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

Part 1 slides for public – ACIC redacted

Multiple Technology Appraisal

Technology appraisal committee D [14 December 2023]

Chair: Megan John

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 2+** who have at **least one F508del mutation**	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.

Draft guidance recommendation

ELX/TEZ/IVA, TEZ/IVA and LUM/IVA are **not recommended:**

- Clinical trial evidence shows that ELX/TEZ/IVA improves lung function, growth and weight gain and reduces the number of lung infections more than standard treatment.
- Clinical trial evidence shows that TEZ/IVA and LUM/IVA also improve symptoms, but the short and long-term improvements are smaller than with ELX/TEZ/IVA
- Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA are above the range that NICE considers an acceptable use of NHS resources.

RECAP

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

Consultation comments

Received from:

- **3 patient organisations:**
  - CF Trust
  - CF Voices
  - Quest for a CF Cure
- **6 professional organisations:**
  - British Dietetic Association (BDA)
  - CF Digicare/CF Health Hub
  - Cystic Fibrosis Nursing Association (CFNA)
  - Royal College of Paediatric and Child Health (RCPCH)
  - UK Cystic Fibrosis Medical Association (UKCFMA)
  - UK Psychosocial Professionals in Cystic Fibrosis (UKPPCF)
- **1 clinical expert**
- **Public comments (524 responses) –** including comments from people with CF, carers and clinicians*
- **Company: Vertex**

*__Note:__ After the committee meeting, it was confirmed that the British Paediatric Respiratory Society submitted a response as a public comment

Abbreviations: CF, cystic fibrosis.

Patient organisation comments (1/5)

Issue	Consultation comments summary

NICE's draft guidance recommendation	• The announcement of the negative recommendation has caused a huge amount of disappointment, anxiety and concern in the CF community:
	  • "Whilst we welcome the commitment that this appraisal does not affect anyone currently receiving treatment, there remains significant worry in the CF community about those not yet initiated on treatment."
	  • "We urge a recalculation [of the cost-effectiveness] taking all comments and recent research into account, before any further guidance is issued"

Abbreviations: CF, cystic fibrosis.

Patient organisation comments (2/5)

Issue	Consultation comments summary
Uncaptured benefits of CFTRms for people with CF	• The analysis only incorporates impact of CFTRms on lung function, PEx and weight. There are many more important benefits that should be captured including: • Pancreatic recovery and ability to stop or reduce enzyme replacement • Reduced pancreatic scarring and liver disease or failure • Improved abdominal symptoms • Improved glycaemic control and reduced diabetes • Improved sinus inflammation, bowel and bladder control • Reduced bacterial colonisation of the lungs • Reduced hospitalisations and requirement for IV antibiotics • Lung infections have become easier to treat • People are no longer on lung or liver transplant waiting list • Reduced need for prescribed medications and time-consuming physiotherapy • Ability to work without needing to take time off, and impact this has on wellbeing • Reduced travel time to hospital appointments • Ability to increase activities with friends and family, positive impact on confidence, social life and starting relationships • Increased fertility and ability to start a family • Better sleep, more energy, motivation and not feeling constantly tired • Increased health stability

Abbreviations: CF cystic fibrosis; CFTRms, cystic fibrosis transmembrane conductance regulator modulators; PEx, pulmonary exacerbations

Patient organisation comments (3/5)

Issue	Consultation comments summary

Uncaptured benefits of CFTRms for carers of people with CF	• Also, many benefits of CFTRms for carers and wider families that should be captured:
	  • Ability to return to work, bring in an income and contribute to the economy
	  • Huge impact on mental health – positivity and hope about the future rather than fear and anxiety
	  • Time savings because of reduced need for burdensome medicines and physiotherapy
	  • No more hospital visits

Caregiver utility benefit	• A caregiver utility benefit should apply with CFTRms without an upper age limit
	  • "A survey conducted by CF Voices showed similar results for carers of patients under and over 12 years"
	  • "The older the patient is, the more care that is required"
	  • "The committee recognised that CF affects the wider family and certainly more than just one carer, its current allowance for care utility is very conservative"
	  • "The impact on carers and families throughout [the life of a person with CF] and beyond in the case of death of the person, has not been fully captured"
	  • "Now most families can hope that their children with CF have a chance to pass in the 'natural order' of age"

Abbreviations: CF, cystic fibrosis; CFTRms, cystic fibrosis transmembrane conductance regulator modulators

Patient organisation comments (4/5)

Issue	Consultation comments summary

Additional benefits of CFTRms in young children	• Treating children with CFTRms from 2+ will avoid long-term lung damage and provide near-normal lifetime lung function:
	  • "Most of the data available [and used in the model] is from older patients with existing disease"
	  • "With CFTRms, children will grow up healthier than ever before and with a different disease profile, to those who have started treatment in later life."

Severity modifier	• A severity modifier of 1.7 should be applied:
	  • "There is ample evidence that CF is a severe, multi-system disease which should qualify for the severity modifier"
	  • "It is unclear what more would be required to qualify CF as a severe disease"
	  • "[Aware that] severity modifiers can only be applied to a relatively small number of severe diseases, and we ask – if not CF, which?"

Annual discount rate	• The criteria for applying annual discount rates of 1.5% are met, as ELX/TEZ/IVA restores people to full or near-normal health:
	  • "ELX/TEZ/IVA goes far beyond preventing decline in young children and greatly increases the quality of their lives"
	  • Sweat tests have improved to near normal or normal range – as if the patient no longer has CF."
	  • "I felt all the benefits of Kaftrio within 24 hours of taking my first dose."

Abbreviations: CF, cystic fibrosis; CFTRms, cystic fibrosis transmembrane conductance regulator modulators

Patient organisation comments (5/5)

Issue	Consultation comments summary

EQ-5D	• EQ-5D is not appropriate for use in CF:
	  • "For a treatment that is as transformational as this, the EQ-5D falls far short of a useful and appropriate assessment of the benefits"
	  • "The use of EQ-5D questionnaires for CF is not fully valid and asks the wrong questions to be sensitive"
	  • "CFQ-R data collected during the interim access period accurately reflects the experiences of people with CF"

Treatment-specific utility benefit	• A treatment specific utility benefit should apply: • "The benefits of modulator treatment are far more extensive [than captured by the analysis] and HRQoL tools have limited capacity to measure them in CF"
Disease management costs	• Clinical guidelines at CF centres are already changing to recognise the reduced need for many prescribed therapies, for people on ELX/TEZ/IVA: • "While CFTR modulators may have been an addition to ECM to date, they will increasingly replace it, particularly when prescribed to people aged 2-5"

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; EQ-5D, EuroQoL 5 dimensions; HRQoL, health related quality of life

Professional organisation comments (1/4)

Issue	Consultation comments summary
Reduced nutritional support (BDA)	• With CFTRms, there is less of a requirement for oral nutritional supplements, enteral tube feeding and placement of feeding tubes, and less reliance on healthcare services • This has significant cost savings and quality of life benefits
Co-adherence to inhaled therapy (CFDigicare)	• Preliminary results from the National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) study should be considered • Results for 642 patients on ELX/TEZ/IVA with ≥ 2 years of data shows ppFEV1 was reduced in people with low adherence to inhaled therapies at year 2 of treatment • This suggests that the cost-effectiveness of ELX/TEZ/IVA may be influenced by co-adherence to inhaled therapies • Any implementation of ELX/TEZ/IVA should include measurement of co-adherence • **UKCFMA** – Whilst more evidence is required to ensure the safety of reducing nebulised medicines use, this reflects the perceived benefit of treatment and people's desire to reduce their substantial treatment burden.

Abbreviations: BDA, British Dietetic Association; CFTRms, cystic fibrosis transmembrane conductance regulator modulators; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFMA, UK Cystic Fibrosis Medical Association

Professional organisation comments (2/4)

Issue	Consultation comments summary
Uncaptured benefits (CFNA, UKPPCF, RCPCH)	• The focus on pulmonary complications is understandable, however CF is a multi-system disease. Other clinical complications have a significant care burden and cost to the NHS. • Reductions in pancreatic supplements, insulin use, central lines and totally implantable venous access devices and associated cost savings should be considered • Psychological and social benefits are not adequately captured • There should be a formal consideration of the societal cost and wider benefits to NHS
Carer impact (CFNA)	• Applying carer utility up to age 11 only does not reflect real world experience • It is acknowledged that burden of care increases with age/disease severity

Cost savings (UKPPCF)	• There are cost savings due to reduced:
	  • sickness and carer benefits
	  • housing adaptions and moves due to ill health
	  • social services costs for children and adults
	  • community support services
	  • mental health support services
	  • prescription costs
	  • higher tier specialist services in favour of primary care

Abbreviations: CF, cystic fibrosis; CFNA, Cystic Fibrosis Nursing Association; RCPCH, Royal College of Paediatric and Child Health; UKPPCF, UK Psychosocial Professionals in Cystic Fibrosis

Professional organisation comments (3/4)

Issue	Consultation comments summary
Employment rates (CFNA, UKPPCF)	• We urge that the wider financial benefits of employment rate of both those with CF, and their parents/spouses/families is considered
Annual discount rate (CFNA, UKPPCF, UKCFMA, RCPCH)	• Failure to apply the 1.5% annual discount rate implies a lack of recognition of the severity of the disease and impact of the modulators. • Many people with CF, especially younger people without established lung disease, will be able to enjoy normal health, they are on a different life journey • The Phase 3 open-label trial of ELX/TEZ/IVA (Goralski et al.) shows clear benefits in children aged 2-5
Equality	• A negative recommendation would be discriminatory based on age, and would lead to a two-tier system within the community and within families between siblings • Withholding these treatments from young children discriminates against those who are likely to benefit the most

Abbreviations: CF, cystic fibrosis; CFNA, Cystic Fibrosis Nursing Association; RCPCH, Royal College of Paediatric and Child Health; UKCFMA, UK Cystic Fibrosis Medical Association; UKPPCF, UK Psychosocial Professionals in Cystic Fibrosis

Professional organisation comments (4/4)

Issue	Consultation comments summary
Dual vs triple therapies (UKCFMA)	• Dual and triple therapies should not be conflated • Dual therapies are minimally effective. In contrast, ELX/TEZ/IVA has been transformational
Severity (UKCFMA)	• Without standard therapy, most patients would die in childhood, and with standard therapy many die in their early adult life
CE threshold (UKCFMA)	• There is a cogent argument for a higher ICER than £30,000, in light of the limited number of eligible patients and the impact.

Abbreviations: UKCFMA, UK Cystic Fibrosis Medical Association.

Clinical expert comments

Issue	Consultation comments summary

Equality of access	• Concerned that the outcome of the MTA may result in a two-tier system of care for people with CF. Such a situation would leave:
	  • Tier A - existing patients on ELX/TEZ/IVA aged [>2] continue to access treatment
	  • Tier B – a child who turns [2] could not be started on treatment
	• A 'date of birth lottery' is unacceptable in a publicly-funded health service

Effectiveness in very young people	• The very young are those who will be disadvantaged most by being denied access • Lopez et al. (2023) demonstrated that projected gains in life expectancy are greater if ELX/TEZ/IVA is started earlier with projected survival up to 82.5 years if treatment is started between the ages of 12 and 17
Economic modelling	• Concerned that a medication that is so overwhelmingly clinically effective cannot be recommended due to being unable to be demonstrated as being cost-effective • I urge NICE to consider the economic models and whether these are designed for the evaluation of a drug such as ELX/TEZ/IVA • Benefits should include increased time in work and school for people with CF and caregivers, impact of reduced travelling, increased virtual delivery of care
Price	• I also urge Vertex to revisit the pricing and whether this can be adapted to allow a more favourable cost-effectiveness appraisal

Abbreviations: CF, cystic fibrosis

Public comments

524 comments from patients, carers, clinicians and other commentators. Common themes:

• CF is a severe genetic disease. CFTRms, particularly ELX/TEZ/IVA, are highly effective, groundbreaking treatments and should not be withdrawn based on cost	• There are many uncaptured health benefits. These should be included in the cost-effectiveness calculation	• There will be even greater benefits in children starting treatment at age 2. This population should be considered separately to adults
• The current recommendation discriminates based on age and disability and is unlawful	• ELX/TEZ/IVA restores people, particularly children, to normal health. Therefore 1.5% discount rates should be used	• The impact on carers is much greater than assumed in the analysis and continues for the patient's lifetime, often increasing as the condition worsens with age
• NHS cost savings with CFTRms need to be appropriately accounted for – such as reduced costs of care and prescribed medicines	• Cost savings to the wider economy should also be included	• CF is a severe condition – a severity modifier should apply

Note: The committee has received all web comments in full within its committee papers

Abbreviations: CF, cystic fibrosis; CFTRms, cystic fibrosis transmembrane conductance regulator modulators

Equality considerations

New equality issues raised in response to consultation:

- Recommendations may discriminate against people with protected characteristics, specifically:
    - Age: As access to treatments will continue while the appraisal is ongoing for new and existing patients, the current recommendation means young people will be left without access to CFTR modulators
    - Disability: Stopping access to CFTR modulators results in not providing equal access to children with the same disability (CF)
    - People with some neurological conditions (ADHD / autism spectrum) and their carers, may find managing CF disproportionately difficult – modulator treatment has provided an additional important benefit for them that would be lost if the final guidance is negative

Abbreviations: ADHD, attention deficit hyperactivity disorder; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Company response overview

In response to consultation, the company has:

- Updated base case for some key issues to align with committee's preferences at ACM1
- Submitted additional justification for other key issues where base case was not updated
- Focused response on assumptions for ELX/TEZ/IVA
- Provided an updated version of the EAG's economic model including company preferred assumptions
- Provided updated cost-effectiveness results using the EAG's model

Note: All of the company base case results exceed cost effectiveness threshold, however company 'has an existing commercial arrangement with NHS England, which will be updated following the NICE appraisal'*

*Source - company consultation response

Abbreviations: ACM1, appraisal committee meeting 1; EAG, External Assessment Group.

Key issues from ACM1 (1/4)

#	Key issue and committee conclusions at ACM1	Response from company	Resolved?	ICER impact
1	**Long-term rate of ppFEV1 decline – ECM** • Preferred EAG's approach of using a non-linear decline in ppFEV1 with age based on Szczesniak (2023)	Accepted committee preference	Yes	Small
2	**Long-term relative reduction in ppFEV1 decline – CFTR modulators** • ELX/TEZ/IVA – [redacted]% based on UKCFR data • TEZ/IVA – 61.5% based on OLE study (company) • LUM/IVA – 42% based on OLE study (company) • Requested scenario analysis extending acute treatment effect window to week 24 to ensure acute effect excluded	Prefers no decline for ELX/TEZ/IVA (relative reduction 100%). Committee aligned with company for TEZ/IVA and LUM/IVA	Partially	Moderate
3	**Pulmonary exacerbations (PEx) treatment effect duration** • Agreed with company that PEx treatment effect would be sustained while people remained on treatment	Committee aligned with company	Yes	Unknown

Abbreviations: ACM1, appraisal committee meeting 1; CFTR; cystic fibrosis transmembrane conductance regulator; OLE, open-label extension; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second

Key issues from ACM1 (2/4)

#	Key issue and committee conclusions at ACM1	Response from company	Resolved?	ICER impact
4	**Adherence to CFTR modulators (referred to previously as compliance)** • Should ideally come from the same source as efficacy. Preferred company approach of using adherence based on UKCFR data ([redacted]% for all CFTRms*)	Committee aligned with company	Yes	Small
5	**Adherence to non-CFTR modulator treatments** • The effect of reduced use of non-CFTR modulator treatments on long-term efficacy is uncertain	N/A	Not resolvable at ACM2	Unknown
6	**Suitability of EAG's model for decision making** • The EAG's model is suitable for decision making	Provided preferred company base case in EAG's model	Yes	Small

Notes: *Consultation comments noted this figure was based on home delivery data. **Abbreviations:** ACM, appraisal committee meeting; CFTR; cystic fibrosis transmembrane conductance regulator; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; UKCFR, UK Cystic Fibrosis Registry.

Key issues from ACM1 (3/4)

#	Key issue and committee conclusions at ACM1	Response from company	Resolved?	ICER impact
7	**Health state utility values** • Utilities based on Acaster (2015) best reflect patient experience	Accepted committee preference	Yes	Large
8	**Treatment-specific utility benefit** • Not appropriate to include a separate treatment-specific utility benefit – the effect of treatment on quality of life should already be captured by the model	A treatment-specific utility benefit should apply	No	Large
9	**Caregiver utility benefit** • Agreed with company that a caregiver utility benefit of [redacted] should be applied for carers of children up to age 11 treated with ELX/TEZ/IVA • Requested scenario with benefit applied up to age 18	A caregiver utility benefit should apply without an upper age limit	No	Moderate

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Notes: ACM1, appraisal committee meeting 1; ICER, incremental cost-effectiveness ratio.

Key issues from ACM1 (4/4)

#	Key issue and committee conclusions at ACM1	Response from company	Resolved?	ICER impact
10	**Disease management costs** • Preferred EAG approach based on Granger et al. (2022) and Tappenden et al. (2023) • Assumed no reduction in ECM costs for people on CFTR modulators	The EAG's approach is not appropriate – company proposed approach to reduce disease management costs with CFTR modulators	No	Large
11	**Annual discount rates** • 3.5% for costs and QALYs	Meets criteria for non-reference case discounting of 1.5% for costs and QALYs	No	Large
12	**Severity modifier** • Unable to conclude as neither company nor EAG's analyses incorporated all the committee's preferred assumptions	A severity modifier of 1.7 should apply	No	Large

Notes: ACM1, appraisal committee meeting 1; CFTR; cystic fibrosis transmembrane conductance regulator; EAG, External Assessment Group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issues for discussion at ACM2

= Large impact

#	Key issue	Question for discussion	Options
1	Long-term relative reduction in ppFEV1 decline	What relative reduction in ppFEV1 decline for ELX/TEZ/IVA should apply?	• No decline (company preference) • Relative reduction of [redacted]% (committee preference at ACM1) • Other?
2	Treatment specific utility benefit	Should a treatment-specific utility benefit apply?	• Yes (company preference) • No (committee preference at ACM1)
3	Caregiver utility benefit	At what age range should caregiver utility benefit apply?	• Age 1 to 11 years (committee preference at ACM1) • Age 1 to 18 years • No upper age limit (company preference at ACM2) • Other?
4	Disease management costs	Should a reduction in disease management costs apply? What approach should be used?	• Company approach • EAG scenario • No reduction / other?
5	Annual discount rates	What annual discount rate should apply?	• 3.5% for costs and outcomes • 1.5% for costs and outcomes
6	Severity modifier	What QALY weighting for severity should apply?	• 1, 1.2, 1.7

Abbreviations: ACM, appraisal committee meeting; External Assessment Group; ppFEV1, percent predicted forced expiratory volume in 1 second; QALY, quality-adjusted life year

Additional key issues for discussion at ACM2

#	Key issue	Question for discussion	Options
Additional issues raised by company at consultation			
7	Comparators	Should IVA monotherapy be included as a comparator for the F/Gating and F/R117H genotypes?	• Yes / No
Additional issues raised by stakeholders			
8	Uncaptured benefits	How should the uncaptured benefits be considered?	• Committee to discuss

Abbreviations: ACM2, appraisal committee meeting 2; IVA, ivacaftor

Key issue 1: Long-term ppFEV1 decline (1/7)

Committee conclusions in ACM1 (draft guidance section 3.7, 3.8):

- Preferred data from the UKCFR for the long-term relative reduction in ppFEV1 decline for ELX/TEZ/IVA ([redacted]%)
- COVID-19 likely contributed to some confounding but potential for positive and negative effects – overall impact of COVID-19 on lung function decline is unknown
- Requested a scenario analysis that extended the acute treatment effect window up to week 24 (for TEZ/IVA and LUM/IVA)

Company response (based on EAG summary):

- Maintains that relative reduction in ppFEV1 decline for ELX/TEZ/IVA is higher than committee's preferred assumption and should be 100%
- Presented two new analyses (**see next slides for methods and results**):
  - 445-105 open-label extension (OLE) study – excluding data collected during the pandemic, between March 2020 and July 2021
  - US Cystic Fibrosis Foundation Patient Registry (CFFPR) – comparing patients treated with ELX/TEZ/IVA to a contemporaneous cohort, during the pandemic
- New analyses are supported by data across other age groups and genotypes (studies 445-107 and 445-110)
- Further supported by absolute changes in sweat chloride being sustained during OLE period
- Company data sources are more appropriate than UKCFR, as 445-105 had more data points and a longer follow up; and CFFPR covers a wider range of genotypes

Abbreviations: ACM1, appraisal committee meeting 1; EAG, External Assessment Group; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry.

Key issue 1: Long-term ppFEV1 decline ELX/TEZ/IVA (2/7)

Table 1: Studies reporting rate of change in ppFEV1 for ELX/TEZ/IVA – company consultation response

Study	Sample size	Follow-up duration	Genotype	Age
UKCFR	[redacted]	[redacted]	[redacted]	[redacted]
US CFFPR	[redacted]	[redacted]	[redacted]	[redacted]
OLE 445-105	N = 506 [redacted]	44.3 months (192 weeks) N = 356 (70.4%) with week-192 data Oct 2018 – Jan 2023	F/F, F/MF	12+
OLE 445-107	N = 64	144 weeks Feb 2020 – Apr 2024	F/F, F/MF	6-11
OLE 445-110	N = 251	96 weeks Dec 2019 – Dec 2022	F/RF, F/Gating	12+

Notes: *Annual review + encounter. **Abbreviations:** OLE, open-label extension; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry; US CFFPR, US Cystic Fibrosis Foundation Patient Registry

Key issue 1: Long-term ppFEV1 decline ELX/TEZ/IVA (3/7)

Table 2: Mean annualised rate of change in ppFEV1 estimates in ELX/TEZ/IVA-treated cohorts and matched controls – company consultation response

Data source	Mean annualised rate of change in ppFEV1 % (95% CI)		
	IVA/TEZ/ELX	Matched control	Relative reduction
UKCFR	[redacted]	[redacted]	[redacted]
US CFFPR	[redacted]	[redacted]	[redacted]
445-105 wk 192*	[redacted]	N/A	N/A
445-105 wk 192	0.02 (-0.14, 0.19)	N/A	N/A
445-105 wk 144	0.07 (-0.12, 0.26)	N/A	N/A
445-105 wk 96	0.39 (-0.06, 0.85)	-1.92 (-2.16, -1.69)	120.3% (96.8%, 144.4%)
445-107 wk 144	[redacted]	N/A	N/A
445-107 wk 96	0.51 (-0.73, 1.75)	N/A	N/A

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*Excluding data points from 445-105 study during the COVID-19 pandemic.

New data from company response

Key issue 1: Long-term ppFEV1 decline ELX/TEZ/IVA (4/7)

Public comments:

- Patients and clinical experts agreed that the effects on lung function have been sustained with ELX/TEZ/IVA
- Prediction of lung function benefit with CFTRms should be based on preventing lung function decline
    - For young children, lung function is near-full-health at baseline, and this will be maintained over a long period with CFTRms

Patient and professional group:

- With CFTRms, children will grow up healthier than ever before and with a different disease profile, to those who have started treatment in later life
- Many people, especially younger children without established lung disease, will be able to enjoy normal health – they are on a different life journey

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Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator.

Key issue 1: Long-term ppFEV1 decline ELX/TEZ/IVA (5/7)

EAG response:

- Agrees with committee preference at ACM1 to use rate of decline data from UKCFR but still notes potential confounding of the data from COVID-19 pandemic

Analysis of the 445-105 study excluding data during the pandemic

- Excluding measurements taken during the pandemic may not adequately remove confounding effect
  - If reduced viral transmission led to a reduction in rate of ppFEV1 decline, patient's ppFEV1 after July 2021 would still be expected to be higher than if the COVID-19 pandemic did not occur
  - An analysis of all available data, including a dummy variable of COVID-19 in the model would be the EAG's preferred approach

US CFFPR analysis during the pandemic comparing patients treated with ELX/TEZ/IVA to a contemporaneous cohort

- Company's analysis was not prespecified and details of the conduct of the analysis were limited
  - Unclear why month 2 and month 24 were chosen as two timepoints for rate of change analysis
  - Unclear why patients with only 2 measurements were excluded
- Company's comparison of ELX/TEZ/IVA treated patients (with F508del) to untreated patients (without F508 del) not appropriate as the cohorts expected to have different underlying rates of ppFEV1 decline

Abbreviations: ACM, appraisal committee meeting; EAG, External Assessment Group; ppFEV1, percent predicted forced expiratory volume in 1 second; US CFFPR, US Cystic Fibrosis Foundation Patient Registry

Key issue 1: Long-term ppFEV1 decline (6/7)

EAG response:

- Overall, the EAG notes that:
  - US CFFPR data source likely contains information that could resolve the degree of COVID-19 confounding, but that these data have yet to be presented
  - As a non-pre-specified analysis with no sensitivity analyses, the Company's analysis of US CFFPR data is at high risk of bias
  - EAG considers the results of the Company's new analysis to be compatible with both a 100% reduction in the rate of change for people treated with ELX/TEZ/IVA, and smaller reductions, such as the [redacted]% calculated from the Data Collection Agreement from the UKCFR
  - No further data from UKCFR presented (the most relevant data source which did show a long-term decline in ppFEV1 for treated patients)
  - Company has not provided a scenario extending the length of the acute period for LUM/IVA and TEZ/IVA – EAG considers this would also be informative for ELX/TEZ/IVA
  - Outstanding unresolvable uncertainty concerning whether the "long-term" rate of decline observed in the current data sources will generalise throughout a patient's lifetime

Company clarification response:

- We are not asserting that there is no effect of COVID-19 within the CFFPR contemporaneous cohort, our study was expressly and carefully designed to control for any effects of COVID-19 within both cohorts

Abbreviations: EAG, External Assessment Group; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry; USCFFPR, US Cystic Fibrosis Foundation Patient Registry

Key issue 1: Long-term ppFEV1 decline (7/7)

EAG response:

- It is plausible that an incident CF population that begins treatment prior to any irreversible lung or pancreatic damage may experience greater benefits

What relative reduction in ppFEV1 decline for ELX/TEZ/IVA should apply? 77%,100% or other?

Abbreviations: CF, cystic fibrosis; EAG, External Assessment Group; ppFEV1, percent predicted forced expiratory volume in 1 second

Key issue 2: Treatment-specific utility benefit (1/3)

Committee conclusions in ACM1 (draft guidance section 3.17):

- The EAG's model structure, combined with using health-state utility values from Acaster et al. (2015), means the effect of treatment with CFTR modulators on quality of life should already be captured
- It is therefore not appropriate to include a separate treatment-specific utility benefit.

Company response:

- Accepts the use of Acaster (2015) utilities but maintains that a treatment-specific utility benefit for ELX/TEZ/IVA of [redacted] based on TRAJECTORY data should be applied
- A treatment-specific utility of [redacted] is also applied for TEZ/IVA in the F/RF population
- In the economic model, people who do not move across different levels of disease severity (ppFEV1) show no gains in utility – this ignores the benefits beyond the respiratory domain
- In TRAJECTORY, people treated with ELX/TEZ/IVA had increase in utility even when remaining within same disease severity, highlighting treatment specific utility benefit beyond improvements seen in ppFEV1

Table 1: TRAJECTORY CFQ-R-8D Utility Score following ELX/TEZ/IVA initiation by severity

Disease severity	Mean CFQ-R-8D utility score change from baseline (n at post baseline)
$ppFEV_1$<40	[redacted]
$ppFEV_1$ >40 to <70	[redacted]
$ppFEV_1$ ≥ 70	[redacted]

- This is further supported by CFQ-R data from the UK data collection agreement, as well as data from study 445-102 (AURORA) which show improvements in CFQ-R across a broad range of domains

Key issue 2: Treatment-specific utility benefit (2/3)

Company response:

- Performed a mixed model repeated measures (MMRM) analysis to predict the impact of ELX/TEZ/IVA on CFQ-R-8D utility scores, adjusted for ppFEV1 category (<40%, ≥40 to <70%, ≥70%)

Parameter	Estimate (95% CI) – TRAJECTORY	
Analysis	IA1	IA2
Baseline	[redacted]	[redacted]
Least square mean change from baseline (attributed to ELX/TEZ/IVA)	[redacted]	[redacted]
$ppFEV_1$ category	NR	NR

Public comments:

- Change in overall health and ability to work and contribute to society is not sufficiently captured by the change in lung function and reduction in exacerbations
- Statistically significant improvement in all of the domains of the CFQ-R with ELX/TEZ/IVA
- Many non-respiratory benefits of treatments must be applied to ensure an inclusive, holistic representation of the treatment specific utility benefit.

Patient and professional group:

- The benefits of modulator treatment are far more extensive [than captured by the analysis] and HRQoL tools have limited capacity to measure them in CF

NICE

Abbreviations: IA, interim analysis; CFQ-R-8D; Cystic Fibrosis Questionnaire-Revised-8-Dimensions; CI, confidence interval; HRQoL; health-related quality of life; regulator; ppFEV1, percent predicted forced expiratory volume in 1 second

Key issue 2: Treatment-specific utility benefit (3/3)

EAG response:

- The structure of the company's MMRM is insensitive to changes in patient's quality of life due to changing ppFEV1, as ppFEV1 is treated as ordered categories rather than a continuous variable
- ppFEV1 categories included in the economic model match those used for the MMRM analysis → utility values used in the economic model are equally insensitive to changes in quality of life attributed to, for example, a 10% increase in ppFEV1 within the same ppFEV1 severity category
- Therefore, the EAG does not consider it unreasonable to include the additional utility benefit associated with ELX/TEZ/IVA calculated by the company, on the understanding that this does not represent a treatment specific utility benefit of ELX/TEZ/IVA independent of ppFEV1 category, but instead likely captures both:
  - A QoL benefit associated with increased ppFEV1 due to treatment with ELX/TEZ/IVA within a ppFEV1 category;
  - Any other treatment specific utility benefit not captured by ppFEV1
- Limited details available to critique inclusion of TEZ/IVA treatment-specific utility
- Notes that applying a treatment specific utility apply for ELX/TEZ/IVA, may also capture further increases in quality of life experienced if benefits do not correlate with ppFEV1, and therefore may address some uncaptured benefits

Should a treatment specific utility benefit apply?

Abbreviations: EAG, External Assessment Group; MMRM, mixed model repeated measures; ppFEV1, percent predicted forced expiratory volume in 1 second; QoL, quality of life.

Key issue 3: Caregiver utility benefit (1/2)

Committee conclusions in ACM1 (draft guidance section 3.18):

- A caregiver utility benefit of [redacted] should be applied in the model for carers of children from the start of ELX/TEZ/IVA treatment to 11 years of age, as proposed by the company (prior to ACM1)
- The actual benefit is likely to be greater than this – would like to see a scenario analysis with carer utility benefit applied from treatment initiation to 18 years of age

Company response:

- A caregiver utility benefit should be applied for the patient's lifetime (that is, no upper age limit)
- The final conclusions in the draft guidance do not reflect discussions at ACM1:
  - Caregivers providing evidence at ACM1 believed they were impacted equally, if not more, in caring for people with CF beyond childhood as the condition worsens and pulmonary exacerbations increase
  - Multiple committee members agreed they would like to see a scenario assuming a lifetime benefit
  - Committee discussed how applying a benefit to 18 would likely be conservative as utility for secondary caregivers is not reflected
- Provided additional evidence for a caregiver burden beyond age 11 (Suthoff 2019, Neri 2016)
- Primary caregivers of children with CF report significantly increased burden during PEx, which become more common in teenage years

Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis; PEx, pulmonary exacerbations

Key issue 3: Caregiver utility benefit (2/2)

Public comments:

- There are extreme emotional challenges of CF diagnosis to children, their parents and their wider families
- Carer responsibility and financial burden does not go away at 18, it extends and increases into adulthood
- It also extends well beyond primary caregivers to wider family and friends

Patient and professional group:

- A caregiver utility benefit should apply without an upper age limit
- It is acknowledged that burden of care increases with increased age and disease severity
- CF affects the wider family and certainly more than just one carer, committee's current allowance for carer utility is very conservative

EAG response:

- Notes that the available evidence for carer HRQoL was based on carers of patients aged 6-11
- Acknowledges the discussions at ACM1 and has provided a scenario assuming a benefit up to age 18

At what age range should caregiver utility benefit apply? Up to 11 years, up to 18 years, or lifetime?

NICE

Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis; HRQoL, health-related quality of life; PEx, pulmonary exacerbations

Key issue 4: Disease management costs (1/4)

Committee conclusions in ACM1 (draft guidance section 3.19):

- The EAG's disease management costs, based on Granger (2022) and Tappenden (2023) should be used
- Cost savings from a reduced need for ECM associated with CFTRms is a potential uncaptured benefit in the model

Company response:

- EAG's approach is flawed, lacks face validity and is not reflective of clinical practice as it assumes:
  - The costs for ECM pharmacotherapy, disease management and the duration a PEx event are the same, irrespective of whether people are treated with ECM or CFTR modulators
  - Mild and severe lung disease have the same healthcare resource use
  - Costs for people in the mild health state (ppFEV1≥70) are high (£10,453 annually)
- Propose an alternative approach of adjusting EAG's cost inputs to recognise reductions in drug and disease management costs for people treated with CFTRms and reflecting health state costs vary by severity:
  1) Reductions in ECM drug and health state costs for people on CFTRms
  2) Health state costs differentiated by severity based on ppFEV1
  3) PEx cost reduction in people on CFTRms
  4) Reduction in ECM drug costs for the least severe (ppFEV1 >= 70) state

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; EAG, External Assessment Group; ECM, established clinical management; PEx, pulmonary exacerbation; ppFEV1, percent predicted forced expiratory volume in 1 second

Key issue 4: Disease management costs (2/4)

Public comments:

- The cost savings to the NHS of reduced healthcare costs with CFTRms will be significant
- Hospital admissions and the requirement for IV antibiotics have greatly reduced, and for some people, have completely stopped, since starting treatment with CFTRms
- Between 1 April 2020 to 31 March 2023, no children with CF have undergone lung transplantation
- Given the very high costs of managing CF, the reduction in these existing costs associated with the use of CFTRms cannot be ignored

Patient and professional group:

- Clinical guidelines at CF centres are already changing to recognise the reduced need for many prescribed therapies, for people on ELX/TEZ/IVA
- While CFTRms may have been an addition to ECM to date, they will increasingly replace it, particularly when prescribed to people aged 2-5
- With CFTRms, there is less of a requirement for oral nutritional supplements, enteral tube feeding and placement of feeding tubes and less reliance on healthcare services
- Reductions in pancreatic supplements, insulin use, central lines and totally implantable venous access devices and associated cost savings should be considered

Abbreviations: CF, cystic fibrosis; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECM, established clinical management.

Key issue 4: Disease management costs (3/4)

Company preference	Company approach and rationale	EAG critique
1. Reductions in ECM drug and health state costs for people on CFTRms	• Assumed a 70% reduction in ECM drug and health state costs for all CFTRms • Based on studies of IVA showing ~50% reduction in costs compared to ECM – ELX/TEZ/IVA expected to have a greater impact than IVA	• Company sources show reduced costs through fewer PEx hospitalisations and IV antibiotics • This is already captured by the model • Acknowledges that use of ECM drugs may decline with use of CFTRms but no evidence to support reduction of 70% • Presented scenarios assuming 23% and 40% (based on Granger 2022) reduction in ECM drug costs and ECM drug and health state costs
2. Health state costs differentiated by severity based on ppFEV1	• Stratified costs from Tappenden (2023) by severity using ratios from Ramagopalan (2014) – the only available UK source of costs by ppFEV1 range	• Ratios applied are not sourced directly from Ramagopalan (2014) • Based on company's original estimation, which may not have fully removed PEx cost • Mean health care costs due to HCP visits in Ramagopalan (2014) were similar across severity groups in line with Tappenden (2023)

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; EAG, External Assessment Group; ECM, established clinical management; HCP, healthcare professional; IVA, ivacaftor; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry

Key issue 4: Disease management costs (4/4)

Company preference	Company rationale and approach	EAG critique
3. PEx cost reduction in people on CFTRms	• UKCFR data shows a [redacted]% reduction in IV antibiotic days with ELX/TEZ/IVA • Simmonds (2022) showed 75% reduction in PEx duration for people treated with IVA • Therefore, a conservative 50% reduction should be applied to the cost of PEx for people on CFTRms	• UKCFR data may be confounded by COVID-19 • However, EAG acknowledges feedback from clinical experts that people having CFTRms may have less need for IV antibiotics to treat a PEx event • Provided a scenario using company's proposed 50% cost reduction
4. Reduction in ECM drug costs for the least severe (ppFEV1 >= 70) state	• Applied a reduction of 81% for drug costs based on difference between most severe and least severe health states in Ramagoplan (2014)	• 81% difference between health states is based on the Company's analysis of Ramagopalan (2014) • Company adjustments may not have fully removed the costs of PEx

Should a reduction in disease management costs apply? What approach should be used?

Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulator; EAG, External Assessment Group; ECM, established clinical management; HCP, healthcare professional; IVA, ivacaftor; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, UK Cystic Fibrosis Registry

Key issue 5: Annual discount rates (1/3)

Committee conclusions in ACM1 (draft guidance section 3.15):

- An annual discount rate of 3.5% should be used for costs and QALYs

Company response

- Maintains that a differential discount rate of 3.5% for costs and 1.5% for outcomes is most appropriate
- However, evidence is provided to support case for a 1.5% discount rate for costs and outcomes, and this has been applied in the company base case

Table 1: Criteria for non-reference case (1.5%) discount rate – NICE health technology evaluations manual

Criterion	Committee (ACM1)	Company
1. The technology is for patients that would otherwise die or have a severely impaired quality of life	Criterion met	Agree
2. The technology is likely to restore patients to full or near normal health	Criterion not met – ELX/TEZ/IVA does not restore people with CF to full health but prevents decline. Acknowledged the potential additional benefits in young children but had not seen evidence for this.	Presented evidence to show criterion is met (**see next slide**)
3. Benefits are likely to be sustained over a very long period	Criterion met	Agree

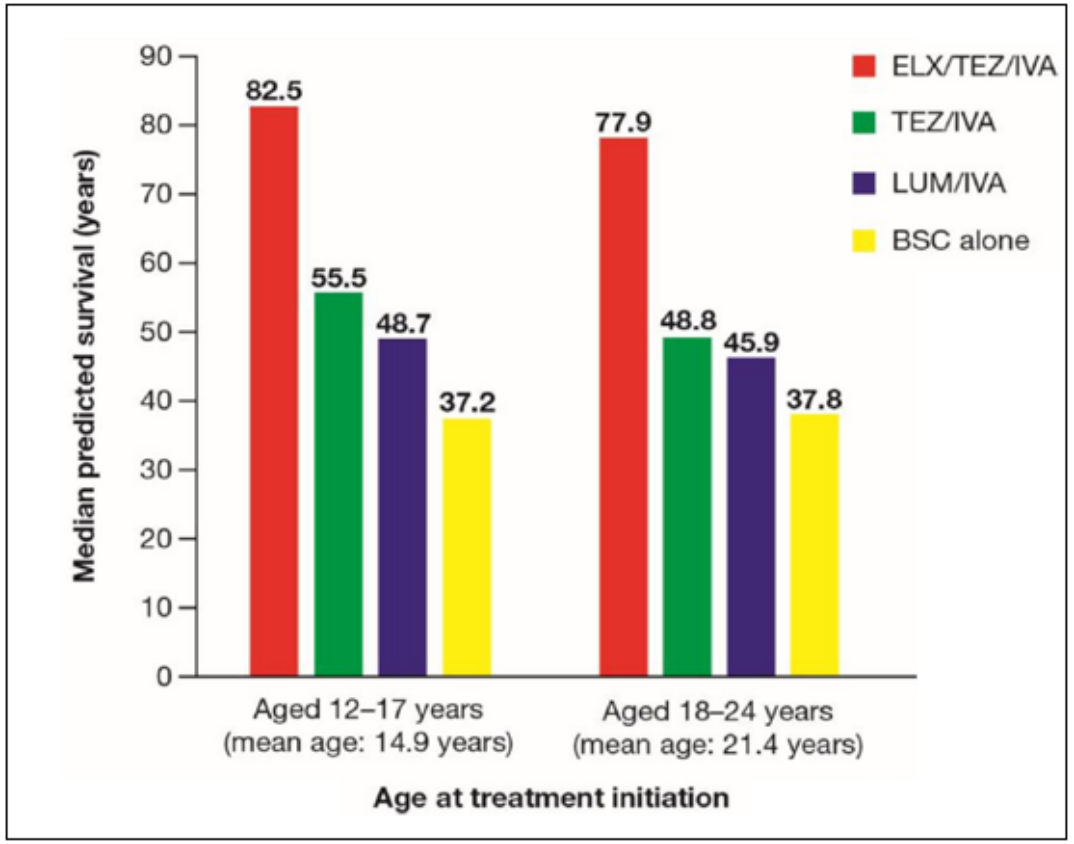
Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis; QALY, quality-adjusted life year

Key issue 5: Annual discount rates (2/3)

Company response:

- Substantial improvements in mortality for people with CF since the approval of ELX/TEZ/IVA
  - US CFFPR data: median predicted survival in 2020 = 59.0 years, in 2022 = 68.2 years
  - UKCFR data: 5-year predicted survival 2016-2020 = 50.6, 2018-2022 = 56.1
- ELX/TEZ/IVA [is now available] from age 2+
- Starting treatment before lung damage occurs, preserves lung function leading to substantial, prolonged clinical benefits
- There is potential for significant extension of life to near normal life expectancy (**Figure 1**)
- Age-specific simulation modelling of younger people shows acute improvement in ppFEV1 paired with long-term reduction in decline led to preserved lung function over lifetime horizon, which translates into maximised survival benefit (Lopez 2023)
- Treatment with ELX/TEZ/IVA also leads to rapid and stable reductions on sweat chloride – to lower than diagnostic threshold in most people

Figure 1: Mean predicted survival with ELX/TEZ/IVA, TEZ/IVA and LUM/IVA versus best supportive care (BSC) alone, by age at treatment initiation. Adapted from Lopez et al. (2023)



Abbreviations: CF, cystic fibrosis; US CFFPR, US Cystic Fibrosis Foundation Patient Registry. UKCFR; UK Cystic Fibrosis Registry

Key issue 5: Annual discount rates (3/3)

Patient, professional group and public comments:

- Criteria for 1.5% annual discount rate met – ELX/TEZ/IVA restores people to full or near normal health
- Failure to apply 1.5% discount rate implies lack of recognition of severity of CF and impact of CFTRms
- Many people, especially young people without established lung disease, will be able to enjoy normal health
- If "full health or near-full health" is defined as the ability to live life as if no longer had CF, lived experience shows the majority of people with CF treated with CFTRms would claim this
- Sweat tests, which indicate whether the cause of CF is present, are either near normal or in many cases within normal ranges with CFTRm treatment – as if they no longer have CF

EAG response:

- Provided a scenario analysis using non-reference case discount rates of 1.5% for costs and outcomes

What annual discount rate should apply – 1.5% or 3.5%?

Abbreviations: CF, cystic fibrosis; CFTRm, cystic fibrosis transmembrane conductance regulator modulator

Key issue 6: Severity modifier (1/3)

Committee conclusions in ACM1 (draft guidance section 3.15):

- Neither the EAG's nor the company's analyses incorporated all of the assumptions identified as the most plausible – therefore unable to conclude if a severity modifier should be applied.

NICE Technical Team comments ACM1:

- 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

Company response:

- Severity modifier of 1.7 is applied – CF is extremely severe and should qualify for the highest weighting – the QALY shortfall calculation is inadequately recognising severity
- Using a discount rate of 3.5%, as clarified by NICE, is biased against chronic diseases
- It is notable how the modifier differs between STA and HST – modifiers in the HST appraisal route are underpinned by undiscounted QALYs
- Using 3.5% discount rate, severity modifier of 1.2 is met. However, from a methodological and consistency perspective, no discount rate, or a lower discount rate of 1.5% should apply in the shortfall calculation where there is a case for the non-reference case discount rate
- When this is the case, CF is appropriately considered a severe disease with a 1.7 severity weighting

Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis; EAG, External Assessment Group; HST, highly specialised technologies; QALY, quality-adjusted life year STA, Single Technology Appraisal

Key issue 6: Severity modifier (2/3)

Public comments:

- Evident from patient, caregiver and clinician testimonies that cystic fibrosis is a severe disease associated with considerable morbidity and substantial shortening of life

Patient and professional group:

- Ample evidence CF is severe, multi-system disease which should qualify for the severity modifier
- Without standard therapy, most patients would die in childhood, and with standard therapy many die in their early adult life

EAG response:

- The severity modifier is based on a pre-determined calculation estimated from the inputs of the economic model and not on a subjective judgement of disease severity
- Adopting the committee's preferred assumptions at ACM1, a 1.2 severity modifier applies for the F/F, F/MF and F/Gating genotypes. A severity modifier of 1.0 applies for the F/RF genotype

Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis.

Key issue 6: Severity modifier (3/3)

EAG's severity modifier calculations based on committee ACM1 preferences with shortfall calculations estimated from Schneider *et al*. (2021)

	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	1.2	1.2	1.2	1.0

NICE Technical Team comments ACM1:

- F/RF genotype accounts for 6% of population in the scope of this appraisal
- Severity modifier = 1.2 for all genotypes when reducing the mean starting age to 2 years

What QALY weighting for severity should apply?

Abbreviations: Abs., absolute; CF, cystic fibrosis; EAG, External Assessment Group; prop., proportional; QALY, quality adjusted life year

Key issue 7: Ivacaftor as a comparator

Background

- This was an additional issue raised by the company at consultation and not discussed during ACM1

Company:

- Ivacaftor monotherapy (IVA) should be included as a comparator to ELX/TEZ/IVA for patients with an F/Gating or F/R117H mutation
- This was explained to NICE during scoping, but the request was not incorporated into the final scope
- NICE stated that: *"Ivacaftor monotherapy is licensed for use in people "who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R". Ivacaftor is not considered a relevant comparator in people with at least one F508del mutation."*
- This response misunderstands the fact that a patient can have at least one F508del mutation and be eligible for IVA if they have an R117H or gating mutation on the second allele
- Ivacaftor monotherapy is established clinical management and should be included as a comparator in the F/R117H and F/Gating mutation (8.6% of total CF population)

Clinical expert: Should IVA monotherapy be included as a comparator for the F/Gating and F/R117H genotypes?

Abbreviations: ACM1, appraisal committee meeting 1; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator

Key issue 8: Uncaptured benefits and cost savings (1/3)

Stakeholder comments:

- At consultation, stakeholders listed a wide range of uncaptured benefits for people with CF, their carers and wider families that should be included within the analysis
- Stakeholders also emphasised that treatment with CFTRms, particularly ELX/TEZ/IVA, will lead to significant cost savings for the NHS and have a beneficial impact on the wider economy
- Direct health benefits and cost savings are listed in **Table 1**

Direct health benefits and cost savings	
• Pancreatic recovery and ability to stop or reduce enzyme replacement • Improved abdominal symptoms • Reduced bacterial colonisation of the lungs • Reduced hospitalisations and requirement for IV antibiotics • Infections are easier to treat • Improved glycaemic control and reduced diabetes • Increased health stability • Better sleep, more energy, motivation and not feeling constantly tired • Increased confidence	• Reduced need for prescribed medications • Improvements in sinus inflammation, bowel and bladder control • Reduced pancreatic scarring and liver disease or failure/ transplants • Huge impact on mental health of patients and carers and families • Positivity and hope about the future rather than fear and anxiety • Use of primary care rather than higher tier services • Preserved lung function if treatment started in children aged 2

Abbreviations: CF, cystic fibrosis; CFTRm, cystic fibrosis transmembrane conductance regulator modulator

Key issue 8: Uncaptured benefits and cost savings (2/3)

Stakeholder comments:

- Indirect benefits and cost savings are listed in **Table 2**

Indirect benefits and cost savings	
• Patients and carers ability to work, and contribute to the economy without needing to take time off and impact on wellbeing • Less travel time to hospital appointments • Increased fertility and ability to start a family • Reduced transplant waiting list • Reduced need for burdensome medicines and physiotherapy – time savings for patients and carers • Ability to increase activities with friends and family, positive impact on social life and starting relationships	• Reduced sickness and carer benefits • Reduced housing adaptions and moves due to ill health • Reduced social services costs for children and adults • Reduced community and mental health support services • Reduced prescription charges

Key issue 8: Uncaptured benefits and cost savings (3/3)

EAG response:

- Agrees that ELX/TEZ/IVA will have large and clinically meaningful effects in most of these areas
- Notes that although these features are not individually tracked, effects on peoples' HRQoL are partially tracked through HRQoL measures and overall pooled statistics for costs
- Should a treatment-specific utility benefit apply, this may capture further increases in HRQoL

NICE Technical Team comments:

- NICE technology evaluations manual, section 4.2.7:
- "For the reference case, the perspective on outcomes should be all relevant health effects, whether for patients or, when relevant, other people (mainly carers).
- The perspective adopted on costs should be that of the NHS and PSS."

How should uncaptured benefits and cost savings be handled?

Abbreviations: HRQoL, health related quality of life; PSS, personal and social services.

Committee and company preferred assumptions

= Large impact

Assumption	Committee & EAG (ACM1)	Company (for ACM2)	Agree?
Long-term rate of ppFEV1 decline – ECM	Szczesniak (2023)	Szczesniak (2023)	Yes
Long-term RR in ppFEV1 decline – ELX/TEZ/IVA	[redacted]%	100%	No
Long-term RR in ppFEV1 decline – TEZ/IVA	61.5%*	61.5%	Yes
Long-term RR in ppFEV1 decline – LUM/IVA	42%*	42%	Yes
Separate tx effect for PEx applied long-term?	Yes	Yes	Yes
Health-state utility values	Acaster (2015)	Acaster (2015)	Yes
Treatment specific utility benefit	No	Yes	No
Caregiver utility benefit	Age 1-11	Age 1+	No
Reduction in disease management costs	No	Yes (company approach)	No
Severity modifier	Unable to conclude	1.7	No
Economic model used	EAG's model	EAG's model	Yes
Compliance (post-acute)	[redacted]%	[redacted]%	Yes
Annual discount rates	3.5%	1.5%**	No

Notes: *EAG's original base case values presented as scenarios. **Company prefer discount rates of 3.5% for costs and 1.5% for benefits but has presented a case for using 1.5% discount rates for costs and benefits. **Abbreviations:** ACM, appraisal committee meeting; EAG, External Assessment Group; ECM, established clinical management; PEx, pulmonary exacerbations; ppFEV1, percent predicted forced expiratory volume in 1 second; RR, relative reduction; tx; treatment

Cost-effectiveness results

Cost-effectiveness results are confidential and will be presented in Part 2 of this meeting – **Note:** All of the company base case results exceed cost effectiveness threshold, however company 'has an existing commercial arrangement with NHS England, which will be updated following the NICE appraisal'*

*Source - company consultation response

NICE National Institute for Health and Care Excellence