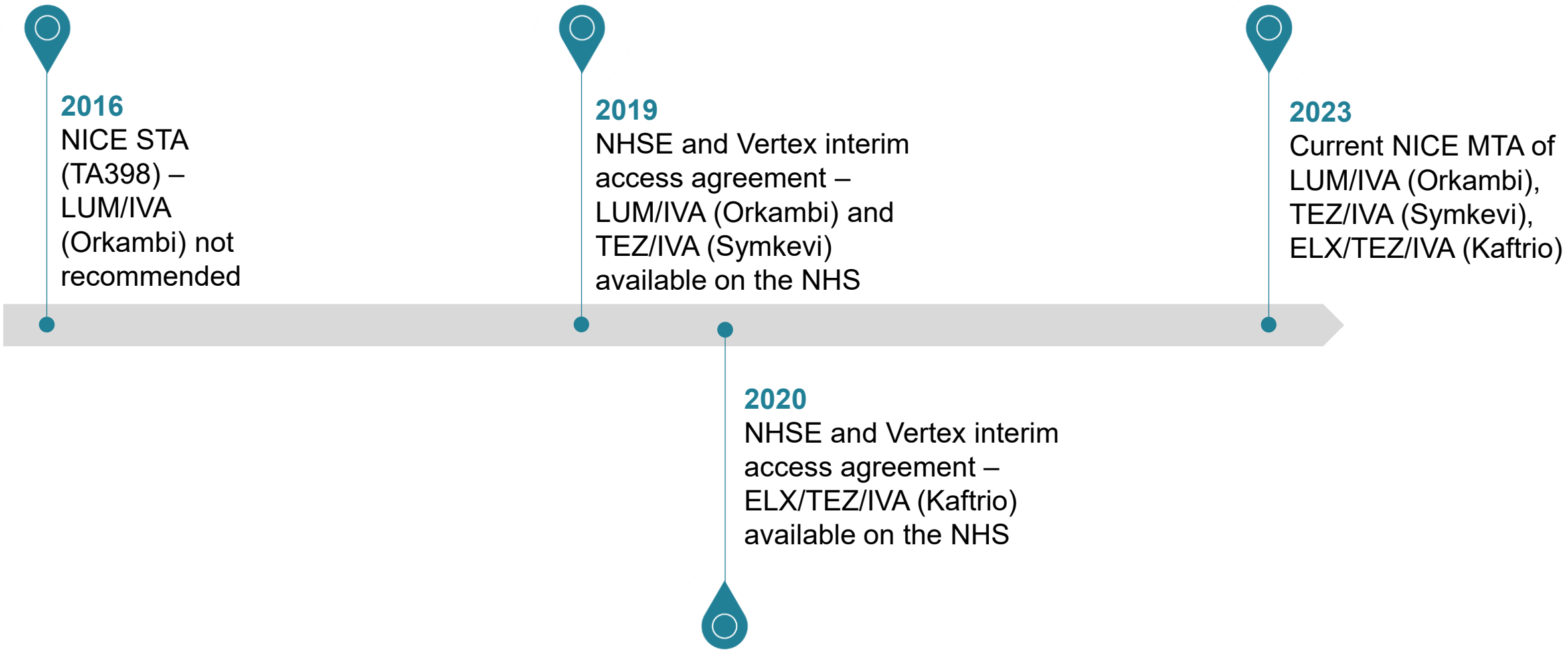
Company: Vertex

The technologies

Technology	Elexacaftor–tezacaftor–ivacaftor (ELX/TEZ/IVA, Kaftrio, Vertex)	Tezacaftor–ivacaftor (TEZ/IVA, Symkevi, Vertex)	Lumacaftor–ivacaftor (LUM/IVA, Orkambi, Vertex)
Marketing authorisation	In combination with ivacaftor for CF in people **aged 6+** who have at **least one F508del mutation** **CHMP positive opinion for children aged 2-5**	In combination with ivacaftor for CF in people **aged 6+** who are **homozygous for the F508del mutation or who are heterozygous for the F508del mutation and another mutation***	CF in people **aged 1+** who are **homozygous for the F508del mutation**
Mechanism of action	All drugs are CFTR modulators. ELX, TEZ and LUM are CFTR correctors that improve protein folding and increase CFTR expression at the cell membrane. IVA is a CFTR potentiator which binds to the CFTR protein at the cell membrane increasing its ability to transport chloride		
Administration	Tablets, taken in the morning. Ivacaftor taken in the evening.	Tablets, taken in the morning. Ivacaftor taken in the evening.	Tablets or granules, taken in the morning and evening
List price	£8,346 per 28-day supply (Ivacaftor £7,000 per 28-day supply)	£6,294 per 28-day supply (Ivacaftor £7,000 per 28-day supply)	£8,000 per 28-day supply
Commercial arrangements	There are confidential commercial arrangements in place (simple PAS discounts) for all treatments		

Abbreviations: CF, cystic fibrosis; CHMP, Committee for Medicinal Products for Human Use; CFTR, cystic fibrosis transmembrane conductance regulator. **Notes:** *Other mutations include P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

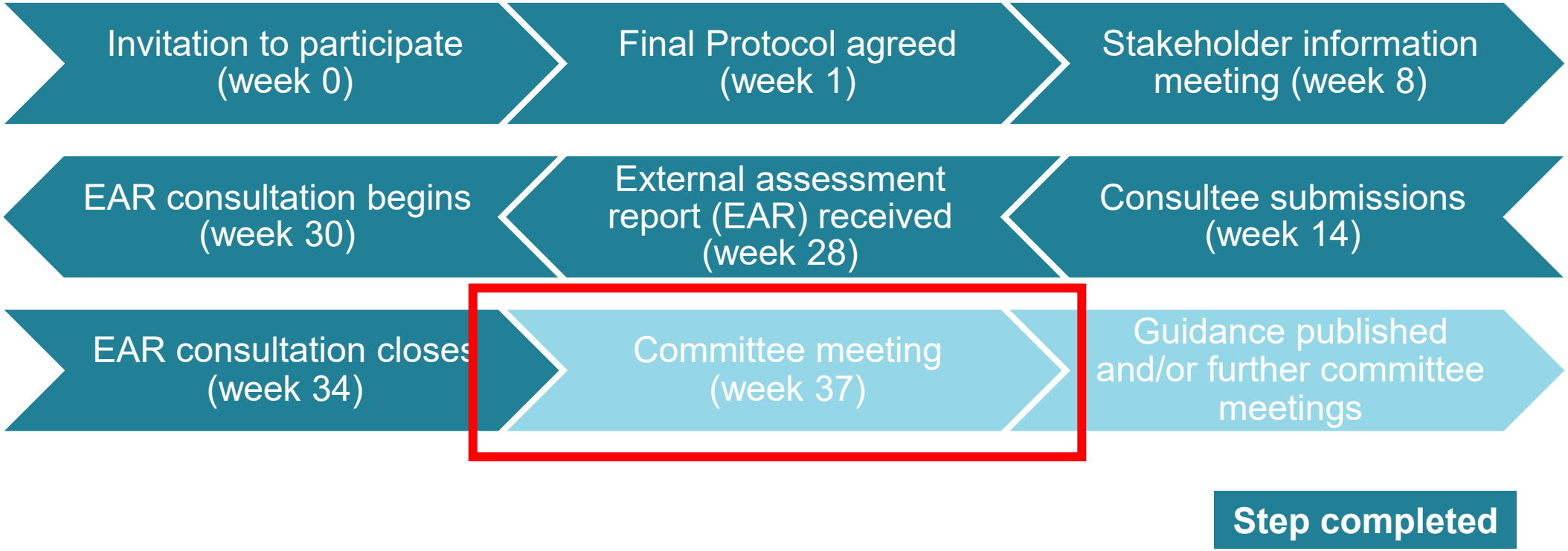
Topic history



Abbreviations: ELX/TEZ/IVA, elexacaftor–tezacaftor–ivacaftor; LUM/IVA, lumacaftor–ivacaftor; MTA, Multiple Technology Appraisal; NHSE, NHS England; STA, Single Technology Appraisal; TEZ/IVA, tezacaftor–ivacaftor.

Multiple Technology Appraisal (MTA) process

Figure 1: MTA process



Abbreviations: EAR, External Assessment Report; MTA, Multiple Technology Appraisal.

Data collection agreement (1/3)

- The data collection agreement (DCA) was part of the interim access agreement
- Parties to the agreement were NHS England and NHS Improvement (NHSE&I), NICE, UK CF Trust and Vertex
- The purpose of the agreement was:
  - To enable eligible patients in England to access treatment with CFTR modulators
  - To capture data that may address the clinical uncertainties in the evidence bases to inform a future appraisal by NICE
- **Table 1** presents primary and secondary sources of data collection

Table 1: Primary and secondary sources of data collection

Source	Description
Primary source	Real world data collected by the UK Cystic Fibrosis Registry

Secondary sources	• Pharmacy home delivery data to inform compliance rates (compiled by Vertex).
	• Vertex Quality of Life (QoL) study in the UK collecting patient and caregiver QoL.
	• Ongoing Vertex clinical trials:
	  ◦ VX 18 445-104
	  ◦ VX 17 445-105
	  ◦ VX18 445-109.
	• Any other Vertex studies that will require data collection and are yet to be defined.

ELX/TEZ/IVA trials

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; QoL, quality of life. **Source:** https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement

Data collection agreement (2/3)

Key uncertainties

Key clinical uncertainties to be addressed by the Data Collection Agreement were identified from the original appraisal of lumacaftor/ivacaftor (NICE TA398):

- Long-term (more than 1 year) treatment effects on absolute ppFEV1
- The impact of treatment on lung function decline over time
- Discontinuation rates of CFTRm and reasons for discontinuation
- Compliance rates of CFTRm 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

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second.
Source: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement

Data collection agreement (3/3)

Table 1: Description of data sources discussed in the DCA

Data source	Description
UK Cystic Fibrosis Registry (UKCFR)	The UKCFR includes data from consenting patients from all CF care centres and clinics in the UK, covering 99% of the UK CF population. The registry holds information on demographics, treatment and health outcomes.
Pharmacy home delivery data	Vertex has arrangements for homecare delivery vendors to periodically provide delivery volume and frequency data, from which Vertex will estimate patient compliance
Vertex Quality of Life (QoL) study	Vertex will conduct a study in the UK to capture data on QoL in patients and caregivers, (MAGNIFY and TRAJECTORY). The Cystic Fibrosis Questionnaire - Revised (CFQ-R) will be used to capture QoL data in patients. Generic instruments for QoL will be used to capture data in caregivers
Clinical trials (of ELX/TEZ/IVA)	Randomised controlled trials: VX-18-445-104, VX18-445-109 Open-label extension study: VX-17-445-105

The output of the DCA was a report and workbooks produced by Vertex

Abbreviations: CF, cystic fibrosis; DCA, data collection agreement; QoL, quality of life; UKCFR, UK Cystic Fibrosis Registry. **Source:** https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement

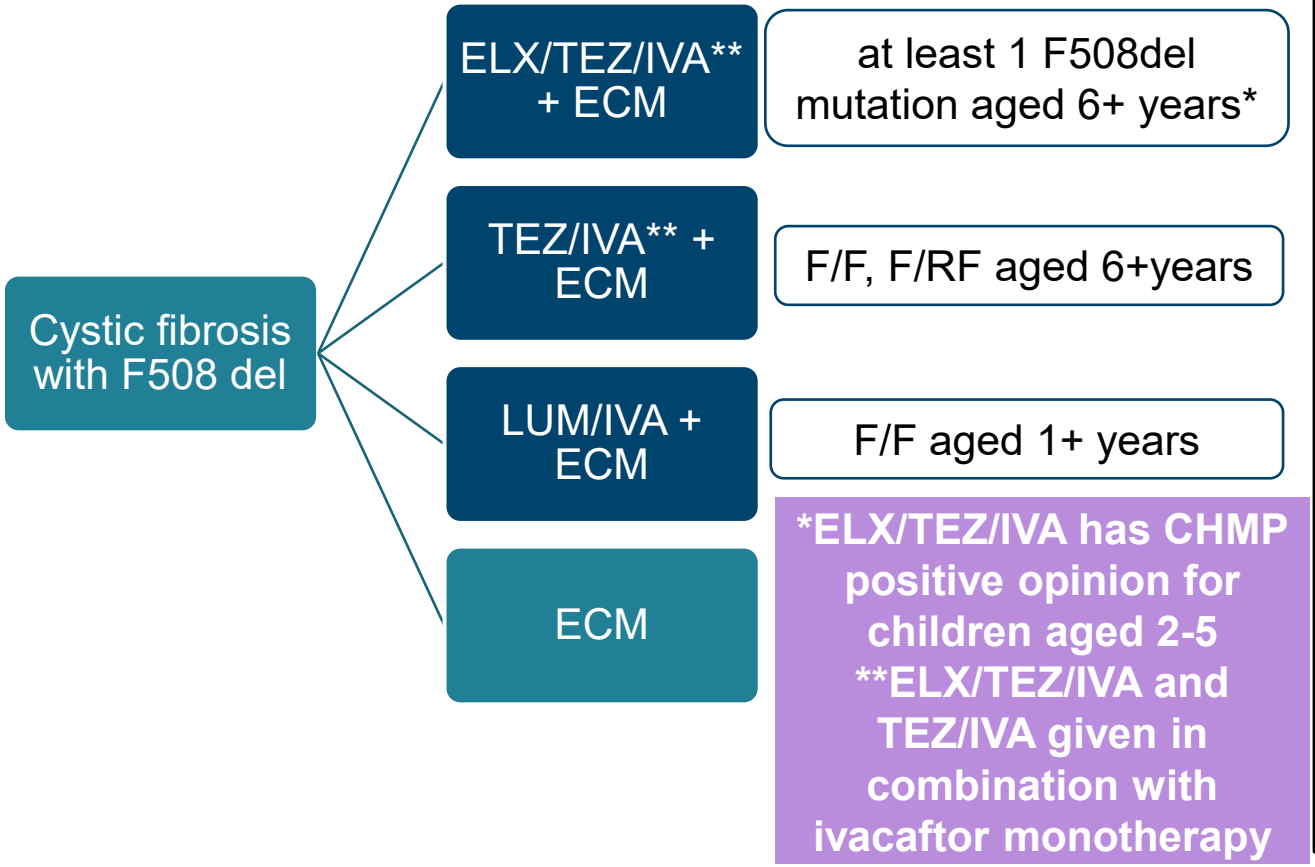
Access to treatments

- Access to treatments will continue while the appraisal is ongoing for new and existing patients
- Once the appraisal has ended, new patients will only be initiated on treatments that have been recommended in NICE's final guidance
- Existing patients will be unaffected as the flexible commercial mechanism ensures continued access for patients already receiving any of the licensed treatments following the conclusion of a full NICE evaluation

Source: NHS England

Treatment pathway

Figure 1: Cystic fibrosis treatment pathway, licensed ages and genotypes



- Established clinical management (ECM) is co-ordinated by a multidisciplinary team and includes:
  - Airway clearance, mucoactive agents, inhaled and oral antibiotics, immunomodulatory agents, nutritional support, and pancreatic enzyme replacement
- CFTR modulators are add-on therapies to ECM
- Choice of CFTR modulator depends on genotype and age
- Based on data from the UK CF Registry in December 2021:
  - 72.6% were taking a CFTR modulator
  - Of those, 72.1% were taking ELX/TEZ/IVA
  - The proportion on ELX/TEZ/IVA [redacted] in 2022

What is the current treatment pathway for people with CF?

Abbreviations: CF, cystic fibrosis; CHMP, Committee for Medicinal Products for Human Use; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; ELX/TEZ/IVA, elexacaftor–tezacaftor–ivacaftor; LUM/IVA, lumacaftor–ivacaftor; TEZ/IVA, tezacaftor–ivacaftor.
Notes: *Calculated from data on EAR page 51

Background on cystic fibrosis

Causes

- Cystic fibrosis (CF) is a life-limiting genetic condition
- Most commonly caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene, resulting in the loss of phenylalanine at position 508 in the CFTR protein (F508del mutation)

Epidemiology

- There are around 9,500 people with CF in England and Wales, 89% of whom have the F508del mutation

Symptoms and prognosis

- Impaired function of CFTR protein affects salt and fluid transport causing a build-up of thick mucus in the lungs and digestive system, and the tubes that transport enzymes out of the pancreas
- Mucus build up in the lungs leads to difficulty breathing, inflammation, severe infections which require hospitalisation for intravenous antibiotics and progressive lung function loss over time
- Other symptoms include difficulty putting on weight and growing, and CF-related diabetes
- Lung disease is the primary cause of death for people with CF – the median age of death in 2021 was 38 years

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Overview of patient and professional submissions

Submissions received from:

- 1 patient expert
- 2 patient organisations
  - CF Trust
  - CF Voices
- 3 clinical experts
- 7 professional organisations
  - Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)
  - British Dietetic Association (BDA)
  - British Paediatric Respiratory Society (BPRS)
  - British Thoracic Society (BTS)
  - CF Digicare
  - UK CF Medical Association (UKCFMA)
  - UK Psychosocial Professionals in Cystic Fibrosis (UKPPCF)
- Additional organisations who provided consultation comments on the EAG's report included:
  - Quest for a Cure (QFAC)
  - Cystic Fibrosis Nursing Association (CFNA)
  - UK Cystic Fibrosis Pharmacy Group (UKCFPG)

Abbreviations: CF, cystic fibrosis.

Patient perspectives – life before CFTR modulators

- People with CF experience a wide range of challenging symptoms affecting the whole body, in particular the lungs and gut:
  - Bacteria can colonise leading to inflammation, tissue damage, repeated infections and permanent scarring
  - People with CF are particularly vulnerable to antimicrobial resistance
  - Pancreatic enzyme supplements are required to help digest food
  - Not taking these causes abdominal pain, bloating, excess wind, and difficulty gaining weight
  - Scarring of the pancreas can lead to CF-related diabetes
- Significantly shortens life
- CF has a high treatment burden, requiring medication and physiotherapy stay well
- CF substantially impacts quality of life and mental and emotional wellbeing and also has a substantial financial burden

Physiotherapy, whilst essential, can be a huge daily burden particularly alongside a rigorous regime of medicines and nebulisers. On average, the time spent on daily CF care was 2.5 hours

It is common for people with CF to spend weeks in hospital several times a year for intravenous antibiotic treatment and monitoring

Being unwell can interfere with work, education, and social activities – people living with CF describe there being no day off from relentless symptoms

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Carer perspective – life before CFTR modulators (1/2)

- The chronic and severe nature of CF makes caring demanding and time consuming
- Caring for someone with CF involves daily activities such as manual physiotherapy, administration of medicines, sterilising medical equipment and facilitating hospital visits
- Parents have also described the difficulty of ensuring their children are a healthy weight and managing the high-calorie diet required

"Within a month [of CF diagnosis] I was having to perform percussion physiotherapy on my tiny baby and administer several medicines by syringe and through nebuliser causing him huge distress, after he was found to have pseudomonas in his lungs"

"[He] could never enjoy eating; mealtimes were very long and full of conflict and upset"

"My son struggled to gain weight from very early on and takes quite a lot of Creon [pancreatic enzymes]…we had to mound the cheese…heap on the butter until it's like so gross that you wouldn't want to eat it yourself"

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Carer perspective – life before CFTR modulators (2/2)

- Carers highlighted the psychological burden:
  - Most carers surveyed experienced moderate or severe depression or anxiety, which can lead to physical health problems
  - As CF is lifelong, carers can be subject to these impacts for decades
  - There is an impact on the whole family including siblings and grandparents, and relationship difficulties are common
  - Many interviewed were in households with 2 or more carers

Caring also has a financial burden:

- Carers report decreases in productivity, ability to work and job satisfaction
- 69% of people felt they had less money compared to those around them, due to either their own or their child's CF

"Seeing your loved one suffer and the sacrifices of your own life required in the care are hard enough – but the worst was that you knew they were never going to be enough, merely postponing the inevitable"

"The unpredictability of CF meant that life, physical and mental health could be massively interrupted at any time, hence anxiety was constant"

"My wife lost her good job because she didn't want anyone else to look after our [child] and I…was virtually not working. Both of us became fulltime carers and dedicated our life to our [child]."

"[My son's] elderly grandmother couldn't bear to witness this and became depressed, which was very difficult to handle on top of everything else."

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Patient perspectives – life after CFTR modulators (1/3)

- Treatments have changed the nature of CF from a progressive, life limiting condition to a manageable chronic illness

- Benefits to patients include:
  - Improved physical health and mental wellbeing
  - Increased energy levels
  - Dramatically improved lung function and reduced coughing
  - Fewer medical interventions, and less time in hospital
  - Potential for a reduced treatment burden because of increased health stability
  - Increased opportunities for education and employment and ability to plan for the future

- After Kaftrio became available, the overwhelming emotion felt by young people living with CF was hope (**Figure 1,** next slide)

"I am fitter and healthier than I have been in decades. I have reclaimed hours a day by not needing time consuming physiotherapy or nebulisers. I have been able to increase my work hours, go for a promotion, and provide security for my family."

"I never realised it was possible to feel this good day after day"

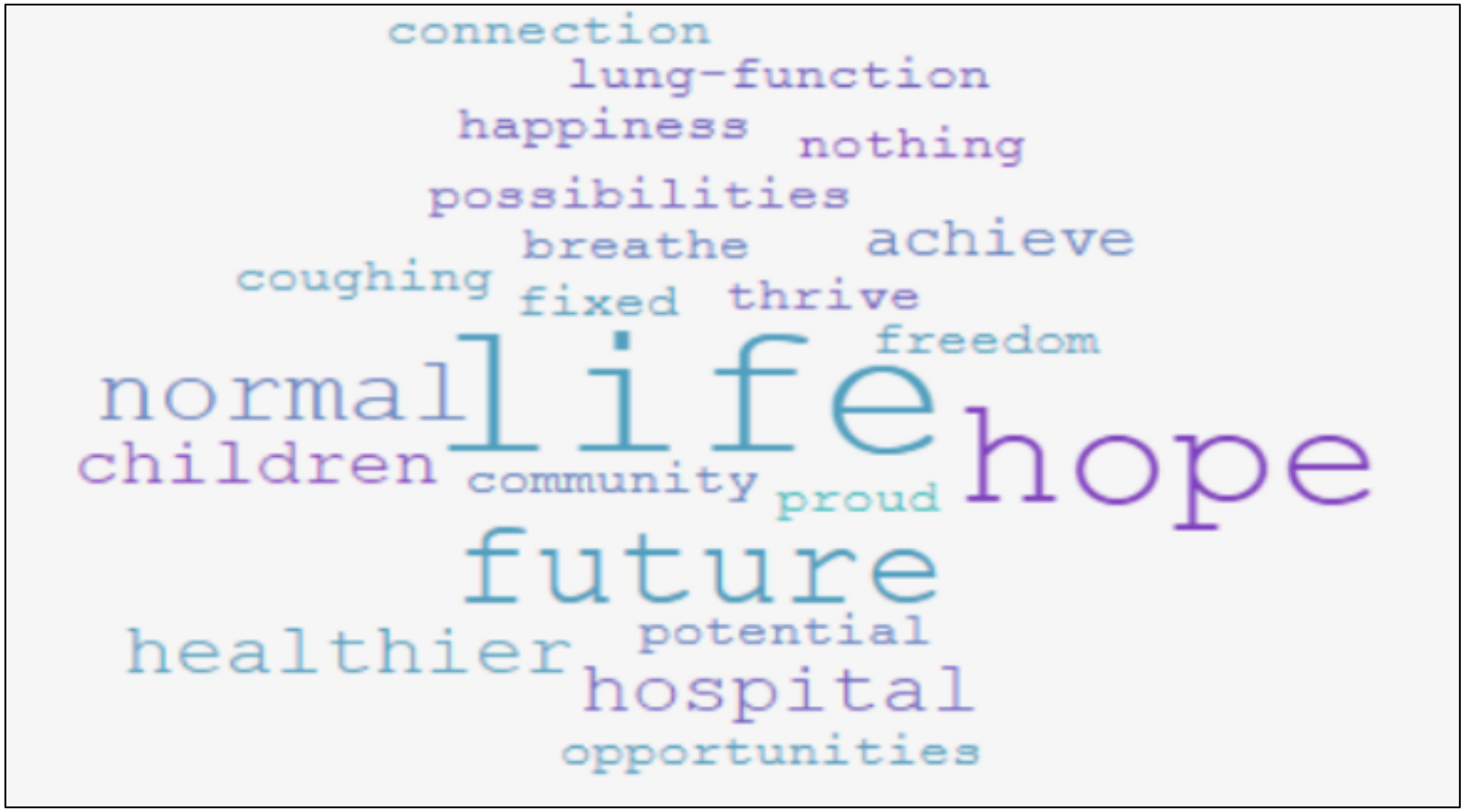
"My son no longer has sinus problems, he needs fewer pancreatic enzymes, and has had no time in hospital for nearly 2 years. He doesn't need to do any airway clearance physiotherapy anymore"

"My daughter's lung function went down to 44% last year and thanks to Kaftrio it is back up to 90%. I don't think this would have been possible without modulators."

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Patient perspectives – life after CFTR modulators (2/3)

Figure 1: Word cloud* of responses from young people living with CF, after Kaftrio



Notes: *Words appear larger depending on the frequency they were mentioned.
Source: Cystic Fibrosis Trust's Youth Advisory Group

Patient perspectives – life after CFTR modulators (3/3)

Cystic Fibrosis Trust ran an online survey between February and March 2023:

- 66% of survey respondents felt that access to CFTR modulators had significantly improved their quality of life, with 25% reporting an improved quality of life
- 80% of survey respondents felt significantly more positive about the future of living with CF because of access to CFTR modulators, with 15% reporting feeling slightly more positive
- Some of the CF community are apprehensive about the long-term use of such transformative medicines, particularly the mental health effects and challenges around weight gain

"It gives options which were never necessarily there before…I feel positive about my future for the first time ever…which is a wonderful thing."

"I had 35 years to learn how to eat, you know, eat everything and so to suddenly have that big change psychologically of actually having to watch what I'm doing…it's a lot"

"I've gotten so used to being sick during my childhood that the prospect of being so well feels slightly unknown and scary to me. I'm fully versed on how to be sick, not so much on how to be healthy."

"I believe the mental effects of having these new tablets can be very overwhelming and having lived your whole life with the idea that you'll die younger and having to retrain your mind to the fact that you will live longer – there should be more help regarding that"

NICE

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Carer perspective – life after CFTR modulators

- CFTR modulators have had hugely positive effects on carers directly as well as patients
- There have been immediate psychological boosts for carers, possibly translating into mental health improvements
- The future now appears vastly different and the improvement in family life is substantial
- Carers of very young eligible patients, receiving a diagnosis, will never experience the same as carers have previously because the condition has been changed so dramatically
- Some parents have described the difficulty of their child coming to terms with a different identity since starting modulator treatment

"My constant anxiety has finally ebbed away, and we can plan more confidently. Wider family and friends no longer worry regularly about us."

"The ability to say you're not hungry. That's fine. You don't have to finish your plate is a joy. I love that."

"Everything about our family life has really been more positive. He's up for going out. He's very artistic and has been in the workshop a lot more. It's a better household to be in. The impact on us as a family has been amazing"

"She doesn't know who she is without CF. She missed so much school and qualifications. What kind of job can she do now?"

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Clinical expert perspectives

Benefits of CFTR modulators include:

- Improved lung function and airway clearance
- Improved nutrition and weight, and reduced the need for nutritional supplementation
- Reduced hospital admissions, bed days and the need for IV antibiotics – although some professional organisations had concerns about long-term reductions
- Reduced outpatient review appointments
- Reduced referrals for lung transplants – with some people being removed from waiting lists
- Easier for females to conceive
- Improved quality of life for both patients and carers
- Increased productivity at work and school

"People with CF being healthier is a huge weight lifted off the shoulders of parents and carers"

"Monitoring for side effects is straightforward and in line with SmPC"

"Prior to CFTR modulator therapies there were no treatment for patients that addressed the basic cause of the condition"

"There is still an unmet need for a modulator treatment for rarer genotypes."

NICE

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; IV, intravenous; SmPC, Summary of Product Characteristics.

Professional organisations – life before CFTR modulators

- CF is a multiorgan disease, dominated by respiratory manifestations, eventually lead to bronchiectasis, respiratory failure and need for lung transplant
- People with CF experience considerable morbidity despite high treatment burden with current standard care, in particular physiotherapy, multiple inhaled/nebulised treatments, airway clearance, exercise and oral medicines
- Prior management consisted of managing symptoms including airway clearance, antibiotics, and nutritional support
- Despite conventional therapy, people with CF still had shorter life expectancy and decreased quality of life
- Before CFTR modulators, there was an urgent unmet need for treatments to address the underlying cause of CF

"many [people with CF are] still dying in childhood or young adult life"

"There is an urgent need for therapies that correct the underlying genetic and molecular defect"

NICE

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Professional organisations – life after CFTR modulators

- It is important to assess these technologies independently and not conflate results
- Triple modulator therapy has improved the lung function, nutritional status and growth and quality of life of eligible patients
- Average age of death has increased from 31 in 2019 to 38 in 2021
- 10% of people with CF are ineligible - continue to experience deterioration with higher rates of lung transplant referral and death
- People are reducing uptake of 'standard care', despite advice to continue – lack of data on impact of this
- Overall safety profile is good. Some predictable side effects (elevated liver markers, etc) and some significant, less predictable and less understood effects, such as mental health issues
- Potential to reduce health inequalities
- No agreement on clinically meaningful benefit for outcomes

"[clinically meaningful benefits have been demonstrated] since interim access, with improved lung function, quality of life and with meaningful changes to the ability to achieve life events, for example pregnancies"

"This therapy has a profound impact on the lives of our patients, impacting social and life experiences"

"Access to appropriate care for those ineligible or unable to tolerate the technologies needs to be considered"

NICE

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Potential equalities issues and other considerations

- Marketing authorisations for all CFTR modulators require at least 1 F508del mutation
- Around 10% of people do not have an F508del mutation and these people are more likely to be from Black, Asian and Minority ethnic backgrounds
    - For people not eligible, *"being in a clinic where 85% of your peers are getting what is billed as a 'wonder drug' by the media has been very difficult for several of our families"*

- Health inequalities are significant in CF:
    - The care provided depends much on the carer's available time/resources and ability to care
    - People with lower socioeconomic status have poorer outcomes. CTFR modulators could reduce health inequalities in people who are less supported financially and socially
    - There is still potential for a lack of equity in outcomes if support for co-adherence to inhaled therapy is not adopted

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Key issues

#	Issue	Resolved?	ICER impact
Clinical-effectiveness			
1	Long-term rate of ppFEV1 decline – ECM	No	Large
2	Long-term relative reduction in ppFEV1 decline – CFTR modulators	No	Large
3	Pulmonary exacerbations (PEx) treatment effect duration	No	Unknown
4	Compliance (post-acute)	No	Small
5	Co-adherence to ECM	No	Unknown
Cost-effectiveness			
6	Suitability of EAG's model for decision making	Unknown	Unknown
7	Health state utility values (EQ-5D versus CFQ-R)	No	Large
8	Treatment-specific utility benefit	No	Large
9	Caregiver utility benefit	No	Small
10	Disease management costs	No	Small
11	Annual discount rates	No	Large
12	Severity modifier	No	Large

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR, cystic fibrosis transmembrane conductance regulator; EAG, External Assessment Group; ECM, established clinical management; EQ-5D, EuroQol-5-dimensions; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second.

Decision problem – population and subgroups

- All CFTR modulators included this MTA are indicated for people with CF who have an F508del mutation
- ~90% of people with CF have this mutation
- The choice of treatment is dependent on specific genotype and age group
  - ELX/TEZ/IVA for aged 6+* with at least 1 F508del mutation (F/any genotype)
  - LUM/IVA is licenced for aged 1+ with F/F genotype
  - TEZ/IVA for aged 6+ with F/F or F/RF genotype
- The median age of people with CF is 21 years (UK CF Registry 2021)

Table 1: The prevalence of CF genotypes of people with CF aged 6+

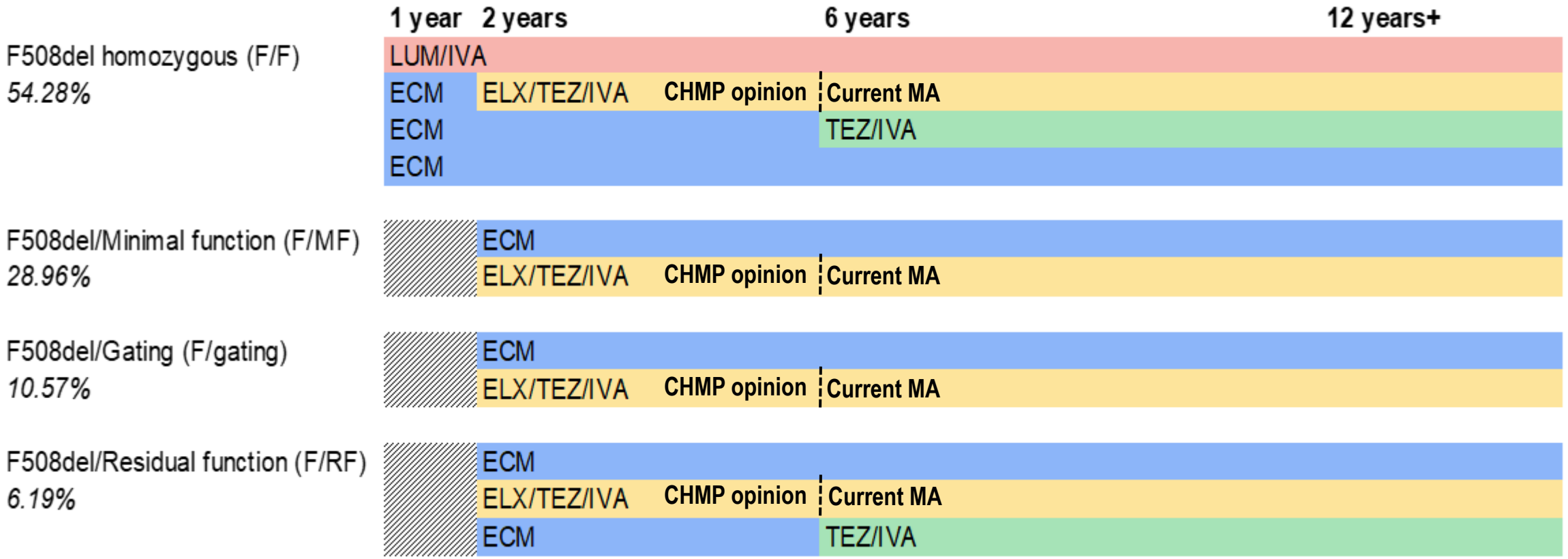
Subgroup / genotype	Notation	% prevalence of all CF genotypes		% of genotypes in scope
		England	Wales	
homozygous for the F508del mutation	F/F	[redacted]	[redacted]	54.28%
heterozygous for the F508del mutation and a minimal function mutation	F/MF	[redacted]	[redacted]	28.96%
heterozygous for the F508del mutation and a residual function mutation	F/RF	[redacted]	[redacted]	6.19%
heterozygous for the F508del mutation and a gating function mutation	F/Gating	[redacted]	[redacted]	10.57%

*** ELX/TEZ/IVA has CHMP positive opinion for children aged 2-5**

Abbreviations: CF, cystic fibrosis; CHMP, Committee for Medicinal Products for Human Use; CFTR, cystic fibrosis transmembrane conductance regulator; MTA, multiple technology appraisal. **Source:** UK CF registry, 2021.

Decision problem – interventions and comparators

Licenced treatments by genotype and age group



Note: All CFTRm's given in combination with ECM, ELX/TEZ/IVA and TEZ/IVA given in combination with ivacaftor monotherapy

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CFTRm, Cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management; ELX/TEZ/IVA, elexacaftor–tezacaftor–ivacaftor; LUM/IVA, lumacaftor–ivacaftor; TEZ/IVA, tezacaftor–ivacaftor.

Decision problem – outcomes and interpretation

Commonly reported outcomes

Outcome	Definition and interpretation
Sweat chloride	• Used for diagnosis, as chloride can be elevated in the sweat of people with CF • A sweat chloride concentration of <40 mmol/L is considered normal, whereas a concentration >60 mmol/L supports a diagnosis of CF • Increased sweat chloride = increased severity of CF
Percent-predicted forced expiratory volume in one second (ppFEV1)	• Measure of lung function, representing the volume of air that can be blown out in the first second • Increased ppFEV1 = better lung function
Pulmonary exacerbations (PEx)	• Acute worsening of symptoms usually associated with infection and requiring IV antibiotics • Fewer PEx = slower rate of lung function decline and better quality of life
Weight-for-age z-score	• Marker of the effect of CF on the digestive system and growth / weight • Z-score of 0 = population mean • Z-score of -1 = one standard deviation below the population mean • Increased z-score = increased growth / weight

What is a clinically significant change for each of these outcomes?

Abbreviations: CF, cystic fibrosis; IV, intravenous; ppFEV1, percent predicted forced expiratory volume in 1 second.

Decision problem – outcomes and interpretation

Other outcomes

Outcome measure	Definition and interpretation
Lung clearance index 2.5 (LCI2.5)	• A measure of lung function in younger children where ppFEV1 is difficult to measure or unreliable • LCI2.5 measures the number of lung volume turnovers required to clear a tracer gas to 2.5% of its starting volume • A lower LCI2.5 = better lung function
Pulmonary bacterial colonisation	• Chronic infection of the lung with *pseudomonas aeruginosa* or other bacterial species • Associated with lung function decline, morbidity and mortality
Pancreatic insufficiency and CF related diabetes (CFRD)	• Inability to pancreatic enzymes to reach the digestive system, requires pancreatic enzyme replacement therapy (PERT) • Pancreatic insufficiency is a marker of CF severity • Damage to endocrine function of pancreas can lead to CFRD
Cystic Fibrosis Questionnaire-Revised (CFQ-R)	• CF-specific measure of health-related quality of life (HRQL), on a 0-100 scale • Higher CFQ-R score = better HRQL

Abbreviations: ppFEV1, percent predicted forced expiratory volume in 1 second.

Clinical effectiveness – acute outcomes

NICE National Institute for Health and Care Excellence

Clinical trials

Overview of randomised controlled trials used for **acute** changes in outcomes

#	Study	Genotype	Age	Interventions, comparators
1	Sutharsan 2022	F/F	12+	ELX/TEZ/IVA, TEZ/IVA
2	Barry 2021	F/RF, F/Gating	12+	ELX/TEZ/IVA, TEZ/IVA, IVA
3	Middleton 2019	F/MF	12+	ELX/TEZ/IVA, Placebo
4	Heijerman 2019	F/F	12+	ELX/TEZ/IVA, TEZ/IVA
5	Mall 2022	F/MF	6 to 11	ELX/TEZ/IVA, Placebo
6	Zemanick 2021	F/F, F/MF	6 to 11	ELX/TEZ/IVA
7	NCT04537793	F/F, F/MF	2 to 5	ELX/TEZ/IVA
8	Taylor-Cousar 2017	F/F	12+	TEZ/IVA, Placebo
9	Rowe 2017	F/RF, F/Gating	12+	TEZ/IVA, Placebo, IVA
10	Davies 2021	F/F, F/RF	6 to 11	TEZ/IVA, Placebo, IVA
11	Walker 2019	F/F, F/RF	6 to 11	TEZ/IVA
12	TRAFFIC	F/F	12+	LUM/IVA, Placebo
13	TRANSPORT	F/F	12+	LUM/IVA, Placebo
14	Wilson 2021	F/F	12+	LUM/IVA, Placebo
15	Ratjen 2017	F/F	6 to 11	LUM/IVA, Placebo
16	Stahl 2021	F/F	2 to 5	LUM/IVA, Placebo
17	McNamara 2019	F/F	2 to 5	LUM/IVA
18	Rayment 2022	F/F	1 to 2	LUM/IVA
19	Ramsey 2011	F/Gating, G551D mutation	12+	IVA, Placebo
20	De Boeck 2014	F/Gating, non-G551D mutation	6+, 12+ subgroup	IVA, Placebo
21	Moss 2015	F/R117H mutation	6+, 12+ subgroup	IVA, Placebo

Clinical effectiveness – acute outcomes

EAG preferred data sources for **acute** outcomes

Subgroup	F/F genotype	F/MF genotype	F/RF genotype	F/Gating genotype
12+ years	ELX/TEZ/IVA vs TEZ/IVA vs LUM/IVA vs PBO	ELX/TEZ/IVA vs PBO	ELX/TEZ/IVA vs TEZ/IVA vs PBO	ELX/TEZ/IVA vs PBO
6 to 11 years	ELX/TEZ/IVA vs TEZ/IVA vs LUM/IVA vs PBO	ELX/TEZ/IVA vs PBO	ELX/TEZ/IVA vs TEZ/IVA vs PBO	ELX/TEZ/IVA vs PBO
2 to 5 years	ELX/TEZ/IVA vs LUM/IVA vs PBO	ELX/TEZ/IVA vs PBO	ELX/TEZ/IVA vs PBO	ELX/TEZ/IVA vs PBO
1-2 years	LUM/IVA vs PBO	No interventions	No interventions	No interventions

All treatments and placebo given in combination with ECM. ELX/TEZ/IVA included in aged 2-5 age group based on CHMP positive opinion

RCT data
Single-arm trial data
NMA
No data / no interventions

Notes: An accessible version of this table can be provided on request to tateam5@nice.org.uk.
Abbreviations: CHMP, Committee for Medicinal Products for Human Use; ELX/TEZ/IVA, elexacaftor–tezacaftor–ivacaftor; LUM/IVA, lumacaftor–ivacaftor; RCT, randomised controlled trial; TEZ/IVA, tezacaftor–ivacaftor; PBO, placebo.

EAG preferred inputs for acute increase in ppFEV1

Key outcome: ppFEV1 absolute change from baseline vs placebo at week 24 (week 8 for F/Gating and F/RF genotypes)

	Aged 12+		Aged 6-11	
	Acute increase in ppFEV1 (95% CI)	Data source	Acute increase in ppFEV1 (95% CI)	Data source
F/F genotype				
LUM/IVA	2.83 (1.84 to 3.82)	Ratjen 2017 (RCT)	2.4 (0.4 to 4.4)	Ratjen 2017 (RCT)
ELX/TEZ/IVA	14.20 (12.07 to 16.31)	EAG NMA	11.2 (7.2 to 15.2)	Zemanick 2022 (single arm)
TEZ/IVA	4.0 (3.1 to 4.8)	Taylor-Cousar 2017 (RCT)	2.8 (1.0 to 4.6)	Davies 2021 (single arm)
F/MF genotype				
ELX/TEZ/IVA	14.3 (12.7 to 15.8)	Middleton 2019 (RCT)	11.0 (6.9 to 15.1)	Mall 2022 (RCT)
F/Gating genotype				
ELX/TEZ/IVA	[redacted]	EAG NMA	11.0 (6.9 to 15.1)	Assumed equal to F/MF
F/RF genotype				
ELX/TEZ/IVA	8.80 (7.01 to 10.61)	EAG NMA	6.776 (4.99 to 8.57)	EAG analysis
TEZ/IVA	6.8 (5.7 to 7.8)	Rowe 2017 (crossover RCT)	2.8 (1.0 to 4.6)	Davies 2021 (single arm)

Clinical effectiveness – longer-term outcomes

NICE National Institute for Health and Care Excellence

Key issue 1: Long-term rate of ppFEV1 decline – ECM (1/2)

EAG

- Modelled a **non-linear** long-term decline in ppFEV1 for people on ECM based on Szczesniak (2023):
  - Natural history cohort of 35,252 people aged 6+ with CF in the US Cystic Fibrosis Foundation Patient Registry (CFFPR)
  - Based on data from between 2003 and 2016
  - Provided curves for rate of change vs age for F/F genotype and overall CF population
  - Reported on different methodologies used to model ppFEV1 decline – concluded that the best fitting model was non-linear stochastic mixed-effects model
  - Conclusion – rate of decline decreases with age
- EAG applied digitised values for the F/F population to the F/F, F/MF and F/Gating populations
- EAG applied digitised values for the overall CF population for the F/RF population as this group has a slower rate of lung function decline

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 1: Long-term rate of ppFEV1 decline – ECM (2/2)

Company

- Prefers to model the long-term decline in ppFEV1 based on Sawicki (2022):
  - A retrospective study investigating lung function decline across different age groups in CFTR modulator-untreated people with CF
  - Used data from the US CFFPR between 2006 and 2014
  - Reported separate **linear** rates of decline for ages 6-12, 13-17, 18-24 and 25+
    Reported separate rates according to genotype (F/RF versus all remaining)
  - After age 25 same constant annual rate of decline was applied, equal to -1.06 for F/RF genotype and -1.86 for all remaining genotypes
- EAG's preferred source does not have an exclusion criterion for people on CFTR modulators and may have included these people in the analysis
- EAG's assumption [that people with the F/RF genotype have the same rate of decline as the overall CF population] indicates that people with this genotype decline faster than observed by Sawicki (2022)

What is the most appropriate source for the long-term relative reduction in ppFEV1 decline with ECM?

Abbreviations: CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; ppFEV1, percent predicted forced expiratory volume in 1 second.

Clinical evidence CFTRm – open-label extension studies

Open-label extension studies provide data on **longer-term** outcomes

#	OLE study	N	Start date	Primary comp. date	Vertex Protocol Number	Genotype	Age	Intervention
1	Griese 2022	N=507	Oct 2018	Jan 2023	VX17-445-105	F/F, F/MF	12+	ELX/TEZ/IVA
2	Ratjen 2021	N=64	Feb 2020	Apr 2024	VX19-445-107	F/F, F/MF	6+	ELX/TEZ/IVA
3	Study 445-110	N=251	Dec 2019	Dec 2022	VX18-445-110	F/RF, F/Gating	12+	ELX/TEZ/IVA
4	Flume 2021	N=1131	Aug 2015	May 2019	VX14-661-110	F/F, F/RF	12+	TEZ/IVA
5	Sawicki 2022	N=130	Apr 2018	Oct 2020	VX17-661-116	F/F, F/RF	6+	TEZ/IVA
6	Konstan 2017	N=1164	Oct 2013	Apr 2016	VX12-809-105	F/F	12+	LUM/IVA
7	Chilvers 2021	N=246	Aug 2015	Aug 2018	VX15-809-110	F/F	6+	LUM/IVA

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; OLE, open label extension;

Key issue 2: Long-term relative reduction in ppFEV1 decline – CFTR modulators

Table 1: EAG and company preferred sources for relative reduction in ppFEV1 decline

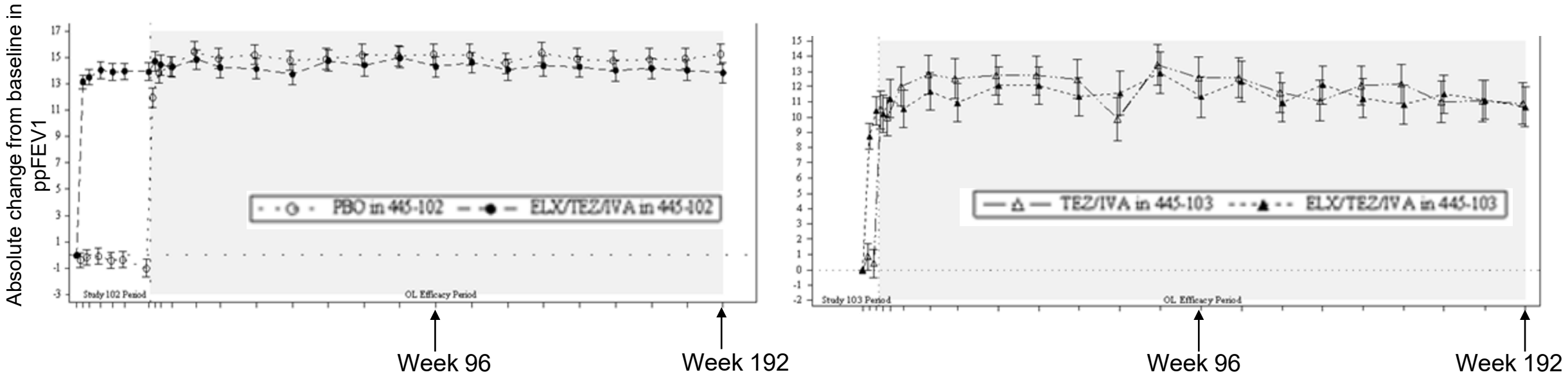
	EAG	Source	Company	Source
ELX/TEZ/IVA	61.0%	Newsome (2022) – based on IVA monotherapy, adjusted according to acute treatment effect of IVA versus ELX/TEZ/IVA	100%	Lee (2023) Griese (2022) – VX17-445-105
TEZ/IVA	17.2%	Assumption based on ratio of acute treatment effect between TEZ/IVA and ELX/TEZ/IVA	61.5%	Flume (2021)
LUM/IVA	0%	Assumed no long-term treatment effect	42%	Konstan (2017)
[redacted]				

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry.

Clinical evidence – OLE studies, Griese 2022, VX17-445-105

Company preferred source for long-term ppFEV1 decline for ELX/TEZ/IVA

Figure 1: Absolute change from parent studies **(left)** 445-102 (F/MF) and **(right)** 445-103 (F/F) baseline in ppFEV1 at each visit up to Week 192 in the OLE Study 445-105



- Start date: 9 October 2018
- Primary completion date: 9 January 2023

Abbreviations: OLE, open-label extension; ppFEV1, percent predicted forced expiratory volume in 1 second.

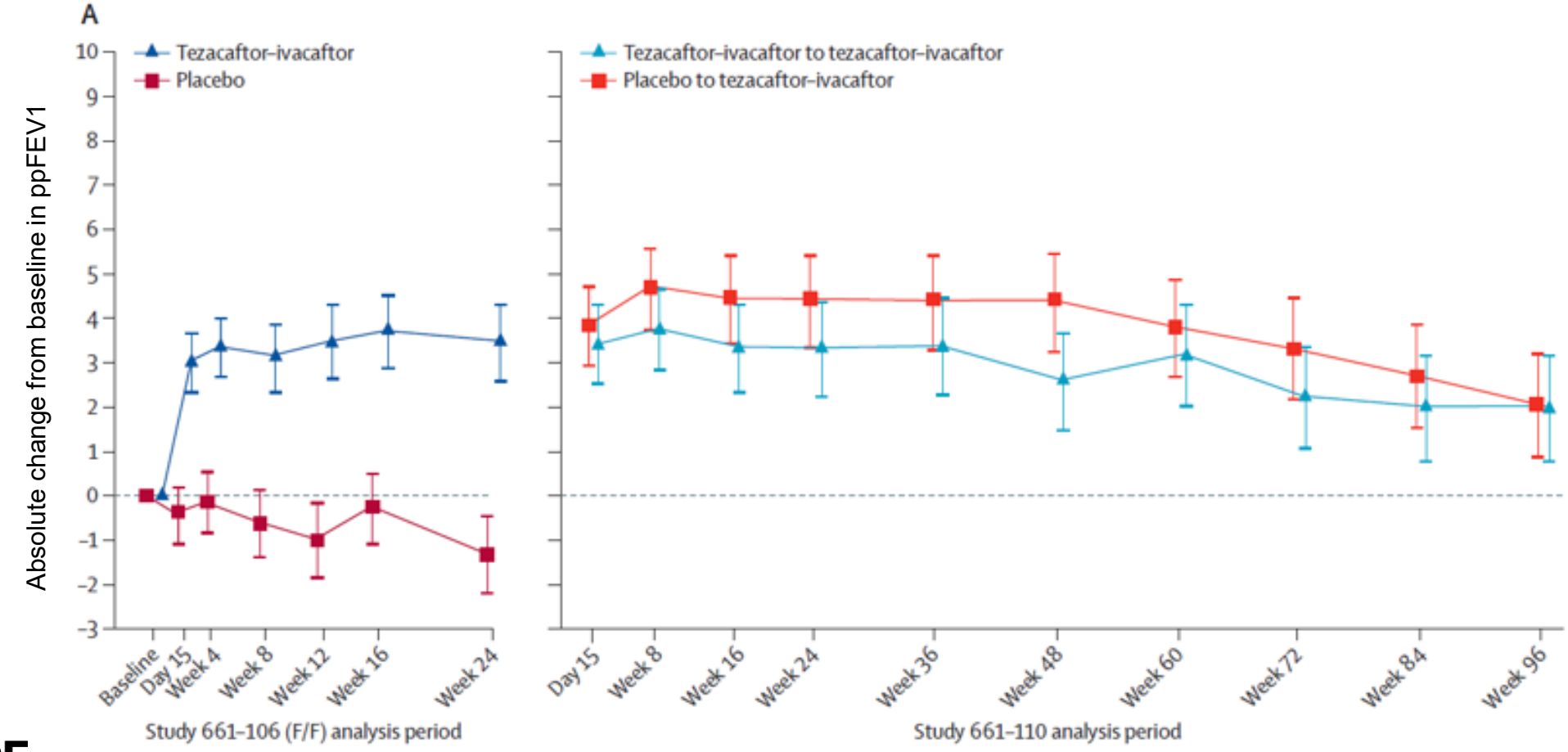
Clinical evidence CFTRm – company analysis of UK Cystic Fibrosis Registry data, longer-term ppFEV1, ELX/TEZ/IVA

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second.

Clinical evidence CFTRm – OLE studies, long-term ppFEV1, TEZ/IVA, Flume 2021, VX14-661-110

Company preferred source for long-term ppFEV1 decline for TEZ/IVA

Figure 1: Absolute change from baseline in ppFEV1 – study 661-110 (F/F)

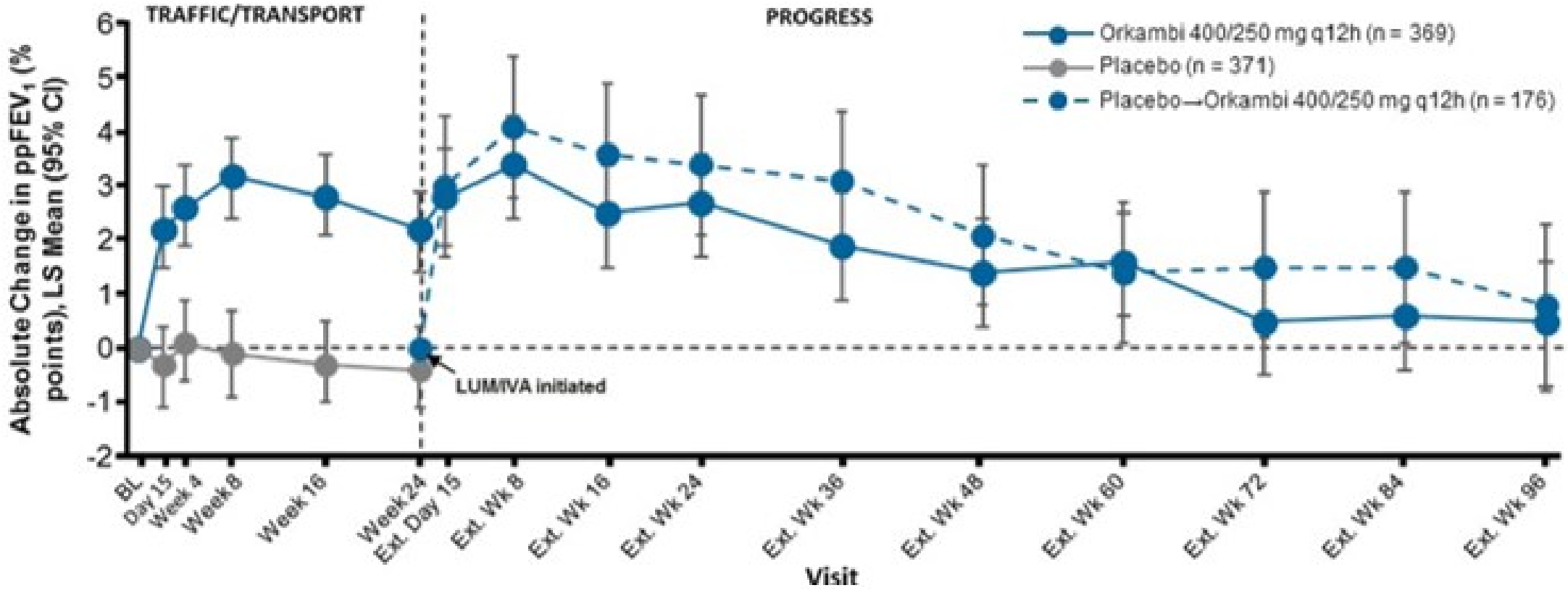


Abbreviations: OLE, open-label extension; ppFEV1, percent predicted forced expiratory volume in 1 second.

Clinical evidence CFTRm – OLE studies, long-term ppFEV1, LUM/IVA, Konstan 2017, F/F

Company preferred source for long-term ppFEV1 decline for LUM/IVA

Figure 1: Absolute change from baseline in ppFEV1 – Konstan 2017 (F/F)



Abbreviations: OLE, open-label extension; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 2: Long-term relative reduction in ppFEV1 decline – CFTR modulators – ELX/TEZ/IVA

EAG

- Considered a range of longer-term data sources including the open-label extension studies and the company's analysis of the data collection agreement to inform rate of decline for ELX/TEZ/IVA
- However, these studies are at high risk of overestimating the treatment benefit of ELX/TEZ/IVA:
  - No control group
  - Viral shielding due to COVID-19 pandemic may have prevented lung function decline
  - Acute effects of treatment not adequately removed
- Prefers to use data for IVA monotherapy based on Newsome (2022) which is not affected by COVID-19
- Estimates adjusted based on ratio of acute treatment effect between IVA monotherapy and ELX/TEZ/IVA
- EAG considers base case not to be conservative as the treatment effect applied for lifetime in model
- Alternative scenarios explored with both more conservative and more favourable assumptions

Company

- Data was collected during data collection agreement specifically to inform this appraisal
- Prefers to use data from OLE studies which show no decline in ppFEV1:
  - Improvements in ppFEV1 in RCTs (445-102) and (445-103) for F/MF and F/F genotype, respectively, were maintained throughout the 192-week OLE study (445-105)
  - Mean annualised rate of change in ppFEV1 for ELX/TEZ/IVA was 0.02 (95% CI -1.04,0.19)
  - This covered a time period before, during and after COVID-19

NICE

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second; OLE, open-label extension; UKCFR, UK Cystic Fibrosis Registry.

Key issue 2: Long-term relative reduction in ppFEV1 decline – CFTR modulators – TEZ/IVA, LUM/IVA

EAG

- Unlike ELX/TEZ/IVA, OLE studies for TEZ/IVA and LUM/IVA were completed prior to COVID-19
- Company performed post-hoc comparisons with ECM using propensity score matched-control analyses with historical US CF Registry data
- However, company's analyses at high risk of underestimating rate of ppFEV1 decline:
  - Unlikely that all confounding will have been adjusted for when comparing trial participants with historical registry controls
  - Inadequate removal the acute treatment effect
- Prefers to assume relative reduction in long-term ppFEV1 decline for TEZ/IVA based on ratio of acute treatment effect between TEZ/IVA and ELX/TEZ/IVA
- Prefers to assume no reduction in the rate of long-term ppFEV1 decline for LUM/IVA

Company

- EAG's assumptions-based approach is not appropriate
- Company's propensity score matched analysis unlikely to underestimate rate of ppFEV1 decline and consistent with literature estimates. Company's preferred rates for mean annual decline in ppFEV1:
  - LUM/IVA: -1.33 vs -2.29 in untreated matched controls = 42% reduction
  - TEZ/IVA: -0.80 vs -2.08 in untreated matched controls = 61.5% reduction

NICE

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second; OLE, open-label extension;.

Key issue 2: Long-term relative reduction in ppFEV1 decline – CFTR modulators

Patient and professional groups

- Disheartening that the data collection which involved a lot of work by clinicians, patient groups, NICE and Vertex, has not been used
- No concerns were raised about the data collection agreement in light of the COVID-19 pandemic
- EAG's evidence for preserved lung function during COVID-19 was based on an Australian study – government restrictions within Australia differed to the UK
- There may also be a negative effect on lung function during the COVID-19 pandemic through reduced ability for physical activity
- We hope that the committee, with full sight of the final data collection analysis, can assess the data pragmatically with a measured approach to COVID-19 confounding
- Analyses to understand the full impact of the COVID-19 pandemic on lung function in CF will require longer-term data collection

How has the COVID-19 pandemic impacted on lung function for people with CF?
What was/is the extent of viral shielding during and after the COVID-19 pandemic?
What is the most appropriate source for the long-term relative reduction in ppFEV1 decline with ELX/TEZ/IVA, TEZ/IVA and LUM/IVA?

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 3: Pulmonary exacerbations treatment effect duration

EAG

- Annual pulmonary exacerbation (PEx) rates are a function of ppFEV1
- There is a risk of double counting if separate treatment effects are applied for both ppFEV1 and PEx
- To adjust for this, calibration techniques were used to derive a rate ratio for PEx for CFTR modulators versus ECM to account for the acute ppFEV1 increase (**Table 1**)
- Calibrated rate ratio for PEx applied in the acute period only
- No separate treatment effect on PEx, beyond that applied through the effect on ppFEV1, is applied long term

Table 1: PEx calibrated rate ratios

Genotype	Treatment	EAG	Company
F/F	LUM/IVA	[redacted]	[redacted]
	ELX/TEZ/IVA	[redacted]	[redacted]
	TEZ/IVA	[redacted]	[redacted]
F/MF	ELX/TEZ/IVA	[redacted]	[redacted]
F/Gating	ELX/TEZ/IVA	[redacted]	[redacted]
F/RF	ELX/TEZ/IVA	[redacted]	[redacted]
	TEZ/IVA	[redacted]	[redacted]

Company

- Prefers to apply a separate PEx treatment effect (rate ratio) for patients' lifetime
- OLE data (Study 445-105) showed a 78% and 71% reduction in annualised PEx requiring treatment with antibiotics or leading to hospitalisation, respectively
- Real world DCA data provide evidence to support the long-term decline on PEx – lower annualised rate of PEx with ELX/TEZ/IVA, with a [redacted] in the annual rate of PEx

How long should the PEx treatment effect be applied for?

Abbreviations: DCA, data collection agreement; ECM, established clinical management; OLE, open label extension

Key issue 4: Compliance (post-acute)

EAG

- Compliance during the acute period was based on the key clinical trials for each genotype and age group
- EAG assumed 100% compliance following the acute period:
  - As impact of compliance in model is through reduction in costs, applying a lower compliance rate beyond trial period would not account for differences in efficacy that result from lower compliance
- EAG's clinical experts expect compliance to remain high due to the quick decline in health that is experienced when people discontinue

Company

- Prefers to assume compliance rate of [redacted]% following the acute period
- This is based on UKCFR evidence collected during the data collection agreement on compliance rates for all treatments:
  - [redacted]
  - [redacted]

EAG response

- Provided an additional scenario analysis with [redacted]% compliance, but notes the uncertainty around applying this for a lifetime horizon

What is the rate of compliance after the acute period?

Abbreviations: CF, cystic fibrosis; UKCFR, UK Cystic Fibrosis Registry.

Key issue 5: Co-adherence to ECM

EAG

- Clinical outcomes for people treated with CFTR modulators may be influenced by co-adherence to ECM therapies, such as inhaled mucolytics and prophylactic antibiotics
- Reduced co-adherence may lessen the real-world effectiveness of CFTR modulators

Professional group comments:

- Reduced use of nebulised therapies, pancreatic enzymes and insulin observed in clinical practice is a result of reduced need and not a reflection of lack of adherence
- It is likely that a difference in co-adherence to inhaled therapy between the highly engaged trial/open label extension participants and the real world play an important role
- Benefit observed in clinical trials and data collection agreement may reduce long-term without measuring and supporting co-adherence to inhaled therapy

Will co-adherence to ECM influence clinical outcomes for people treated with CFTR modulators?

Abbreviations: ECM, established clinical management; CFTR, cystic fibrosis transmembrane conductance regulator.

Cost effectiveness

Cost-effectiveness results are confidential and will be presented in Part 2 of this meeting

Economic model

EAG's critique of company's model

- Company submitted 3 separate models, one for each intervention – no incremental analysis was presented
- Models did not include all age groups covered by licence extensions
- Some aspects of company model were not aligned with NICE reference case:
  - Use of 1.5% discount rate for health outcomes
  - Use of non-EQ-5D generated utility values
- Some company assumptions may be inappropriate or lack clinical validity

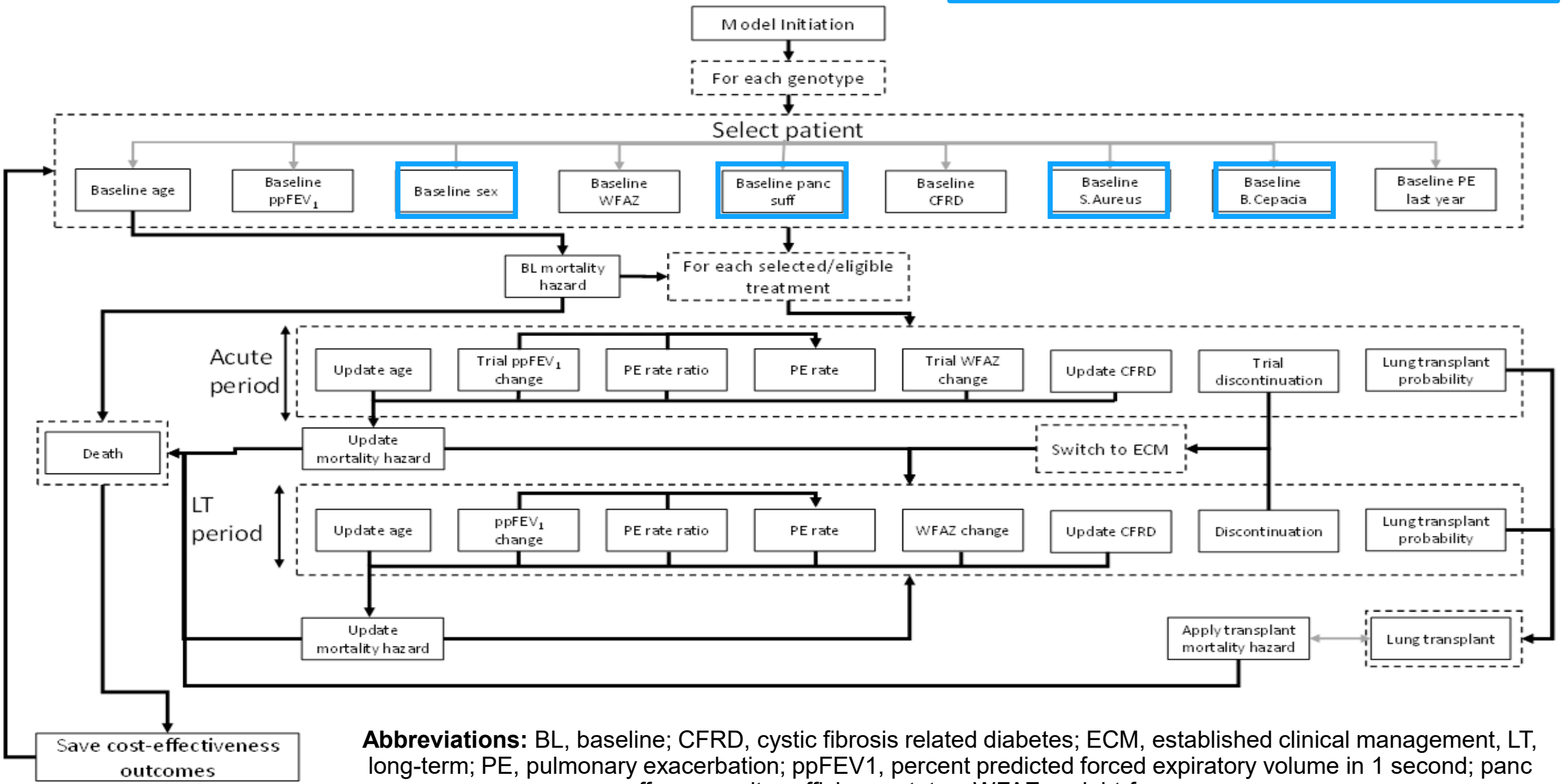
EAG's model

- Patient level microsimulation, which included all three treatments and a full incremental analysis
- Model largely followed the structure of the models submitted by the company and used in TA398, as well as CF models used by other HTA agencies
- Model predicted survival using a Cox proportional hazards model (Liou 2001), which was based on nine individual characteristics:
  - Age, sex, weight-for-age z score, ppFEV1, pulmonary exacerbations, *S. aureus* infection, *B. cepacia* infection, pancreatic sufficiency status and CFRD status
- The model used a lifetime horizon with discount rates of 3.5% for costs and QALYs
- The perspective of the analysis was NHS and personal social services (PSS) in England

Abbreviations: CFRD, cystic fibrosis-related diabetes; EQ-5D, EuroQoL-5-dimensions; HTA, health technology assessment; ppFEV1, percent predicted forced expiratory volume in 1 second; QALY, quality-adjusted life year.

EAG's model structure

Characteristics in the blue boxes are assumed to remain constant in each cycle



Abbreviations: BL, baseline; CFRD, cystic fibrosis related diabetes; ECM, established clinical management, LT, long-term; PE, pulmonary exacerbation; ppFEV1, percent predicted forced expiratory volume in 1 second; panc suff, pancreaitc sufficiency status; WFAZ, weight-for-age z score

Key issue 6: Suitability of EAG's model for decision making

Company

- Identified several technical errors in the EAG's model, which have a significant impact on the ICER
- The complexity of the equations and programming used are not in line with general good practices in economic modelling
- This has led to the model being slow and unresponsive, and extremely long run times
- The company's original submission model should be used as this has been thoroughly quality-control checked, peer-reviewed and published
- It has also received favourable feedback from several HTA organisations, including NICE in TA398

EAG response

- Technical errors identified have now been corrected
- Notes that the incorporation of model fixes did not have a substantial impact on any of the ICERs
- EAG's model uses the same structure of that used by the company but with updates to key clinical parameters. It recovers key features of CF that the company model does not
- When incorporating the company's preferred assumptions in the EAG's model, similar ICERs are generated (see next slide)

Abbreviations: HTA, health technology assessment; ICER, incremental cost effectiveness ratio.

Key issue 6: Suitability of EAG's model for decision making

EAG response

- Additional quality assurance step, used company preferred assumptions for ELX/TEZ/IVA in EAG model and compared to company original submitted model in ages 6+ years using list prices
- EAG model not an exact replicate of company model so some expected differences in costs in both the ECM and ELX/TEZ/IVA arms, but results are largely similar and resulting ICERs broadly comparable, providing evidence of reliability of the EAG model

	F/F population		F/MF population		F/gating population		F/RF population	
	EAG model	Company model	EAG model	Company model	EAG model	Company model	EAG model	Company model
ECM QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA QALYS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (no severity modifier)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Is the EAG's model suitable for decision making?

Abbreviations: ECM, established clinical management; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

EAG's model inputs and evidence sources (1/3)

Input	Evidence source / assumption	EAR section
Patient characteristics	• **Baseline characteristics** – clinical trials, UK CF Registry, assumptions • **ppFEV1 decline** – non-linear decline with age based on Szczesniak (2023) • **PEx frequency** – included as a function of age and ppFEV1 based on formula derived by Whiting (2014) • **CFRD status** – incidence by age group and sex based on UK CF Registry data, 1996-2005	4.2.1.5
Effectiveness (acute)	• CTFR modulators assumed to have a treatment effect on ppFEV1, PEx number and weight-for-age z score • Inputs used in model presented in back up slides 73 onwards • Assumptions were used where there were data gaps	4.2.1.6.1
Effectiveness (long-term relative reduction, ppFEV1 decline)	• For ELX/TEZ/IVA, based on rate of decline for IVA monotherapy from UK CF Registry, adjusted according to acute tx effect of IVA versus ELX/TEZ/IVA • For TEZ/IVA, relative reduction in ppFEV1 decline calculated based on ratio of acute effect between TEZ/IVA and ELX/TEZ/IVA • For LUM/IVA assumed 0% relative reduction in decline compared to ECM	4.2.1.6.2

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis-related diabetes; EAR, external assessment report; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second.

EAG's model inputs and evidence sources (2/3)

Input	Evidence source / assumption	EAR section
Discontinuation rate	• **Acute period** – trial data • **Long-term** – no discontinuation beyond year 5	4.2.1.7
Compliance	• **Acute period** – trial data • **Long-term** – assumed 100%	4.2.1.8
Lung transplantation	• **Probability** – 20.3% based on UK CF Registry (2019), applied as one-off when ppFEV1 < 30 • **Mortality** – NHS annual report on Cardiothoracic Organ Transplantation (2021/22)	4.2.1.9
Adverse events	• Probability of rash and liver events included based on trial data	4.2.1.10
Health-related quality of life (HRQL)	• **Age-adjusted utilities –** Health Survey for England EQ-5D-3L general population value set • **ppFEV1 utility –** EQ-5D-3L data per ppFEV1 based on LUM/IVA trials • **PEx disutility –** disutility of 0.07 applied for 30 days based on data from IVA monotherapy trial • **Post-lung transplant utility –** assumed equal to value for people with ppFEV1 >= 70% • **Caregiver disutility –** not included	4.2.1.11

Abbreviations: EQ-5D-3L, EuroQol-5 Dimensions-3 Level; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second.

EAG's model inputs and evidence sources (3/3)

Input	Evidence source / assumption	EAR section
Mortality	• Baseline mortality based on a published flexible parametric spline model fit to UK CF Registry data from 2011-2015 from Keogh (2018) • Mortality risk based on Cox proportional hazards model by Liou (2008)	4.2.1.2
Resource use and costs	• **CFTR modulators –** provided by the company • **ECM –** proportions on each drug therapy according to ppFEV1 status based on UK CF Registry data, Granger (2022); drug costs – BNF; healthcare costs – Tappenden (2023) and NHS reference costs (2020-2021) • **PEx –** 14 days inpatient stay in hospital, receiving IV antibiotics; costs based on Tappenden (2023) • **Monitoring –** Liver function tests and ophthalmologist visits in line with SmPC • **Lung transplant –** NHS reference costs (2020-2021), weighted average of elective inpatient, non-elective inpatient long stay and non-elective inpatient short stay	4.2.1.12
Severity modifier	QALY weighting of 1.0	4.2.2.1

Abbreviations: BNF, British National Formulary; CFTR, cystic fibrosis transmembrane conductance regulator; EAR, external assessment report; ECM, established clinical management; IV, intravenous; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 7: Health-state utility values, EQ-5D versus CFQ-R (1/4)

EAG

- Used health state utility values based on EQ-5D-3L data from the LUM/IVA trials (TRAFFIC/TRANSPORT)
- Approach is in line with NICE reference case

NICE Technical Team comments:

- Section 4.3.10 of NICE manual states to make a case that EQ-5D is inappropriate, provide qualitative empirical evidence on lack of content validity for EQ-5D, showing that key dimensions of health are missing

Company

- EQ-5D is a generic measure and not sensitive to meaningful differences in lung function in CF
- People who have had CF since birth score highly leading to ceiling effects
  - CF trials report baseline EQ-5D higher than UK general population norms
- When CFQ-R mapped to EQ-5D, respiratory dimension of CFQ-R not found to be predictor of EQ-5D and not included in mapping algorithm, despite being a key symptom in CF
- Prefers utilities based on disease-specific CFQ-R scored using the validated, preference-based CFQ-R-8D algorithm
- Does not agree with EAG's approach as EAG utilities mean people with ppFEV1<40 have utility higher than general population, which is not plausible

NICE

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 7: Health-state utility values, EQ-5D versus CFQ-R (2/4)

Professional group comments:

- CFQ-R results from the ELX-TEZ-IVA trials are of a magnitude not seen previously in CF trials
- Generic quality of life measures, such as EQ-5D, do not represent accurately the lived experience of our people with CF – this reflects people's resilience and ceiling effects

Patient group comments:

- The difference that these drugs, in particular the triple therapy drug, has made to the lives of people with CF is incomparable to any other drug or combination of drugs on the market
- Concerned by applying the utility values from LUM/IVA study EQ-5D, the transformative effect of ELX/TEZ/IVA in the real-world environment has not been captured in the EAG model

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 7: Health-state utility values, EQ-5D versus CFQ-R (3/4)

EAG

- Recognises that CFTR modulator therapy has a substantial impact on the quality of life of people with CF
- Notes that it is the relative differences between ppFEV1 categories that drive cost effectiveness, which are similar between EQ-5D and CFQ-R data sources
- EAG present two scenarios, one using lower EQ-5D utility values (based on Acaster 2015) and one using the company base case values (based on CFQ-R from an interim analysis of the TRAJECTORY study)
- Using company's preferred CFQ-R utility values increases the ICER
- A comparison of all sources of utility values is presented in **Table 1** (next slide)

Additional comments:

- EAG's utilities were scaled to account for general population average HRQL at the average age in the model, and were also age-adjusted, which was not done in the company's models
- CFQ-R can be mapped to EQ-5D using a validated and published algorithm. This was not done by the company (the EAG do not have access to the data to do this)

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R, Cystic Fibrosis Questionnaire-Revised; EQ-5D, EuroQol-5 Dimensions; HRQL, health-related quality of life.

Key issue 7: Health-state utility values, EQ-5D versus CFQ-R (4/4)

Table 1: Utility sources and values

	EAG base case	EAG / company scenario	Company base case
Study characteristics			
Data source	LUM/IVA trials – TRAFFIC and TRANSPORT	Acaster (2015)	[redacted]
Study type	RCT	Cross-sectional observational study	[redacted]
Country	Multiple	UK	[redacted]
Sample size	N = 1108 people aged 12+ (F/F genotype)	N=401 adults with self-reported CF diagnosis	[redacted]
Measure	EQ-5D	EQ-5D (& CFQ-R)	[redacted]
Health state utility values			
$ppFEV_1$ >=70	0.91	0.74*	[redacted]
$ppFEV_1$ 70-40	0.88	0.70*	[redacted]
$ppFEV_1$ <40:	0.85	0.54*	[redacted]

Notes: *Based on EQ-5D.

What are the most appropriate health-state utility values?

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 8: Treatment-specific utility benefit

EAG

- Health-state utility values were applied based on ppFEV1 status with decrements applied for PEx
- No additional treatment-specific utility increments were applied

Company

- A treatment-specific utility benefit of [redacted] for ELX/TEZ/IVA (all genotypes) and [redacted] for TEZ/IVA (F/RF genotype only) should be applied
- Applying utilities based only on ppFEV1 and PEx fails to capture additional non-respiratory benefits
- In phase 3 trials of ELX/TEZ/IVA, treatment provided substantial benefit across multiple non-respiratory domains of the CFQ-R
- Model captures these benefits by incorporating a treatment-specific utility increment – that is, an increase in the utility above that predicted based on ppFEV1

EAG response

- Insufficient evidence for an additional utility benefit for treatment beyond its impact on outcomes
- An additional treatment benefit is already captured in the model indirectly through reduced PEx

Should a treatment-specific utility benefit be applied for ELX/TEZ/IVA and TEZ/IVA?

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 9: Caregiver utility benefit

Company

- Included a caregiver utility benefit for carers of children aged 6-11* on ELX/TEZ/IVA
- Based on data collected in the UK-based, longitudinal, MAGNIFY study:
  - Included n=25 carers of children aged 6-11 with CF, who received ELX/TEZ/IVA
  - Used the CarerQoL measure
  - Based on an interim analysis, utility at baseline was 0.85 compared with 0.88 post-baseline
- Therefore, a utility increment of 0.03 was applied for carers of children aged 6-11* on ELX/TEZ/IVA

Patient groups

- There is a multifaceted, often decades-long impact of the condition on carers and whole families
- The impact on carers has been transformed where patients were receiving treatment

EAG

- Does not apply a caregiver utility benefit in base case as evidence for this is uncertain
- Company's carer utility increment is the equivalent of moving between ppFEV1 states <40 and 40-70 and therefore may be an overestimate
- It is unclear if all carers have the same experience and how long the carer impact should apply for
- Data from MAGNIFY final analysis not provided to EAG
- EAG conducted a scenario with carer utility included, which had limited impact on the ICER

Should a caregiver utility benefit be applied?

Note: *Company's model did not include children <6 at that time. **Abbreviations:** ICER, incremental cost-effectiveness ratio; ppFEV1, percent predicted forced expiratory volume in 1 second.

Key issue 10: Disease management costs

EAG

- Included medicine costs and healthcare costs as separate disease management cost categories
  - For medicine costs, EAG used UKCFR data for the proportion of people taking the most common medicines to treat CF, split by ppFEV1 (Granger 2022)
  - For healthcare costs, EAG used a resource use questionnaire, which was part of a trial to assess adherence to inhaled medications (Tappenden 2023)

Company

- Preferred to use a retrospective chart review of patients with CF aged ≥6 years old across eight specialist CF centres in the UK (Ramagopalan 2014)
- Provides a comprehensive and accurate source of data using medical record data to inform costings, whereas EAG's approach of using questionnaires inherently introduce inaccuracy and bias

Professional group comment:

- Since the introduction of CFTR modulators, patients are using less prescribed oral nutritional supplements, vitamin supplements and pancreatic enzymes. Some patients have had gastrostomy tubes removed
- There has also been a reduction in hospital admissions and antibiotic use
- This all has a cost saving to the NHS which should be considered

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PEx, pulmonary exacerbations; UKCFR, UK CF Registry.

Key issue 10: Disease management costs

EAG response:

- Company's preferred source was based on data from 2007-2011 and standard practice has since changed
- Data used by company was only available in abstract / poster form, EAG unable to assess the specific treatments and resource use included in the pharmacotherapy costs to be able to apply updated prices
- The source used by the EAG to inform healthcare costs has been published in a peer-reviewed article and as part of a NIHR HTA report
- EAG presents scenarios applying lower ECM drug costs for patients on CFTR modulators based on professional group feedback – reductions of 23% and 40% explored based on Granger 2022

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; NIHR, National Institute for Health and Care Research; PEx, pulmonary exacerbations.

Key issue 10: Disease management costs

Table 1: EAG's annual disease management costs, excluding PEx costs

ppFEV1	Medicine costs (Granger 2022)	ppFEV1	Healthcare costs (Tappenden 2023)
ppFEV1 > 80%	£10,453	ppFEV1 > 70%	£3,368
ppFEV1 60–80%	£12,107	ppFEV1 40–69%	£3,774
ppFEV1 < 60%	£13,449	ppFEV1 < 40%	£3,320

Table 2: Company's annual disease management costs, excluding PEx costs

ppFEV1	Medicine and healthcare costs		Source
	CFTR arm	ECM arm	
≥70	£6,252	£8,748	Ramagopalan (2014); impact of CFTRms on inpatient and pharmacotherapy costs derived from Simmonds (2022)
40-69	£11,483	£24,920	
<40	£16,429	£39,885	

Which disease management costs should be used?

NICE

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; ppFEV1, percent predicted forced expiratory volume in 1 second;

Key issue 11: Annual discount rates

EAG

- Model uses discount rates of 3.5% for costs and QALYs in line with NICE reference case

Company

- Differential discount rates of 1.5% for QALYs and 3.5% for costs should be used
- Uniform discounting undervalues medicines which incur health gains far into the future
- NICE has in the past accepted differential discounting in an appraisal for a rare paediatric condition – TA235: mifamurtide for the treatment of osteosarcoma (2011)

The latest NICE methods (2022) apply to this MTA (**Figure 1**).

Figure 1: Non-reference case discounting – NICE health technology evaluations manual (2022)

4.5.3 The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

4.5.4 When considering analyses using a 1.5% discount rate, the committee must take account of plausible long-term health benefits in its discussions. The committee will need to be confident that there is a highly plausible case for the maintenance of benefits over time when using a 1.5% discount rate.

4.5.5 Further, the committee will need to be satisfied that any irrecoverable costs associated with the technology (including, for example, its acquisition costs and any associated service design or delivery costs) have been appropriately captured in the economic model or mitigated through commercial arrangements.

What discount rate/s should be used?

Abbreviations: QALY, quality adjusted life years; MTA, multiple technology appraisal

Key issue 12: Severity modifier (1/3)

Background

- As outlined in the NICE manual, *"the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS"*
- The thresholds of quality-adjusted life-year (QALY) weightings for severity are shown in Table 1

Table 1: QALY weights based on NICE health technology evaluations manual

QALY weight	Prop. shortfall	Abs. shortfall
1	<0.85	<12
x1.2	0.85 to 0.95	12 to 18
x1.7	>=0.95	>=18

NICE

Abbreviations: Abs.; absolute; prop., proportional; QALY, quality adjusted life year

Key issue 12: Severity modifier (2/3)

EAG

- Calculated absolute and proportional QALY shortfall for each genotype using published calculator (Schneider 2021) – see **Table 1** on next slide
  - Absolute shortfall ranged from [redacted] years
  - Proportional shortfall ranged from [redacted]
  - Therefore, severity modifier of 1 applies across all genotypes
- The severity modifier is sensitive to discount rate:
  - When discount rate of 1.5% is used, a severity modifier of 1.2 applies (see **Table 2** on next slide)

Company

- Cystic fibrosis is a severe respiratory disease, which leads to a significant shortening of life
- A severity modifier of 1.7 applies in the company's base case
- The EAG's base case EQ-5D utility values lack face validity and contribute to overestimation of QALYs

EAG response

- The application of the severity modifier is a consequence of the modelling assumptions applied and not specific to the use of EQ-5D values
- When the company's utility values are used in the EAG model, a severity modifier is still not applicable

Abbreviations: EQ-5D, EuroQoL-5-dimensions; QALY, quality adjusted life year

Key issue 12: Severity modifier (3/3)

Table 1: EAG's base case estimates of QALY shortfall, 3.5% discount rate

	F/F	F/MF	F/Gating	F/RF
Mean age (years)	20.15	20.91	20.71	28.61
Female (%)	51	51	52	55
QALYs with CF	[redacted]	[redacted]	[redacted]	[redacted]
QALYs without CF	22.67	22.52	22.51	21.10
Abs. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
Prop. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1	1	1	1

Table 2: EAG's estimates of QALY shortfall, with 1.5% discount rate

	F/F	F/MF	F/Gating	F/RF
Mean age (years)	20.15	20.91	20.71	28.61
Female (%)	51	51	52	55
QALYs with CF	[redacted]	[redacted]	[redacted]	[redacted]
QALYs without CF	34.91	34.51	34.51	31.11
Abs. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
Prop. shortfall	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1.2	1.2	1.2	1.2

NICE Technical Team comments:

- Section 6.2.17 of NICE manual states absolute and proportional shortfall calculations should include discounting at the reference-case rate of 3.5% for costs and QALYs

Should a severity modifier apply?

Abbreviations: Abs.; absolute; CF, cystic fibrosis; EQ-5D, EuroQoL-5-dimensions; prop., proportional; QALY, quality adjusted life year.

EAG and company assumptions

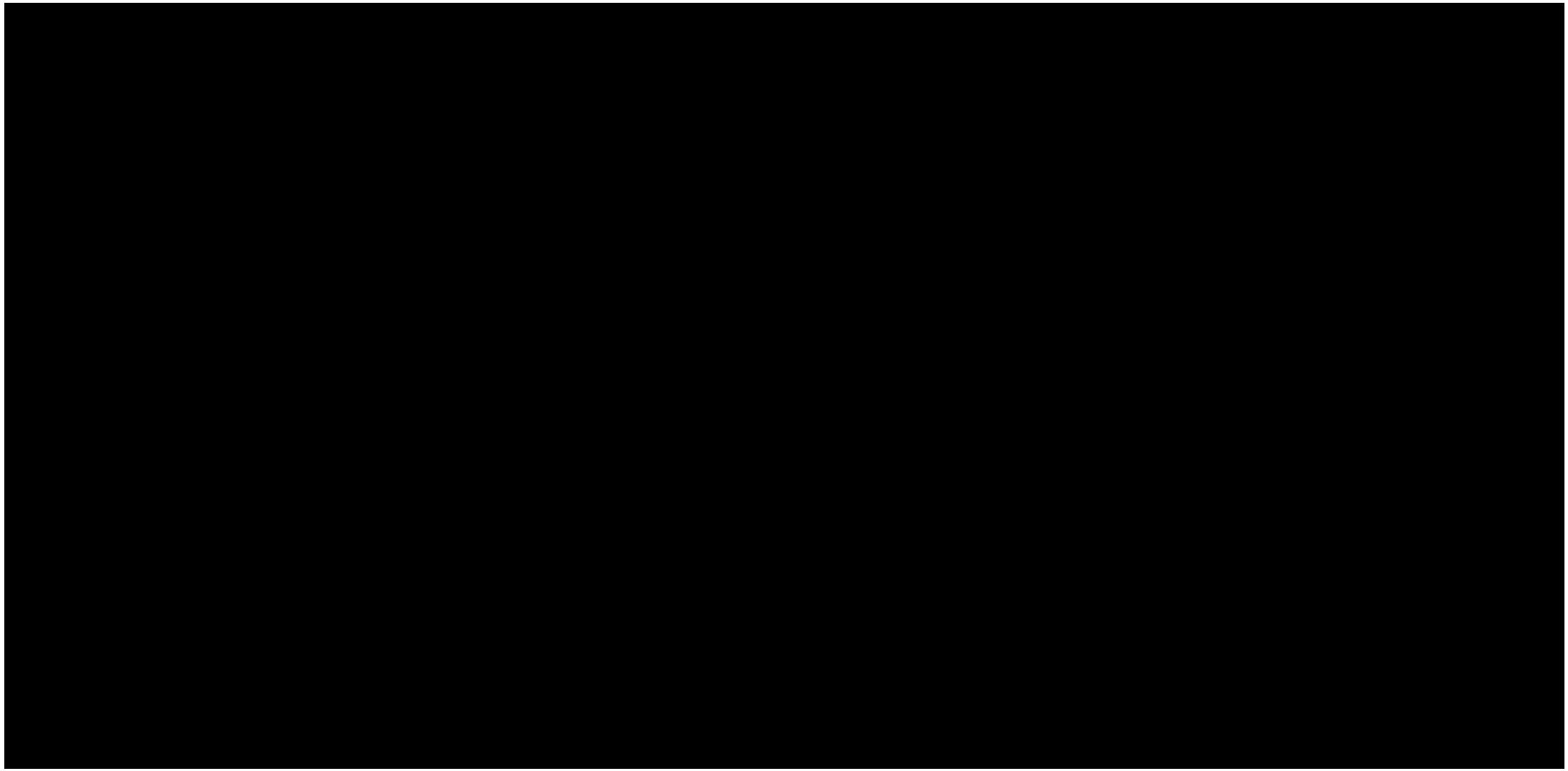
Assumption	EAG	Company
Long-term rate of ppFEV1 decline – ECM	Szczesniak (2023) – non-linear	Sawicki (2022) – linear rates, same rate age 25+
Long-term RR in ppFEV1 decline – ELX/TEZ/IVA	61.0%	100%
Long-term RR in ppFEV1 decline – TEZ/IVA	17.2%	61.5%
Long-term RR in ppFEV1 decline – LUM/IVA	0%	42%
Separate tx effect for PEx applied long-term?	No	Yes
Health-state utility values	Based on EQ-5D-3L	Based on CFQ-R-8D
Treatment specific utility benefit	Not included	Included for ELX/TEZ/IVA and TEZ/IVA
Caregiver utility benefit	Not included	Included
Severity modifier	1.0	1.7
Preferred model	EAG's model	Company's model
Compliance (post-acute)	100%	[redacted]%
Annual discount rates	3.5% - costs and benefits	3.5% costs, 1.5% benefits

Abbreviations: CFQ-R-8D, Cystic Fibrosis Questionnaire-Revised-8-Dimensions; ECM, established clinical management; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; ppFEV1, percent predicted forced expiratory volume in 1 second; RR, relative reduction.

Cost-effectiveness results

Cost-effectiveness results are confidential and will be presented in Part 2 of this meeting

EAG base case results – predicted survival



Uncaptured benefits of CFTR modulators

- Positive impact on employment rates, education and financial wellbeing
- Positive impact on fertility leading to an increase in pregnancy rates
- Reductions in pulmonary bacterial colonisation over time – not included in model
- Changes to CF-related diabetes status – not included in model
- Psychological aspects not captured by tools such as EQ-5D or CFQ-R such as people's perceptions and beliefs about their health, themselves and the future
- Impact of initiating treatment in young children before any lung damage has occurred

Abbreviations: CF, cystic fibrosis; CFQ-R-8D, Cystic Fibrosis Questionnaire-Revised-8-Dimensions; EQ-5D, EuroQol-5 Dimensions;.