Multiple Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

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

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3. **Comments on the Draft Guidance from experts:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 24 November 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. *The Appraisal Committee is interested in receiving comments on the following:* • *has all of the relevant evidence been taken into account?* • *are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* • *are the provisional recommendations sound and a suitable basis for guidance to the NHS?* *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:* • *could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.*
Organisation name – Stakeholder or respondent	Vertex Pharmaceuticals Ltd.
Disclosure	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

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Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	**Executive Summary** Economic model • Vertex has identified another error in V6.0 of the EAG model. Vertex identified that the calculation of PEx costs in the CFTRm arm are still estimated based on the total number of PEx events of the ECM arm leading to an overestimation of the disease management costs in the CFTRm arm. We have corrected this in our working version of the EAG model, and the updated base case has been run with this correction. Rate of change in lung function • Vertex maintains that the reduction in Rate of Change in lung function for IVA/TEZ/ELX is higher than the committee's preferred assumption and should be 100%. This is supported by additional analyses and available long-term evidence, presented in detail below. Disease management costs • The EAG's approach to costs is flawed and lacks face validity. Vertex proposes an updated approach which recognises reductions in drug and disease management costs for patients who are on CFTRm vs ECM, as well as reflecting the fact that health state costs should vary by severity (in the EAG's approach costs across mild, moderate and severe disease are very similar). Treatment specific utility increment • Vertex accepts the use of Acaster utilities but maintains that the treatment specific utility for patients on IVA/TEZ/ELX should be included to account for extra-pulmonary utility gain related to being treated with a CFTRm. Caregiver utility • It is appropriate to apply a caregiver utility benefit for caregivers without an upper age limit, as was reflected by the caregivers providing evidence to the committee on 12th October. Severity • The highest severity weighting should apply to cystic fibrosis. NICE's clarification that the 3.5% discount rate should apply in the QALY shortfall calculation for the severity weighting, even when the non-reference case discount rate applies is biased against chronic diseases. It is evident from patient, caregiver and clinical opinion that the 1.7 maximum weighting should apply.

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	Discounting • Vertex maintains that a differential discount rate of 3.5% for costs and 1.5% for outcomes would be most appropriate but following discussion with NICE we have also provided evidence that the criteria for the non-reference case discount rate (1.5% for costs and outcomes) are met; this evidence is provided below. Comparators • Ivacaftor monotherapy should be included as a comparator for some F/gating patients in comparison with IVA/TEZ/ELX, as stated in the clarification letter. We request that the EAG updates the model to incorporate IVA as a comparator.
2	**Economic model – corrections and comments** Vertex received an updated model from the EAG in which most of the errors previously identified were corrected. While Vertex agreed with the general structure of the EAG model, Vertex has identified errors in every version of the model shared by the EAG which is currently in version 6.0. In this most recent version, Vertex identified that the calculation of PEx costs in the CFTRm arm are still estimated based on the total number of PEx events of the ECM arm leading to an overestimation of the disease management costs in the CFTRm arm. We had previously verbally highlighted this to NICE, but it has not been corrected. We have corrected this in our working version of the EAG model. Vertex would like to reiterate that the overall complexity of the equations and programming used by the EAG are not in line with general good practices expected in health economic modelling. This has led to the model being slow and unresponsive to scrolling and editing, and extremely long run times often taking up to 90 minutes for a single analysis. This being said we have spent significant resource QCing the EAG model as far as possible in the short consultation period to ensure it is as suitable as possible for decision-making. The updated base case at the end of this document has been run with a corrected version of the EAG model and we request this V7.0 of the model be used for any future analysis.
3	**Impact of COVID-19 on lung function** The committee recognised that COVID-19 had an unknown impact on confounding, but that on balance there would likely have been some positive and some negative effects on people living with CF. Therefore, the committee was satisfied that long-term data collected during the last 4 years was a suitable source of evidence for the long-term effect of the medicines. Additional analyses that evaluate rate of lung function decline with the specific intent of addressing any potential COVID impacts, which are described below, have also demonstrated that the observed impact on lung function decline is due to treatment and not COVID-associated lockdown policies and support the committee's conclusions. To further demonstrate there is no meaningful confounding effect from COVID, Vertex has conducted *additional* analyses for the rate of change in ppFEV1 in the 445-105 study, excluding data collected during the pandemic. When excluding the pandemic data, the estimated annualised rate of change in ppFEV1 among the overall IVA/TEZ/ELX cohort was [redacted] This additional analysis supports the conclusion from

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	the primary analysis of no decline in lung function (as measured in ppFEV1), even when the data collected during the pandemic is excluded (see further detail in section #4). Further, Vertex is presenting the recent findings of a new comparative analysis with a contemporaneous cohort. This is a non-interventional, retrospective, longitudinal study using data from the US CFFPR using robust methodology and statistical analysis to assess the change from baseline in ppFEV1 in the IVA/TEZ/ELX-treated patients compared with a contemporaneous IVA/TEZ/ELX-untreated comparator cohort during the period between 2019 to 2021, i.e. removing any confounding effect of the COVID-19 pandemic from comparative outcomes. The annualised rate of change in ppFEV1 among the IVA/TEZ/ELX-treated cohort (N = 7,360) was [redacted] percentage points [redacted] compared with [redacted] decline observed in the comparator cohort (N=7,288), amounting to a [redacted] reduction in the rate of lung function decline (see further detail in section #4). These additional analyses affirm the committee's opinion.
4	**Rate of change in lung function** **Vertex maintains that the reduction in Rate of Change in lung function for IVA/TEZ/ELX is higher than the committee's preferred assumption and should be 100%.** Vertex has reviewed all available mean annualised rate of change in ppFEV1 estimates in patients treated with IVA/TEZ/ELX as well as data in untreated populations in comparison, some of which were not available at the time of the first committee meeting. As shown in **Figure 1** and **Table 1**, the results from different data sources indicate no decline in lung function following IVA/TEZ/ELX treatment across a number of analyses. [redacted] Considering the totality of data, we consider the UKCFR as well as the other studies (see paragraphs below) to be supportive of the overall conclusion of no decline in ppFEV1 in people with CF treated with IVA/TEZ/ELX, and that the open-label extension (OLE) 445-105 study provides the most robust estimate of rate of change in ppFEV1. As mentioned in Section 3, Vertex is providing additional analyses of the 445-105 study excluding data collected during the pandemic, to remove any potential COVID-19 confounding effect. In addition, Vertex has data from the US Cystic Fibrosis Foundation Patient Registry (US CFFPR) which further addresses the uncertainty of COVID-19 on the rate of change by comparing patients treated with IVA/TEZ/ELX and those untreated with IVA/TEZ/ELX during the same time. Furthermore, we now have longer-term data from the 445-107 paediatric long-term extension study with a rate of change analysis also indicating no decline in ppFEV1. This evidence is presented below. **445-105 long-term extension study including further analysis with pandemic data removed:** **A. Study duration of 445-105 compared to the UKCFR analysis:** The 445-105 study provides the longest follow-up period to date (up to 192 weeks, i.e., 44.3 months), covering the time before, during and after the pandemic (2). In the UKCFR, the comparative IVA/TEZ/ELX matched cohort (which contributed to the rate of change analysis) had a mean follow-up time of [redacted] (1). The longer follow-up time in the 445-105 study provides a more robust estimate of the annual change (in ppFEV1 over time). **B. Quantity of data from the 445-105 analysis compared to the UKCFR analysis:**

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The 445-105 study provides a more accurate best-fit estimate of ppFEV1 change based on a large dataset. Of the 506 patients who received at least 1 dose of IVA/TEZ/ELX in the 445-105 study, 356 (70.4%) completed treatment up to the final treatment period (week 192), contributing to a total of [redacted] of ppFEV1 collected (3). In the UKCFR, [redacted] are available for the [redacted] IVA/TEZ/ELX matched cohort contributing to the rate of change analysis (1). Therefore, the mixed effects model estimates of the annual change in ppFEV1 over time are [redacted] ppFEV1 measurements per patient. The larger set of data points in the 445-105 study provides a more accurate best-fit values of the slope.

C. **Analysis of the 445-105 study excluding data during the pandemic shows no decline in lung function consistent with the primary analysis***(* indicates data that was not available at the time of dossier submission)

The majority of data ([redacted] from the 445-105 study was collected outside the period associated with the COVID-19 pandemic restrictions, i.e. outside the timeframe of March 2020 to July 2021 (3). A post-hoc rate of change analysis was conducted on the final dataset of study 445-105, excluding data collected between March 2020 and July 2021, as a means to reflect the timing of the most severe restrictions associated with the pandemic. The estimated annualised rate of change in ppFEV1 among the overall IVA/TEZ/ELX cohort was [redacted] (**Figure 1, Table 1**). This additional analysis supports the conclusion from the primary analysis of no decline in lung function (as measured in ppFEV1).

US CFFPR analysis during the pandemic shows no decline in lung function in patients treated with IVA/TEZ/ELX compared to a contemporaneous cohort showing a decline in lung function*:

The model input of a 100% reduction in rate of lung function decline for patients treated with IVA/TEZ/ELX, based on the estimates from the 445-105 study, is further supported by data from the US CFFPR. A non-interventional, retrospective, longitudinal study was conducted using data from the US CFFPR from October 21, 2019 through December 31, 2021, to assess the impact of COVID-19 on clinical outcomes. A cohort of people with CF (aged 12 years and older) who were treated with IVA/TEZ/ELX was compared with a contemporaneous cohort who were ineligible for and untreated with IVA/TEZ/ELX. A standardised mortality ratio (SMR) weighting based on propensity scoring methods was used to ensure the comparability between the treated cohort and comparator cohort, and that any impact of COVID-19 on the two cohorts is non-differential. The mean number of ppFEV1 measurements per patient for the IVA/TEZ/ELX-treated and comparator cohorts were [redacted], respectively. The annualised rate of change in ppFEV1 among the IVA/TEZ/ELX-treated cohort [redacted] compared with [redacted] observed in the comparator cohort ([redacted]), amounting to a [redacted] in the rate of lung function decline (**Figure 1, Table 1**, **Appendix 1**). The rate of decline in the untreated cohort of greater than [redacted] percentage points during this period is counter to any protective effect of COVID lockdowns on lung function decline in CF patients. It should also be noted that this study included patients who had at least one F508del mutation (i.e. including F/F, F/MF, F/Gating, F/RF and F/other genotype), covering a wider cohort than that of the 445-105 study and the UKCFR rate of change analyses (both of which included F/F and F/MF patients only), therefore it is considered more generalisable to the indicated CF populations in the UK (4).

Additional studies showing no decline in lung function in patients treated with IVA/TEZ/ELX:

The 445-105 study showing no decline in ppFEV1 over time in IVA/TEX/ELX-treated patients aged 12 years or older (with F/F or F/MF) is aligned with the results from the 445-107 study (in

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CF patients with F/F or F/MF genotypes aged 6-11 years) and the 445-110 study (in CF patients with F/Gating or F/RF genotypes aged 12 years or older) (5, 6). As shown in **Appendix 2**, the ppFEV1 improvement was maintained through 144 weeks and 96 weeks of additional treatment in the 445-107 and 445-110 OLE period, respectively. This data is also complemented by the sweat chloride (SwCl) results from the same studies that show the absolute changes in SwCl from parent study baseline were sustained throughout the analysis period (**Appendix 2**). A post-hoc rate of change analysis was also conducted on the latest interim analysis (OLE Week 144) of study 445-107*. The estimated annualised rate of change for ppFEV1 was [redacted] supporting the conclusion of no decline in lung function following IVA/TEZ/ELX treatment (**Figure 1,Table 1**) (5).

***Please note this data was not available at the time of submission of the dossier**

Figure 1: Mean (±95% CI) annualised rate of change in ppFEV1 estimates in IVA/TEZ/ELX-treated cohorts and the matched control (IVA/TEZ/ELX-untreated), using data from different sources

Abbreviations: ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, United Kingdom Cystic Fibrosis Registry; US CFFPR, United States Cystic Fibrosis Foundation Patient Registry.

Table 1: Mean annualised rate of change in ppFEV1 estimates in IVA/TEZ/ELX-treated cohorts and the matched control (IVA/TEZ/ELX-untreated), using data from different sources

Data source	Mean annualised rate of change in ppFEV1 % (95% CI)		
	IVA/TEZ/ELX	Matched control	Relative reduction vs matched control
UKCFR, age 12+, F/F and F/MF[1]	[redacted]	[redacted]	[redacted]
US CFFPR, age 12+, F/any and non-F ETI-responsive	[redacted]	[redacted]	[redacted]
445-105 wk 192, age 12+, F/F and F/MF[3,4]	[redacted]	N/A	N/A
445-105 wk 192, age 12+, F/F and F/MF[3]	0.02 (-0.14, 0.19)	N/A	N/A
445-105 wk 144, age 12+, F/F and F/MF[3]	0.07 (-0.12, 0.26)	N/A	N/A
445-105 wk 96, age 12+, F/F and F/MF[2]	0.39	-1.92	120.3%

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	<table><tr><td></td><td>(-0.06, 0.85)</td><td>(-2.16, -1.69)</td><td>(96.8%, 144.4%)</td></tr><tr><td>445-107 wk 144, age 6-11, F/F and F/MF[3]</td><td>0.10 (-0.92, 1.12)</td><td>N/A</td><td>N/A</td></tr><tr><td>445-107 wk 96, age 6-11, F/F and F/MF[3]</td><td>0.51 (-0.73, 1.75)</td><td>N/A</td><td>N/A</td></tr></table> [1]annual reviews only [2]registry-matched analysis [3]unmatched analysis [4]excluding data points during pandemic Abbreviations: IVA/TEZ/ELX, fixed dose combination of ivacaftor, tezacaftor and elexacaftor; N/A, not applicable; ppFEV1, percent predicted forced expiratory volume in 1 second; UKCFR, United Kingdom Cystic Fibrosis Registry; US CFFPR, United States Cystic Fibrosis Foundation Patient Registry; vs, versus.
5	**Disease management costs** **The EAG's approach to costs is flawed and lacks face validity. Vertex proposes an alternative approach which recognises reductions in drug and disease management costs for patients treated with CFTRms compared to ECM, as well as reflecting the fact that health state costs should vary by severity (in the EAG's approach costs across mild, moderate and severe disease are very similar).** In their evaluation of cost and resource use inputs in the cost-effectiveness analyses, the appraisal committee concluded that the EAG's costs of established clinical management (ECM), sourced from Tappenden 2023 (7) (healthcare costs) and Granger 2022 (8) (pharmacotherapy costs) were the most appropriate sources for the economic model. There are however four important ways in which EAG's cost and resource use inputs mark a significant departure from the UK clinical practice reality: **1. Reductions applied to ECM drug and disease management costs on CFTRM initiation:** EAG's base case assumes equal ECM drug and disease management costs for patients treated with ECM alone and those treated with CFTR modulators in addition to ECM. There is however a growing body of evidence of a significant long-term impact of CFTRms on healthcare resource use (HCRU) and pharmacotherapy costs in the UK clinical practice, outlined below. Simmonds et al investigated the HCRU of pwCF aged 6 years or older in the UK, Italy and the Netherlands in the 12 months before and after initiation of IVA (VOCAL observational study, Simmonds 2022) (9). The twelve-month all-cause hospitalization rate and the course rate of intravenous (IV) and oral/inhaled antibiotics for 73 patients treated with IVA in the period 2015 - 2020 were reduced by 70% during the first 12 months of IVA initiation compared with 12 months prior to IVA and was maintained at that level throughout the 48 months of prospective data collection. The annualized rate of outpatient visits on the other hand remained stable. A significant decline in inpatient and IV antibiotic days in the first year following IVA initiation was also observed in a retrospective study of 35 adult patients from the Manchester CF Centre followed for 2 years prior and 5 years post-IVA initiation (9.2 ± 4.2 inpatient days and 11.9 ± 4.8 IV antibiotic days during Year 1 post-IVA vs 23 ± 6.8 inpatient days and 27.3 ± 6.1 IV antibiotic days in the year pre-IVA initiation) (10). Estimated marginal means for inpatient days were lower in patients with mild lung disease (FEV1 >70%) compared with those with moderate disease (FEV1 41%–70%, p=0.002), indicating a correlation between disease severity and HCRU. Similar findings have been reported in the longitudinal analyses of the UK CF Registry patients treated with IVA (11)(12). The post-authorisation safety surveillance study of 293 patients treated with IVA and 1433 matched untreated controls who were followed up for up to 4 years reported significant reductions in the proportion of patients needing hospitalisations with IV antibiotic among IVA-treated vs untreated controls (Yr4 RR, 0.59 (0.47-0.73)) and vs baseline (26.3% vs 47.0% of patients). Vega-Hernandez et al. observed a 50% reduction in risk of all-cause hospitalisation in the 12 months after initiation of any CFTRm among 166 UK CF Registry patients in Wales (13). The average length of hospital stay was also more than halved post-

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CFTRm initiation. The effect size was particularly pronounced among 36 patients treated with IVA/TEZ/ELX (annual hospitalisation rate of 2.00 (1.36,2.93) vs 0.60 (0.32, 1.14) before and after IVA/TEZ/ELX initiation, respectively).

Using the RCT and UKCFR data on pwCF aged 12 years or older in the period from 2015 to 2018, Keogh and colleagues developed a model to predict the impact of TEZ/IVA and IVA/TEZ//ELX introduction on NHS resource use, in particular hospital bed utilisation (14). Their results suggest that, in the subset of pwCF eligible for IVA/TEZ/ELX (including those who switched from TEZ/IVA), introduction of IVA/TEZ/ELX is expected to result in a significant reduction in total hospital-IV antibiotic days of between 22.7% (assuming treatment effect on hospital-IV days is causally mediated through ppFEV1) and 50.6% (assuming effect is mediated through reduced rate of PEx) over and above the estimated benefits derived from starting TEZ/IVA (5.3% and 23.7% reduction, respectively).

The evidence of the considerable impact of CFTR modulators on HCRU in CF presented here supports inclusion of the cost offset for the disease management and pharmacotherapy costs of patients treated with CFTRms relative to those treated with ECM. While acknowledging the variation in the specific outcomes reflective of inpatient costs across studies, the impact of IVA was consistently observed to be at ~50% reduction vs ECM. IVA/TEZ/ELX was observed and predicted to have a more substantial impact, which justifies a cost offset of 70%.

2. Cost differentiation between health states based on disease severity (ppFEV1)

Health state resource use data in the economic evaluation by Tappenden 2023 (7) were collected using a questionnaire administered periodically during the CFHH trial to assess adherence and inform disease management costs. The disease management and PEx costs associated with the mild ($ppFEV_1$>70%) and severe ($ppFEV_1$<40%) lung function impairment were estimated to be nearly identical or even slightly lower in the severe state (£3,368 vs £3,320, respectively), implying that **mild and severe lung disease are associated with the same HCRU** including clinic visits, hospitalisations, nurse time, A&E, physiotherapists, dieticians, etc. This is at odds with clinical and observational data showing strong, significant association of moderate ($ppFEV_1$ 40-69%) and severe ($ppFEV_1$<40%) lung function impairment with high costs, particularly for inpatient care, A&E and specialist visits (15, 16, 17, 18). It is also contrary to the costing approach of most other economic evaluations of treatments for pwCF published to date that deploy health states defined by $ppFEV_1$ (**Appendix 3**). In these economic models, health state RU and RU associated with pulmonary exacerbations were stratified by $ppFEV_1$ range, with the cost of the severe lung function state being costlier than the mild by a factor ranging from 2.3 (19) to 6.9 (20). Although Ramagopalan 2014 study is nearly a decade old, it is the only available UK source of costs by $ppFEV_1$ range, and its findings are consistent with the resource use studies from other geographies indicating >3.5 times higher risk of persistent high costs in patients with severe vs mild lung function (15, 21).

In the light of strong evidence for cost differentiation between health states defined by lung function, we question the accuracy of data collected in CFHH trial, given the known limitations of questionnaires associated with recall bias, memory bias, incomplete data trends, inaccurate estimations, and response burden. To reflect the clinical reality, health state costs from Tappenden 2023 (7) should be stratified by $ppFEV_1$ range using ratios from Ramagopalan 2014 (21), as shown in the **Table 2** below.

Table 2: Optimised annual health state costs for cost-effectiveness model sourced from Tappenden 2023 (7), adjusted for severity of lung impairment (Vertex base case)

$ppFEV_1$ (%)	Health care costs for patients on ECM	
	Ratio (Ramagopalan 2014 (21))	Optimised cost input for economic model

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≥70	1	£3,460
40-69	2.85	£9,857
<40	4.65	£15,777

Abbreviations: ECM, established clinical management; ppFEV1, percent predicted forced expiratory volume in 1 second.

3. PEx cost reduction post CFTRM initiation driven by reduced severity

In the EAG model the cost of each PEx is based on 14 days of inpatient stay in hospital, receiving IV antibiotics. The unit cost for inpatient stay and IV drugs received in hospital to treat PEx was taken from Tappenden 2023. **The EAG approach assumes that a PEx event has the same duration for patients treated with ECM and CFTRm**, which is not consistent with real-world evidence. Our UKCFR DCA study observed a 70% reduction on the number of days on IV antibiotics (at home or hospital) with average number of days decreasing from 15.68 to 4.70 days in the 12-month prior to 12-month post IVA/TEZ/ELX initiation, respectively. Further, there was a 50% reduction in the number of days on IV antibiotic per treatment episode in hospital. Similarly, 75% reduction in the duration of PEx events was observed for patients treated with IVA relative to pre-treatment period in Simmonds 2022 (9). Also, the average number of days spent in hospital per person per PEx event reduced by 91.7% from 7.3 days to 0.6. Therefore, based on the evidence presented, **a conservative 50% reduction** should be applied to the cost of PEx that occur while patients are on CFTRms. In addition, as reported in the ACD, the clinical expert to NICE mentioned during the committee meeting that even if patients treated with CFTRm do have an exacerbation, it can be easily treated with oral antibiotics rather than needing hospitalisation for IV antibiotics. It was also reported that there has been a large reduction in the need for IV antibiotics and hospitalisation in children treated with IVA/TEZ/ELX, that has been maintained over time. This supports our position that the cost of a PEx episode for patients treated with a CFTRm is lower than for patients treated with ECM alone.

4. Reduction to the mild health status (ppFEV1≥70) medicines costs

In Granger 2022 (8) health costs for mild patients is reported at £10,453, which is not consistent with other sources of evidence for mild patients' costs (21). The methods used by Granger produce unreliable results. Costs are annualised based on dosage; these are then corrected by the proportion of patients taking each medicine stratified by severity using $ppFEV_1$.This produces results that suggest more patients within each severity group are taking more medicines. However, this is inaccurate based on Ramagopalan 2014 (21) rather, the increase in costs across severity is seen due to more severe patients having a higher volume of medicines.

Vertex proposes applying a reduction based on the variation in health states seen in Ramagoplan (2014) (21) where pharmacotherapy costs for mild patients were 80% and 81% lower than moderate and severe patients, respectively. Therefore, health costs for mild patients were adjusted to be 81% lower than moderate and severe patients, resulting in an annual cost of £2,490.

To conclude, Vertex proposes the following evidence-based optimisation of the EAG's preferred cost inputs in the economic model:

- The health state costs (encompassing inpatient, outpatient and other non-PEx associated costs), should be stratified by severity of lung disease impairment as defined by $ppFEV_1$
- A 50% reduction should be applied to the cost of PEx events that occur when patients are on CFTRms vs ECM
- A 70% reduction should be applied to the cost of health state and pharmacotherapy for patients treated with CFTRms vs ECM.

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The health care and pharmacotherapy costs for patients treated with ECM alone vs CFTRms used in Vertex's base case are outlined in the table below.

Table 3: Annual health state and pharmacotherapy costs for patients treated with ECM alone and those treated with CFTRm+ECM (Vertex base case inputs)

$ppFEV_1$ (%)	Healthcare costs		Pharmacotherapy costs		PEx cost	
	ECM alone	CFTRm+ECM	ECM alone	CFTRm+ECM	ECM alone	CFTRm+ECM
≥70	£3,460.07	£1,038.02	£2,481.96	£744.59	£6,307	£3,153
40-69	£9,857.22	£2,957.17	£12,107.15	£3,632.15		
<40	£15,776.98	£4,733.09	£13,449.63	£4,034.89		

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

6

Treatment specific utility increment

Vertex accepts the use of Acaster utilities but maintains that the treatment specific utility for patients on IVA/TEZ/ELX should be included.

The available evidence shows with no doubt that a patient treated with ELX/TEZ/IVA in a given disease severity feels better than a patient who is not treated with ELX/TEZ/IVA who has the same level of disease severity, this is due to the unique effect and clinical benefits of ELX/TEZ/IVA beyond the respiratory domain. The economic model applies health-state utilities as a function of patient clinical characteristics that include ppFEV1, occurrence of a PEx, and treatment status. Defining the relationship between lung function and quality of life (utility) allows the model to estimate the benefit of effective treatment as mediated by preservation of/improvements in lung function but does not capture the independent impact of treatment with IVA/TEZ/ELX on other body systems and health dimensions, which may be substantial. One way to understand these impacts, above and beyond the HRQoL associated with lung function changes, is to evaluate HRQoL while controlling for ppFEV1 health status.

In TRAJECTORY, an observational, longitudinal study investigating the impact of IVA/TEZ/ELX treatment in patients with CF in the real-world, when controlling for ppFEV1, patients continued to show utility improvements, highlighting a treatment specific utility benefit beyond the improvements seen in $ppFEV_1$. In the EAG and Vertex model, patients who do not move across the different levels of disease severity, mediated by $ppFEV_1$, show no gains in utility, e.g. a patient with an ppFEV1 of 50 at baseline will remain in a moderate state after benefiting from treatment initiation with ELX/TEZ/IVA which ignores the benefits beyond the respiratory domain provided by IVA/TEZ/ELX.

As data in Table 4 indicates, patients post initiation with IVA/TEZ/ELX have an increase in utility even when remaining within the same disease severity (ppFEV1):

Table 4: Descriptive Summary of CFQ-R-8D Utility Score following IVA/TEZ/ELX initiation for Subjects ≥14 Years Old at Enrolment Post-Baseline by Disease Severity Pre- and Post-Baseline

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

Abbreviations: CFQ-R-8D, Cystic Fibrosis Questionnaire-Revised-8 Dimensions; ppFEV1, percent predicted forced expiratory volume in 1 second.

To generate this treatment specific utility, we performed a mixed effects model for repeated measures (MMRM) analysis on the TRAJECTORY data to make statistical inferences about the impact of IVA/TEZ/ELX treatment on CFQ-R-8D (adjusted for ppFEV1). The CFQ-R is a validated CF-specific tool and has a preference-based scoring algorithm (the CFQ-R-8D)

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designed in accordance with NICE guidelines, which enables estimation of health-state utilities based on the CFQ-R, that better reflects preferences in CF. The CFQ-R assesses 12 domains of health-related quality of life, shown in Table 6, thus capturing physical, social, and psychological impacts of the disease.

The updated results of that analysis are presented below in Table 5 which further support the use of this treatment specific utility demonstrating quality of life benefit beyond lung function.

Table 5: MMRM Analysis of CFQ-R-8D Utility Score for Subjects ≥14 Years Old at Enrolment at Baseline and Post-Baseline

Data point	ELX/TEZ/IVA N = 202
Study baseline	
n	[redacted]
LS mean	[redacted]
Post-baseline	
n	[redacted]
LS mean	[redacted]
LS mean Difference (Post-Baseline vs Study Baseline), 95% CI	[redacted]

Abbreviations: ELX/TEZ/IVA, fixed dose combination of elexacaftor, tezacaftor and ivacaftor: LS, least square; vs, versus.

This updated analysis is based on the 1-year analysis that has both CFQ-R-8D and $ppFEV_1$ at baseline (before ELX/TEZ/IVA initiation) and after treatment initiation, allowing us to estimate the treatment effect adjusted for ppFEV1 (22).

As part of UK data collection agreement, objective 14 was designed to analyse the impact CFTRms have on quality of life via the CFQ-R. 96 patients who initiated treatment with IVA/TEZ/ELX were identified in the registry with baseline CFQ-R data and at least one follow-up measure within the subsequent 12 months after treatment initiation; and 129 patients with at least one follow-up measure within the subsequent 24 months after treatment initiation. Positive changes across most CFQ-R domain scores were observed at month 12 and sustained through month 24. Data is presented in Table 6.

Table 6: Change from baseline in CFQ-R scores per domain in IVA/TEZ/ELX patients (UK DCA)

Domain	Change from baseline	
	Group with data within 12 months N=96	Group with data within 24 months N=129
	Mean (SD)	Mean (SD)
Respiratory	[redacted]	[redacted]
Body	[redacted]	[redacted]
Digestion	[redacted]	[redacted]
Eat	[redacted]	[redacted]
Emotion	[redacted]	[redacted]
Health perception	[redacted]	[redacted]
Physical	[redacted]	[redacted]
Role	[redacted]	[redacted]
Social	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]
Vitality	[redacted]	[redacted]
Weight	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

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This analysis is further validated in study 445-102 (AURORA). Treatment with IVA/TEZ/ELX resulted in a numerical increase from baseline through Week 24 in the average CFQ-R non-respiratory domain scores (physical, vitality, weight, health perceptions, social, eat, role, treatment burden, body, emotion, and digestion) compared to placebo (Table 7). An MMRM analysis of absolute changes in CFQ-R non-respiratory domain scores from baseline through Week 24 show numerical improvements in each of the eleven non-respiratory domain scores in IVA/TEZ/ELX group relative to placebo with 10 of 11 domains achieving nominal statistical significance.

Table 7: Change from baseline in CFQ-R scores per domain in patients treated with IVA/TEZ/ELX vs PBO in study 445-102

AURORA 445-102, F/MF			
Domain	**IVA/TEZ/ELX N=200**	**PBO N=203**	**Difference or rate ratio (95% CI)†P Value**
Absolute change in CFQ-R non-RD scores from baseline through Week 24 (95% CI)			
Physical	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]
Emotion	[redacted]	[redacted]	[redacted]
Body	[redacted]	[redacted]	[redacted]
Eat	[redacted]	[redacted]	[redacted]
Treatment burden	[redacted]	[redacted]	[redacted]
Health perceptions	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]
Digestion	[redacted]	[redacted]	[redacted]
Role	[redacted]	[redacted]	[redacted]
Social	[redacted]	[redacted]	[redacted]

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CI, confidence interval; IVA/TEZ/ELX, fixed dose combination of ivacaftor, tezacaftor and elexacaftor; PBO, placebo; RD, respiratory domain.

In conclusion these data demonstrate the strength of the CFQ-R to measure quality of life in CF, the non-respiratory benefits patients gain, and affirm the inclusion of the treatment specific utility in the economic model.

7

Impact of CFTRm on caregiver burden

It is appropriate to apply a caregiver utility benefit for caregivers without an upper age limit, as was reflected by the caregivers providing evidence to the committee on 12th October.

During the committee discussion it was clear that caregivers believed they were impacted equally, if not more, in caring for people with CF beyond childhood. This is reflected in the ACD:

"Patient experts at the committee meeting described the high levels of anxiety, depression, and fear about the future experienced by carers. They explained that the care burden does not stop after childhood because the condition worsens over time."

This is clearly reflected by the evidence that people with CF have more pulmonary exacerbations and a faster rate of decline as they reach teenage years and into early adulthood and pulmonary exacerbations lead to significant caregiver burden (23). Evidence also shows that primary caregivers of children with CF report significantly increased burden during pulmonary exacerbations, as measured by the 12-item Short-Form Health Survey mental health component and the Work Productivity and Activity Impairment including worse outcomes in the domains of absenteeism, presenteeism, work productivity loss, and activity impairment component scores. Compared to the "well state," during pulmonary exacerbations-related hospitalization caregivers

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	reported lower physical health scores on the Child Health Questionnaire-Parent Form 28. More caregivers reported a negative impact on family/social/emotional functioning during pulmonary exacerbations than during the "well state". This study looked at caregivers of CF patients aged 2-17, further supporting the fact that a utility benefit should be applied beyond the age of 11 (24). Similarly, the vocational impact of CF on caregivers, collected from adolescents and their parents at 19 Italian CF referral centres, was substantial (25). The ACD does not reflect the consensus in the committee discussion, which clearly stated that the committee preferred application of the utility benefit for patients aged beyond 11 and would like to see a scenario for a lifetime benefit. Multiple committee members spoke in agreement on this point, including stating that parents would not stop worrying about their child or being negatively impacted by their illness as soon as those patients become 11. Equally, they also discussed the fact that the estimate for caregiver utility applied up to 18 would likely be conservative as patients frequently have more than one caregiver and the utility for those secondary caregivers is not reflected. Based on this, and referring to the caregiver who gave evidence at the committee, we believe it is reasonable for a utility benefit to be applied for the lifetime. Given the committee also acknowledges the evidence gathered from MAGNIFY, a study in caregivers of 6-11 year olds, is likely conservative, we believe this should be used, and that additional flexibility be considered by the committee on this basis. In addition, we will shortly have the final analysis from MAGNIFY which includes data from more patients and further confirms the caregiver utility benefit. We can share this with NICE after the consultation period.
8	**Severity** **The highest severity weighting should apply to cystic fibrosis. NICE's clarification that the 3.5% discount rate should apply in the QALY shortfall calculation used to derive the severity weight, even when the non-reference case discount rate applies is biased against chronic diseases. It is evident from patient, caregiver and clinical opinion that the 1.7 maximum weighting should apply.** **QALY shortfall calculation and discount rate** Considering NICE's severity weighting calculation, and specifically the requirement to discount QALYs at 3.5%, in Vertex's preferred base case, the 1.2 weighting is met. However, it is evident from the evidence given in writing and person by the CF community that the condition is extremely severe and should qualify for the highest weighting (1.7), and that therefore, the shortfall calculation is inadequately recognising severity. We acknowledge that NICE recently clarified that regardless of the discount rate used, QALYs should be discounted at 3.5% in the shortfall calculation for severity. We strongly disagree that the QALYs should be discounted, and this particularly applies where the non-reference case discount rate is used. The severity modifier calculation performs extremely well in situations where near-term mortality risk is high and/or HRQoL is extremely low at baseline. However, progressive diseases in which mortality increases or HRQoL deteriorates substantially over time, such as CF, are penalised by the discounted QALY approach and the only way that these diseases would be eligible for a modifier is by decreasing the QALY discount rate. Furthermore, it is notable how, in this respect, the modifier differs between STA and HST. Modifiers in the HST appraisal route are underpinned by undiscounted QALYs. Indeed, it is evident that a number of HSTs would never have been awarded a modifier had it been reliant

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	on discounted QALYs (26). Therefore, from a methodological and consistency perspective, it is clear that either no discount rate, or a lower discount rate of 1.5% should apply in the QALY shortfall calculation where there is a case for the non-reference case discount rate (as discussed in section #9). When this is the case, CF is appropriately considered a severe disease with a 1.7 severity weighting. **Severity of CF** Building on this, the fact the 1.7 weighting does not apply lacks face validity as it suggests that CF is not a very severe disease. The committee acknowledged the substantial difficulties faced by people with CF. It recognised that CF is a chronic and severe condition that affects the body across multiple organ systems, can impact the mental wellbeing of people with the condition and their carers. It also acknowledged that CF is associated with considerable morbidity and can substantially shorten the lives of people with the condition. However, the committee failed to conclude on the severity of the illness. Therefore, we believe the 1.7 weighting should apply to fully reflect the severity of CF.
9	**Discount rate** **Vertex maintains that a differential discount rate of 3.5% for costs and 1.5% for outcomes would be most appropriate but following discussion with NICE we provide evidence that the criteria for the non-reference case discount rate (1.5% for costs and outcomes) are met.** The NICE manual states that the committee may consider analyses using a non-reference case discount rate if a number of criteria are met. Below we outline those criteria and the evidence that the criteria are met. The three criteria are outlined and discussed in the ACD. The committee accepts that CF is a severe disease and that the benefits of treatment are likely to be maintained over a long period of time, but they were less certain on whether treatments return patients to near normal health. Therefore, we focus our response on this criterion, with the understanding the others are satisfied and the committee accepts this. **1. The technology is for patients that would otherwise die or have a severely impaired quality of life** As discussed by committee, shared by patient and clinical experts, and outlined in the Vertex evidence submission to NICE, without CFTRm treatment patients with CF would be expected to die very young. Median age of death is in the 30s (27). While the committee did not directly conclude whether the severity modifier applied, there was consensus on the fact that CF is a severe disease – as stated in the ACD '*The committee acknowledged the substantial difficulties faced by people with CF. It recognised that CF is a chronic and severe condition that affects the body across multiple organ systems, can impact the mental wellbeing of people with the condition and their carers. It also acknowledged that CF is associated with considerable morbidity and can substantially shorten the lives of people with the condition*.' **2. The technology is likely to restore patients to full or near normal health** The ACD states "*the committee noted that treatment with IVA–TEZ–ELX does not restore people with CF to full health, but rather prevents decline. Patient experts explained that IVA–TEZ–ELX may prevent decline if started early enough in young children before lung damage occurs. The committee acknowledged the potential additional benefits of IVA–TEZ–ELX in young children, but it had not seen any evidence to support this*."

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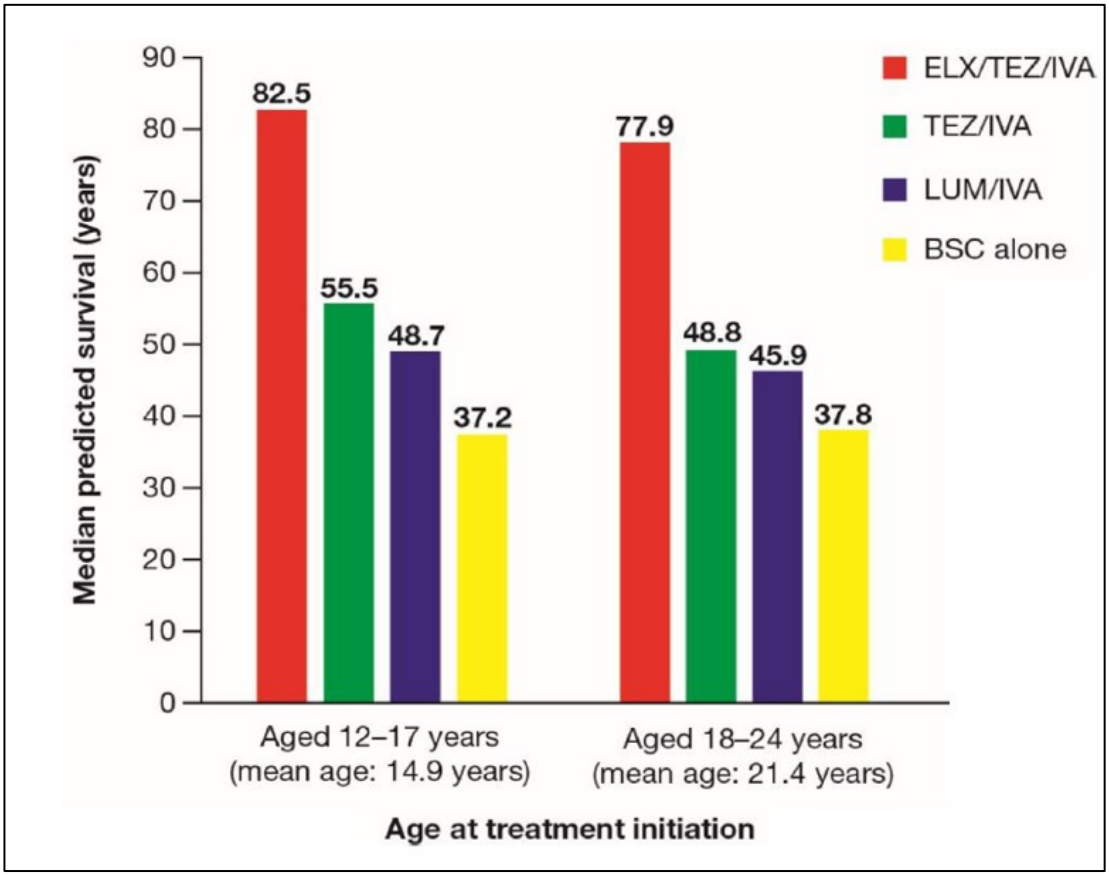
	As shown in the US CFFPR 2022 annual data report (**Appendix 4**), there have been substantial improvements in the survival of people with CF even in just three years since the approval of IVA/TEZ/ELX. The median predicted survival age of an individual born with CF in 2020 was 59.0 years (95% CI: 56.4, 65.1), increased to 65.6 years (95% CI: 59.2, 71.1) in 2021 and 68.2 years (95% CI: 63.0, 76.2) in 2022 (28). This is also consistent with the UKCFC 2022 annual data report which shows that the 5-year predicted survival increased from 50.6 (95% CI: 48.2, 53.1) in years 2016-2020, to 53.5 (95% CI: 51.5, 55.2) in 2017-2021 and 56.1 (95% CI: 54.4, 59.0) in 2018-2022 (**Appendix 5**) (27). These data clearly show the favourable impact of IVA/TEZ/ELX on mortality even in just few years of it being available to patients. It should also be noted that these predicted survivals have not taken into consideration the potential impact of CFTRm on younger individuals with CF and hence are not capturing the full, lifetime benefits that would further improve mortality. It is our strong belief that patients with CF, if treated early with IVA/TEZ/ELX, will be able to maintain near normal health. There is emerging evidence that clearly shows the potential benefit in treating children with IVA/TEZ/ELX, including the potential for significant extension of life to near normal life expectancy (29). As treatment with IVA/TEZ/ELX in patients with at least one F508del mutation and over 6 years of age is now standard of care (30), and we expect the licence for patients aged 2 and older shortly, early initiation of this highly effective treatment in children, before significant irreversible lung damage occurs, would lead to substantial and prolonged clinical benefits, including a reduced mortality risk and near normal life expectancy. A median life expectancy of at least 82.5 years is expected if treatment is started under the age of 18, nearly equivalent to the life expectancy of the general UK population (Figure 3) (29). As discussed in Section 4, results from multiple data sources have demonstrated that patients had no decline in lung function following IVA/TEZ/ELX treatment. These included patients aged over 12 years old as well as those between 6 to 11 years. Age-specific simulation modelling has further supported that in the younger CF patients who have a higher ppFEV1 at baseline than the older groups, the acute improvement in ppFEV1 paired with the long-term reduction in ppFEV1 decline provided by IVA/TEZ/ELX led to preserved lung function over the lifetime horizon, which translates into maximised survival benefit (29). In addition to lung function improvement, it is clear from all IVA/TEZ/ELX studies that treatment with IVA/TEZ/ELX led to rapid and stable reduction in sweat chloride concentration, a direct indicator of systemic CFTR function, leading to benefits being sustained over the long-term. Lower sweat chloride concentrations are associated with better clinical outcomes (31). As shown in Table 8, most participants treated with IVA/TEZ/ELX had sweat chloride concentrations that were lower than the diagnostic threshold for cystic fibrosis (i.e. 60 mmol/L), indicating robust improvement of CFTR function. This was not achieved in the CFTRm-untreated patients – no patients in the placebo group achieved sweat chloride concentration <60 mmol/L in study 445-102. The results also show a greater improvement in younger patients vs the older age groups, suggesting that earlier treatment with IVA/TEZ/ELX led to greater restoration and normalisation of CFTR function. The additional benefits of lung function preservation associated with early initiation of treatment have also been demonstrated for other modulators. The impact of age at initiation of IVA on pulmonary outcomes among patients with CF aged ≥6 years with CFTR gating mutations was evaluated. Across all age group comparisons (ages of 6-10, 11-15, 16-20 years), the younger initiators had significantly higher mean ppFEV1 than older initiators in the outcome assessment period (i.e., a 5-year period during which the comparative cohorts were in the same 5-year age range and receiving IVA treatment). IVA initiation during ages 6-10 vs 11-15 years was also associated with a significantly lower incidence of PEx (32). Bower JK et al. have also evaluated the disease progression in different age groups of LUM/IVA treatment initiation (≥6 to <12 years vs 12 to <18 years vs ≥18 years). The results of change in ppFEV1 by age over time show that

lung function is better preserved in patients who initiated treatment at younger age than the older initiators (33).

Overall, there is accumulating evidence that supports the additional benefits of early IVA/TEZ/ELX treatment initiation, allowing them to grow up to lead full or near-full lives.

Figure 2: Mean predicted survival with IVA/TEZ/ELX, TEZ/IVA and LUM/IVA versus best supportive care (BSC) alone, by age of treatment initiation. Adapted from Lopez et al 2023 (29)



Abbreviations: BSC, best supportive care ELX/TEZ/IVA, fixed dose combination of elexacaftor, tezacaftor and ivacaftor: TEZ/IVA, fixed dose combination of tezacaftor and ivacaftor; LUM/IVA, fixed dose combination of lumacaftor and ivacaftor.

Table 8: Proportion of patients treated with IVA/TEZ/ELX achieving sweat chloride concentration <60 mmol/L

Study, genotype	Age	% of participants with sweat chloride concentration <60 mmol/L
		IVA/TEZ/ELX
445-102 F/MF	12+	[redacted]
445-103 F/F	12+	[redacted]
445-109 F/F	12+	79%
445-104 F/RF	12+	86%
445-104 F/G	12+	82%
445-106 F/MF	6 to <11	80%
445-106 F/F	6 to <11	100%
445-111 F/MF	2 to <6	85.1%
445-111 F/F	2 to <6	100%

Abbreviations: IVA/TEZ/ELX, fixed dose combination of ivacaftor, tezacaftor and elexacaftor; mmol/L, millimoles per litre.

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	3. Benefits are likely to be sustained over a very long period The committee also accepted that '*the benefits of treatment are likely to be sustained over a long period*' as stated in the ACD. This is clearly supported by all evidence for the modulators. The final analysis of study 445-105 has demonstrated that patients (aged 12 and over) treated with IVA/TEZ/ELX had no loss of lung function, sustained sweat chloride improvement and that pulmonary exacerbation rates remained low throughout the entire follow-up period of >3 years (2). The same trend is reported from the 445-107 study in patients aged 6-11, where a flat ppFEV1 and sweat chloride change over the follow-up period of >2 years was observed (Appendix 2) (5). As shown in Figure 1 (Section 4), the rate of change in lung function in the IVA/TEZ/ELX-treated cohort was consistent over time. This data is further supported by the real-world evidence as reported in the US CFPPR and UKCFR. Since IVA/TEX/ELX became available, the median predicted survival increased, pulmonary exacerbations and lung transplants were substantially lower and these benefits were sustained throughout the years up to date (27, 28). The long-term sustained benefits have also been demonstrated for IVA - real-world data from the US CFFPR showed a durable benefit on the rate of lung function change, and no evidence of a reduction in treatment benefit, over the entire study period of up to 5 years (32). Analyses of up to 5 years of experience with IVA in real-world clinical practice across countries also demonstrated consistently favourable outcomes in IVA-treated patients relative to untreated comparators, including a lower risk of death, transplant, pulmonary exacerbation and hospitalisation (34). These results support the long-term benefits of treatment having a significant and sustained impact on the disease trajectory of CF. This is also reflected in the patient expert statement provided by CF Voices: *"While still not a cure, CFTR modulators have changed the whole nature of the condition to one that can be managed over the long term and particularly for patients treated before damage occurs, should provide decades of high-quality life."* The long-term benefit of CFTR modulator treatments in lung function preservation and improvement can be further supported by the findings on structural lung disease progression. Sheikh et al (35) reported significant improvements in structural lung disease (bronchiectasis, mucus plugging and airway wall thickening) following one-year of IVA treatment. Middleton et al. also reported that long-term IVA/TEZ/ELX treatment can improve bronchial wall thickening and mucus plugging, as well as the structural abnormalities of cystic bronchiectasis in a case series of adult patients with F/F mutation (36). While dramatic improvements in lung function, sputum production, daytime functioning and quality of life are seen within weeks of modulator treatment, these findings support the long-term benefits associated with CFTR modulation in reducing some structural lung abnormalities, and potentially regression or reversal of bronchiectasis, which is often considered progressive and irreversible. It also noted the method manual's requirement that the committee must be satisfied that any irrecoverable costs associated with the technology have been appropriately captured in the economic model or mitigated through commercial arrangements. Vertex has an existing commercial arrangement with NHS England, which will be updated following the NICE appraisal, which will address this criterion.
10	**Comparators** **Ivacaftor monotherapy should be included as a comparator for some F/gating patients in comparison with IVA/TEZ/ELX.** During scoping, Vertex explained that ivacaftor monotherapy (IVA) is a relevant comparator against IVA/TEZ/ELX for some patients as it is indicated for patients with an F/gating or F/R117H mutation. NICE rejected this on the basis that:

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	"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. In fact, IVA/TEZ/ELX was studied head to head vs IVA in these genotypes and demonstrated superiority. IVA has been available for all patients within its license indication since it became commercially available in 2013 and represents established clinical management for these patients. Therefore, it is entirely appropriate that it be included as a comparator, as part of ECM for the relevant patients. Furthermore, in the clarification letter sent to Vertex in 2020 and included in the committee papers NICE states: *"NICE accepts that because the objective is to establish whether use of triple therapy in patients otherwise eligible for existing products (ie CFTR modulators) leads to an acceptable use of NHS resources, these products will be the main comparator. In clinical scenarios where patients are not eligible for those products the focus will be a comparison with best supportive care without CFTR modulator therapies."* Therefore, NICE is also acting in contravention of this agreement by excluding IVA as a comparator for eligible patients. We request this be corrected ahead of the second committee meeting.

11	A summary of the deterministic cost-effectiveness results is shown in Table 9. All ICERs shown include confidential PAS prices for LUM/IVA, TEZ/IVA and IVA/TEZ/ELX.
	
	The **base case analysis** comprises the following settings:
	
	• Long term rate of ppFEV$_1$ decline with established clinical management
	  ○ Non-linear decline based on Szczesniak 2023 (37)
	• Long-term relative reduction in the rate of lung function (ppFEV1) decline
	  ○ IVA/TEZ/ELX: 100%
	  ○ TEZ/IVA: 61.5%
	  ○ LUM/IVA: 42%
	• Baseline mortality hazard derived from Keogh 2018 (38), based on the UK CF Registry data collected from 2011 to 2015
	• PEx treatment effect duration applied for a lifetime
	• Adherence to CFTRms of [redacted]
	• Health state utilities derived from Acaster 2015
	• Treatment-specific utility benefit of [redacted] applied for IVA/TEZ/ELX
	• Caregiver utility benefit of [redacted] applied without upper age limit
	• Disutility of a PEx episode

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- Discount rate of 1.5% for costs and 1.5% for health outcomes
- Severity modifier of 1.7

Table 9: Deterministic base case results of fully incremental analyses

F/F Cost-Effectiveness Results								
Treatment	Absolute			Incremental			Incremental ICER	
	Costs	QALY	LY	Costs	QALY	LY		
ECM	[redacted]	[redacted]	[redacted]	-	-	-	0.00	-
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating Cost-Effectiveness Results								
Treatment	Absolute			Incremental			Incremental ICER	
	Costs	QALY	LY	Costs	QALY	LY		
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
F/MF Cost-effectiveness results								
Treatment	Absolute			Incremental			Incremental ICER	
	Costs	QALY	LY	Costs	QALY	LY		
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
F/RF Cost-Effectiveness Results								
Treatment	Absolute			Incremental			Incremental ICER	
	Costs	QALY	LY	Costs	QALY	LY		
ECM	[redacted]	[redacted]	[redacted]	-	-	-	-	
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio IVA/TEZ/ELX, fixed dose combination of ivacaftor, tezacaftor and elexacaftor; LUM/IVA, fixed dose combination of lumacaftor and ivacaftor; LY, life year QALY, quality adjusted life year; TEZ/IVA, fixed dose combination of tezacaftor and ivacaftor.

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Checklist for submitting comments

- *Use this comment form and submit it as a Word document (not a PDF).*
- *Complete the disclosure about links with, or funding from, the tobacco industry.*
- *Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.*
- *Do not paste other tables into this table – type directly into the table.*
- *Please underline all confidential information, and separately highlight information that is* [redacted] *and information that is* [redacted]*. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.*
- *Do not include medical information about yourself or another person from which you or the person could be identified.*
- *Do not use abbreviations.*
- *Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.*
- *If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.*

Note: *We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.*

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix 1. Annualised rate of change in ppFEV1 with ELX/TEZ/IVA treatment, US CFFPR

Estimated annualized rate of change in ppFEV1 in the ELX/TEZ/IVA treated cohort versus contemporaneous comparator cohort (SMR-weighted), ages 12+. Reduction in rate of decline among ELX/TEZ/IVA treated cohort: 99% (95% CI, 96% to 103%). All encounter dates (and associated $ppFEV_1$ measures) were available as month/year and assumed to occur on 15th of the month. All valid $ppFEV_1$ measures (between 10-150) during follow-up period were used except for $ppFEV_1$ measures that occurred in the first month following the index date to avoid values related to the initial acute increase in $ppFEV_1$ associated with ELX/TEZ/IVA treatment (i.e., start of analysis at t = 2 months given month/year encounter dates). Mean $ppFEV_1$ at the 2nd, 12th, and 24th month and the mean annualized rate of change in $ppFEV_1$ were estimated from a mixed model with unstructured covariance structure that included a random intercept and a random slope for each patient and fixed effects for ELX/TEZ/IVA treatment, follow-up time, ELX/TEZ/IVA treatment*follow-up time interaction term. Error bars represent standard errors. See associated table footnotes for additional methodological details. Abbreviations: CI, confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; GLI: Global Lung Function Initiative; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SMR, standardized mortality ratio.

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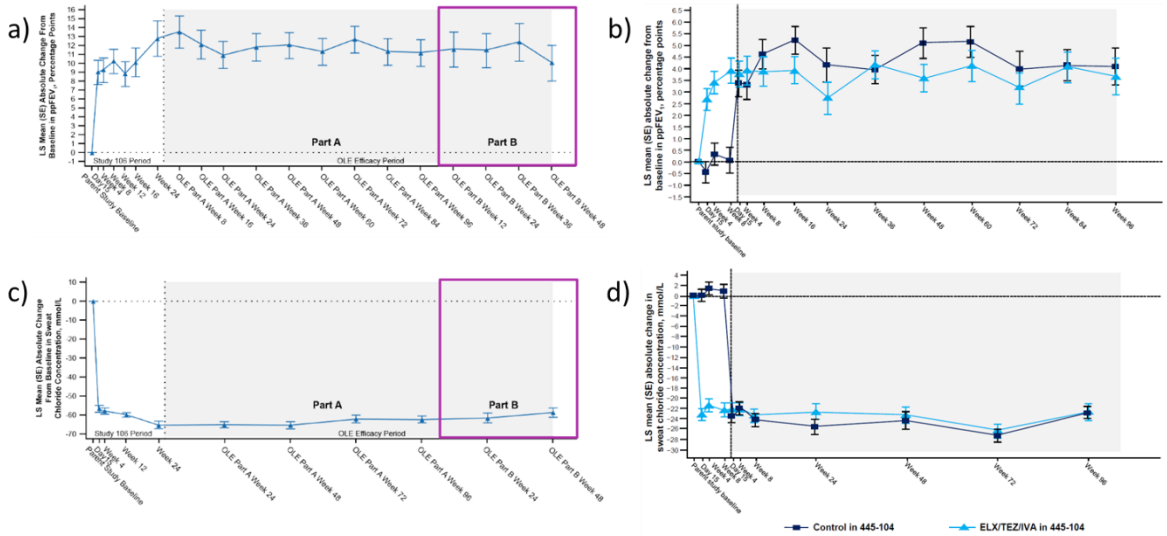
Appendix 2. Absolute change from parent baseline in ppFEV1 and sweat chloride in 445-107 and 445-110 open-label extension period



Absolute change from parent studies baseline in ppFEV1 at each visit up to (a) Week 144 in the OLE study 445-107 and (b) Week 96 in the OLE study 445-110. Absolute change from parent studies baseline in SwCl at each visit up to (c) Week 144 in the OLE study 445-107 and (d) Week 96 in the OLE study 445-110. Purple box shown in (a) and (c) refers to the extended (Part B, 48 weeks) OLE period in 445-107 beyond Part A (96 weeks).

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Appendix 3. Cost inputs in economic evaluations of treatments for cystic fibrosis with health states defined by ppFEV1 status (only studies not associated with Vertex are presented here)

No.	Study/ Author affiliations	Population country	Study type Model type	Health States	Time horizon Cycle length	Intervention Perspective	Cost year Currency Discount rate	Cost of Health State Resource Use and Exacerbations by ppFEV1 thresholds	Costs of ECM pharmacotherapy	Composition and the method of collection of costs
1	**Wherry 2020 (19)** ***Author Affiliations:*** *1. Division of Health Policy and Management, University of Minnesota, School of Public Health, Minneapolis, USA* *2. Institute for Clinical and Economic Review, Boston, USA*	CF patients with the G551D mutation USA	CEA Patient-level simulation	• ppFEV1 ≥70% • ppFEV1 40%-70% • ppFEV1 ≤40% • PEx • LT • Post LT	Lifetime 1 year cycle	IVA + BSC vs BSC US payer perspective	2019 USD ($) Costs: 3.0% Effects: 3.%	**Annual non-PEx costs:** - Mild (ppFEV1 ≥70%): $26,311 - Moderate (ppFEV1 40%-70%): $34,708 - Severe (ppFEV1 ≤40%): $59,340 **PEx costs:** **PEx (age <18)** - Mild (ppFEV1 ≥70%): $54,960 - Moderate (ppFEV1 40%-70%): $87,081 - Severe (ppFEV1 ≤40%): $129,016 **PEx (age ≥18)** - Mild (ppFEV1 ≥70%): $49,802 - Moderate (ppFEV1 40%-70%): $79,163 - Severe (ppFEV1 ≤40%): $113,443	Annual cost of ECM was included in the disease management cost for each health state	The study included annual costs of CF-related ECM and IVA treatment to compare lifetime costs between treatment arms. The analysis assumed the same ECM and related costs in both treatment arms, and that ECM costs increased as disease severity increased based on administrative claims data of commercial and Medicaid CF patients, adjusting them to 2019 dollars and excluding transplant- and CFTRm-related costs to obtain the cost of ECM by ppFEV1 category.
2	**Sharma 2018 (39)** ***Author Affiliations:*** *1. Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy, University of Illinois at Chicago, USA.* *2. Departments of Internal Medicine and Pediatrics, University of Illinois at Chicago, USA* *3. Section of Pulmonary and Sleep Medicine, Department of*	CF patients, aged ≥12 years homozygous for F508del CFTR mutation USA	CEA Markov	• FEV_1 ≥70% • FEV_1 40-69% • FEV_1 <40% • Post LT • Death	2 years, 4 years, 6 years, 8 years, 10 years (base case) 1 year	LUM/IVA vs usual care US healthcare payer perspective	2016 USD ($) Costs: 3.0% Effects: 3.0%	**Annual non-PEx costs:** - Mild (ppFEV1 >70%): $7,566.91 - Moderate (ppFEV1 40%-70%): $9,981.89 - Severe (ppFEV1 <40%): $17,226.80 **PEx costs:** - Mild (ppFEV1 >70%): $2,575.97 - Moderate (ppFEV1 40%-70%): $8,371.9 - Moderate (ppFEV1 40%-70%): $52,646.4	Clinic costs, DNase costs, and cost of pancreatic enzymes and other medications) were assumed to represent the annual costs of maintenance for having mild, moderate, or severe disease.	Costs were sourced from Lieu et. (1999).

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No.	Study/ Author affiliations	Population country	Study type Model type	Health States	Time horizon Cycle length	Intervention Perspective	Cost year Currency Discount rate	Cost of Health State Resource Use and Exacerbations by ppFEV1 thresholds	Costs of ECM pharmacotherapy	Composition and the method of collection of costs
	Pediatrics, The University of Chicago, USA *4. Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy, University of Illinois at Chicago, USA*									
3	**Warren 2019 (40)** ***Author Affiliations:*** *1. HERA Consulting Australia Pty Ltd* *2 Pharmaxis Ltd, Frenchs Forest, Australia* *3 Henley Health Economics, Henley-on-Thames, UK* *4 Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland*	CF patients, aged ≥6 years with severe baseline lung disease Australia	CEA Markov	• No event • PEx • LT • Death	Lifetime Variable: cycle 1, 12 weeks; cycle 2, 2 weeks; Cycle 3+, 12 weeks	Inhaled mannitol + BSC vs BSC Australian NHS perspective	2017 AUD ($) Costs: 5% Effects: 5%	**Annual costs:** - FEV1 ≥30: AU$19,595.03 - FEV1 <30: AU$48,745 *The cost of PEx has not been costed separately and is incorporated into the cost of CF care.*	The cost of co-administered ECM has not been costed separately, as they were incorporated into the cost of CF care (which included inhaled antibiotics, dietary supplements, and oxygen therapy).	The underlying cost of CF have been taken from the only published Australian source (van Gool 2011 and 2013). The cost of CF was stratified into patients with a FEV_1 ≥30 and patients with a FEV_1 <30. The 6-monthly cost of CF in patients with FEV_1 >30 used a weighted average of the costs reported by van Gool et al. for Severity 1 and Severity 2.
4	**Dilokthornsakul 2016 (41)** ***Author Affiliations:*** *1. Center of Pharmaceutical Outcomes Research, Dept of Pharmacy Practice, Naresuan University, Muang, Phitsanulok, Thailand.* *2. Center for Pharmaceutical Outcomes Research,*	CF patients with G551D mutation USA	CEA Markov	• FEV_1 70-99% • FEV_1 40-69% • FEV_1 <40% • LT • Death	Lifetime 1 year	IVA + usual care vs usual care US payer perspective	2013 USD ($) Costs: 3.0% Effects: 0.0%	**Annual costs:** **<u>Mild (ppFEV1 >70%):</u>** - Hospitalisation: $2,406.61 - Clinic visit: $2,406.61 - DNase: $3,008.26 - Outpatient antibiotics: $802.20 - Pancreatic enzymes: $3,008.26 - Other medications: $1,002.75 **<u>Moderate (ppFEV1 40%-70%):</u>** - Hospitalisation: $7,821.47 - Clinic visit: $2,206.06 - DNase: $5,214.32 - Outpatient antibiotics: $1,604.41	Cost of ECM was included in the disease management cost for each health state	Costs and healthcare resource utilisation for each health state were obtained from Lieu et al. (1999)

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No.	Study/ Author affiliations	Population country	Study type Model type	Health States	Time horizon Cycle length	Intervention Perspective	Cost year Currency Discount rate	Cost of Health State Resource Use and Exacerbations by ppFEV1 thresholds	Costs of ECM pharmacotherapy	Composition and the method of collection of costs
	Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, USA *3. Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, USA*							- Pancreatic enzymes: $3,008.26 - Other medications: $1,203.30 **Severe (ppFEV1 <40%):** -Hospitalisation: $56,154.20 -Clinic visit: $6,217.07 -DNase: $10,027.54 -Outpatient antibiotics: $9,425.88 -Pancreatic enzymes: $2,406.61 -Other medications: $2,807.71 *The cost of PEx was incorporated into the cost of CF care.*		
5	**Dilokthornsakul 2017 (20)** ***Author Affiliations:*** *1. Center of Pharmaceutical Outcomes Research, Department of Pharmacy Practice, Naresuan University, Phitsanulok, Thailand.* *2. Center for Pharmaceutical Outcomes Research, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, USA*	CF patients homozygous for F508del mutation USA	CEA Markov	• FEV_1 70-99% • FEV_1 40-69% • FEV_1 <40% • LT • Death	Lifetime 1 year cycle	LUM/IVA + usual care vs usual care US payer perspective	2016 USD ($) Costs: 3.0% Effects: 3.0%	**Annual costs:** **Mild (ppFEV1 >70%):** - Hospitalisation: $2,766.20 - Clinic visit: $2,766.20 - DNase: $ 3,457.76 - Outpatient antibiotics: $922.07 - Pancreatic enzymes: $3,457.76 -Other medications: $1,152.59 **Moderate (ppFEV1 40%-70%):** - Hospitalisation: $8,990.16 - Clinic visit: $3,227.24 - DNase: $7,376.55 - Outpatient antibiotics: $2,996.72 - Pancreatic enzymes: $2,766.20 - Other medications: $922.07 **Severe (ppFEV1 <40%):** - Hospitalisation: $64,544.78 - Clinic visit: $7,146.03 - DNase: $11,525.85 - Outpatient antibiotics: $10,834.30 - Pancreatic enzymes: $2,996.72 -Other medications: $3,227.24	Cost of ECM was included in the disease management cost for each health state	Costs and healthcare resource utilisation for each health state were obtained from Lieu et al. (1999)

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No.	Study/ Author affiliations	Population country	Study type Model type	Health States	Time horizon Cycle length	Intervention Perspective	Cost year Currency Discount rate	Cost of Health State Resource Use and Exacerbations by ppFEV1 thresholds	Costs of ECM pharmacotherapy	Composition and the method of collection of costs
								PEx has not been costed separately and was incorporated into the cost of CF care.		
6	**Whiting 2014 (42)** ***Author Affiliations:*** *1. Kleijnen Systematic Reviews Ltd, York, UK* *2. Institute of Health Policy and Management, Erasmus University, Rotterdam, the Netherlands*	CF patients, aged ≥6 years who have at least one G551D mutation in the CFTR gene UK	CEA and BIM Patient-level simulation	Model simulates disease progression of CF patients included in two trials beyond the trial duration based on decline in $ppFEV_1$. At each time step patient characteristics are updated and fed back into the model	Lifetime NR	IVA + BSC vs BSC UK NHS perspective	2011 GBP (£) Costs: 3.5% Effects: 3.5%	The model assigned annual costs to patients with CF based on the tariff bands reflective of severity of CF: - Band 1: £5210 - Band 1A: £7707 - Band 2: £7707 - Band 2A: £12,457 - Band 3: £19,067 - Band 4: £34,388 - Band 5: £41,458 Regression analysis explored the relationship between annual costs of ECM, $ppFEV_1$, and age: **Constant:** β: 41083.87; SE: 588 **Age**: β: -100.78; SE: 12 **ppFEV1:** β: -254.34; SE: 6	The bands include costs related to patient care, outpatient visits, home care support, home visits conducted by the multidisciplinary team, general support for both patients and their caregivers, i.v antibiotics administered in secondary care, and the investigations conducted during the annual review.	Drug dosage and pricing assumptions were derived from British National Formulary, and then cross-checked with dosage recommendations provided by the CF Trust Antibiotic Working Group.
7	Vadagam 2018 (43) ***Author Affiliations:*** *1. Division of Pharmaceutical, Administrative and Social Sciences, Duquesne University School of Pharmacy, Pittsburgh, Pennsylvania* *2. Pharmacy Practice, Philadelphia College of Osteopathic Medicine, Georgia.*	CF patients, aged ≥12 years homozygous for F508del mutation of the CFTR gene USA	CEA Static decision model	Based on $ppFEV_1$ from the clinical trial	1 year NR	LUM/IVA vs placebo US third party payer perspective	2016 USD ($) NR	**Annual monitoring costs:** - AST: $56 - ALT: $56 - Bilirubin: $52 - Sputum/throat cultures: $633.6 - PFT: $73.04 - Flu shot: 24 - Fat-soluble vitamin blood levels: $408 - OGT: $34 - Clinic visits: $1,382.85 - Outpatient visits: $1,002.53 - Inpatient stays: $1,321.96 **Annual adverse event costs:** - PEx in placebo group: $19,112.14	**Annual cost:** - Albuterol (0.18 mg, Q6 hours inhalation): $2.93 - Tobramycin (300 mg Q12 hours inhalation): $46,852 - Dornase alfa (2.5 mg Q daily inhalation): $39,926.26 - Hypertonic saline (10 ml of 6% solution Q12 hours inhalation): $1,216 - Fluticasone (200 mcg Q daily inhalation): $1,745.21	. Frequency of clinic visits, outpatient visits, and inpatient stays were taken from published literature. The costs for laboratory and monitoring tests were obtained from the Centers for Medicare & Medicaid 2016 Physician Fee Schedule using the Current Procedural Terminology codes, 2016 Healthcare Bluebook, and from published literature.

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								- PEx in LUM/IVA group: $15,191.71		
8	Panguluri 2017 (44) ***Author Affiliations:*** *1. Novartis Healthcare Pvt. Ltd., Hyderabad, India* *2. Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, USA* *3. Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, USA*	CF patients with chronic *Pseudomonas aeruginosa* infection USA	CEA Patient-level simulation	Parameters considered in this model included decline in ppFEV1, frequency of PEx, and overall survival.	10 years 6 months	Tobramycin inhalation powder vs Tobramycin inhalation solution US healthcare payer perspective	2016 USD ($) Costs: 3.0% Effects: 3.0%	Annual disease management cost: $2,043 Mild PEx weighted cost per episode: $894 Severe PEx, weighted cost per episode: $14,422	**Total drug costs for three treatment cycles:** - Tobramycin inhalation powder: $26,588 (package price/month: S$8863 - Tobramycin inhalation solution: $22,013 (package price/month: $7338	Drug costs were sourced from AnalySource®: Premier access to the First Databank drug pricing database. Resource utilisation data were obtained from a UK-based study by Bradley et al. (2013) due to the non-availability of similar US data.
9	Tappenden 2013 (45) and 2014 (46) ***Author Affiliations:*** *School of Health and Related Research, University of Sheffield, UK*	CF patients with chronic *Pseudomonas aeruginosa* infection UK	CEA Markov	• FEV_1 70-99% • FEV_1 40-69% • FEV_1 <40% • Post LT • Death	Lifetime 24 weeks	Colistimethate sodium DPI vs Nebulised Tobramycin; Tobramycin DPI vs Nebulised Tobramycin UK NHS perspective	2011/12 GBP (£) Costs: 3.5% Effects: 3.5%	Cost of minor PEx: £412.74 Cost major PEx: £1,500.14 *Only drug acquisition costs and costs of managing PEx were included in the analyses.*	Nebulised Tobramycin: £21.20 per dose Colistimethate sodium DPI: £17.30 per dose Tobramycin DPI: £31.96 per dose	Costs were sourced from BNF and NHS reference costs 2010-2011

Abbreviations: AUD, Australian dollar; BIM, budget-impact model; BNF, British National Formulary; CEA, cost-effectiveness analysis; CF, cystic fibrosis; CFQR, CFQ-R, Cystic Fibrosis Questionnaire Revised; CFTR, cystic fibrosis transmembrane conductance regulator; DPI, DPI, dry powder for inhalation; ECM, established clinical management ELX/TEZ/IVA, fixed dose combination of elexacaftor, tezacaftor and ivacaftor; EUR, Euros; GBP, GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVA, ivacaftor; LT, lung transplant; LUM/IVA, fixed dose combination of lumacaftor and ivacaftor; NHS, National Health Service; NICE, NICE, National Institute for Health and Care Excellence NR, PEx, pulmonary exacerbation; ppFEV1, Forced expiratory volume in 1 second; PSS, PSS, personal social services; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; rhDNase, recombinant human deoxyribonuclease; SEK, Swedish Kroners' SOC, standard of care; UK, United Kingdom; USA, United States of America; USD, Unites States dollar.

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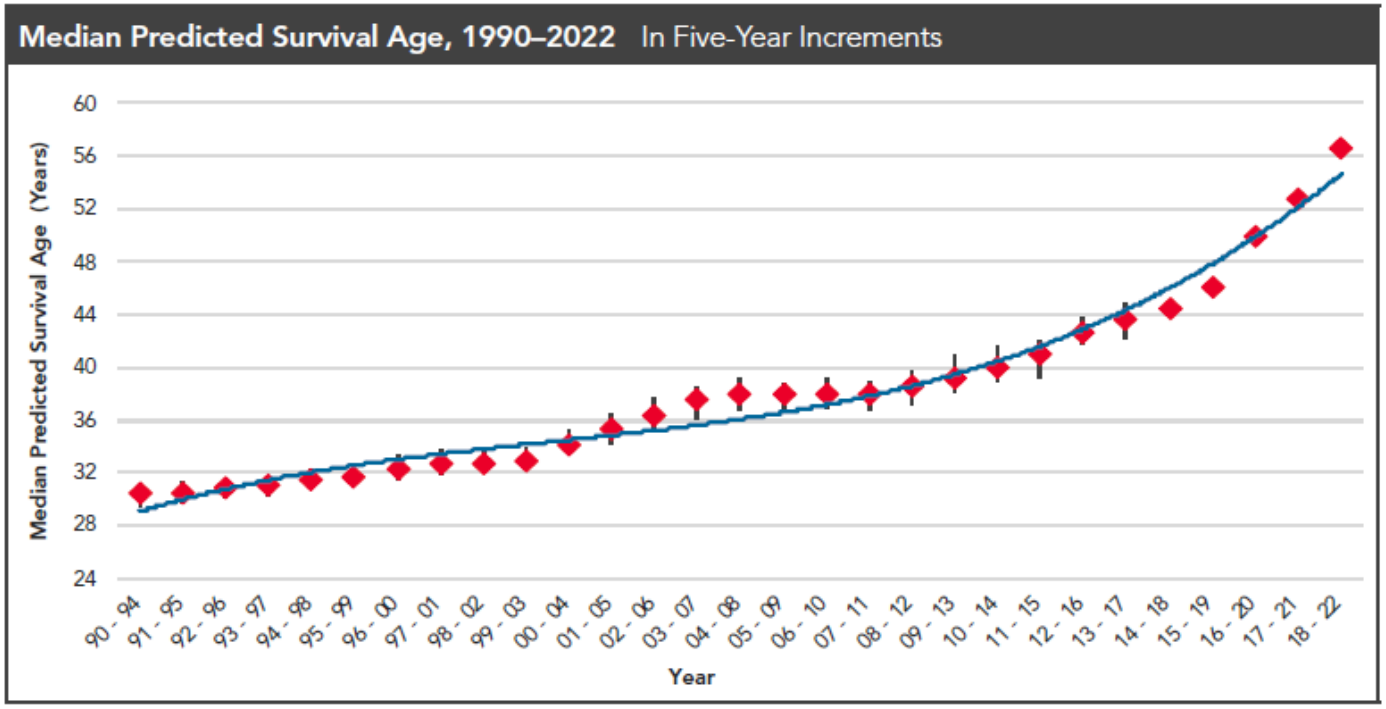
Appendix 4. Rolling median 5-year predicted survival age in patients with CF in US CFPPR



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Appendix 5. Rolling median 5-year predicted survival age in patients with CF in UKCFR (27).

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cystic Fibrosis Trust

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Cystic Fibrosis Trust has received a total of £29,400.00 from Vertex Pharmaceuticals in the last 12 months to support key charitable activity to improve the lives of people with CF: • £6,000.00 for Clinical Trials Accelerator Programme (CTAP) Feasibility Services for VX21-522-001: A Phase 3 study evaluating for the pharmacokinetics, safety, and tolerability of VX121 / Tezacaftor / Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects1 through 11 years of age. • £6,000.00 for sponsorship of the UK CF Registry Annual Meeting 2022 and conference in November 2022. • £8,400.00 for a UK CF Registry epidemiology data request from 2021 cohort. • £3,000 for the Clinical Trials Accelerator Platform • £6,000 for the UK CF Registry meeting 2023 (invoice not yet paid as of 22 November 2023) Cystic Fibrosis Services Limited, a subsidiary of the Cystic Fibrosis Trust, hosts the UK CF Registry and has received funding for ongoing pharmacovigilance studies and the HTA study agreement. The Trust have received no funding from any of the comparator treatment companies in the last 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	CFTR modulators have transformed the lives of the majority of people with CF in the UK. Any prospect that they would not be available to new patients is extremely serious and worrying

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	Cystic Fibrosis Trust is deeply disappointed that Orkambi, Symkevi and Kaftrio have not been recommended for routine use on the NHS in this draft guidance, despite the committee's agreement that these CFTR modulators are clinically effective treatments with important benefits for people with cystic fibrosis (CF) after reviewing all available evidence and hearing from patient and clinical experts. We welcome the committee's acknowledgement of the *"substantial difficulties faced by people with CF"*, the *"chronic and severe condition"* with a wide range of challenging physical symptoms, as well as the impacts on *"mental wellbeing on people with the condition and their carers"*. We particularly highlight the committee's acknowledgement that *"CF is associated with considerable morbidity and can substantially shorten the lives of people with the condition"* (pg. 7). It is clear the committee have listened to the patient testimony at the committee meeting and the extensive submissions from patient organisations as part of this appraisal. However, we do not believe the committee has taken all available evidence into account when reaching a decision, including the weight of uncaptured benefits experienced by people with CF, the impact on quality of life and the severity of the condition. Additionally, the impact of the clinical effectiveness of these medicines for people with CF has not been fully appreciated by the committee, despite extensive evidence presented by patient organisations, and the patient and clinical experts at the committee meeting. We reiterate the significance of these medicines for very young children with CF; for whom the EAG's clinical experts believe may have a *"near normal lifetime lung function"* (pg. 250).
2	The NICE appraisal process is complex, frustrating, and deeply worrying for patient communities, particularly for those appraisals after a period of managed or interim access. After a long, sustained campaign by Cystic Fibrosis Trust and the CF community, a deal was reached to give access to Orkambi, Symkevi in 2019 and later Kaftrio in 2020. The original appraisal of Orkambi concluded in 2016 with a negative recommendation, and it is highly distressing for the CF community that negative draft guidance has once again been issued seven years later. This process, and announcement of the draft guidance, has caused a huge amount of anxiety, worry and concern for the CF community – with some parents describing the news as *"worse than diagnosis day"*. Clinicians have also expressed concern about the deeply unsettling nature of this process for people who have experienced life-changing benefits of these therapies. Whilst we welcome the commitment from NICE, NHS England and Vertex Pharmaceuticals 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. These experiences were also reflected in a managed access learning roundtable hosted by Genetic Alliance UK with the broader rare disease community[1].
3	We welcome the use of Registry data as a key source of data for the appraisal and the committee's conclusion that the evidence base for CFTR modulators was *"large and robust"* (pg. 28).

[1] https://geneticalliance.org.uk/wp-content/uploads/2023/06/Managed-Access-Agreements-Recommednations-from-a-shared-learning-roundtable-.docx-1.pdf

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	The committee will need to correct the data source for the compliance/adhere data. As outlined in the Data Collection Agreement, compliance rates were to be compiled from a secondary data source, notably pharmacy home delivery data (compiled by Vertex). It did not state it would be collected from the primary data source, the UK CF Registry. The UK CF Registry provided data on discontinuation and/or switching of CFTR modulator treatments, however, the UK CF Registry does not collect data on the compliance/adherence of people with CF to treatment regimen. The rationale for acceptance of the data as being from the same source as the efficacy data should be corrected.
4	CF is a rare, genetic, and multi-system condition which causes a build-up of thick mucus in the lungs, digestive system and the tubes that transport enzymes out of the pancreas. As the draft guidance states, *"people with CF experience progressive lung function loss"* (pg. 7). As highlighted in our evidence submission and response to the External Assessment Group (EAG) report, over many years, CF lungs become increasingly damaged. Access to modulator treatments will result in a generation of children and young people with CF growing up healthier than ever before and with a different disease profile, likely less burdensome, to those who have started modulator treatment in later life. Cystic Fibrosis Trust welcomes the view of the EAG's clinical experts in the EAG report, who noted that if Kaftrio is *"initiated in very young patients, such as age 1 to 2, this may avoid long-term lung damage and could potential provide "near normal" lifetime lung function. Therefore, an incident CF population that begins treatment prior to any irreversible lung or pancreatic damage may experience greater benefits in treatment*." (pg. 250). The committee do acknowledge the *"potential of additional benefits of Kaftrio in young children*" (pg. 20) and we urge the committee to use its flexibilities to ensure that generations of children and young people with CF are not potentially denied a treatment from which they would gain the most benefit. Improved physical and mental wellbeing may lead to significantly reduced healthcare costs as well as substantial increases in quality of life.
5	Cystic Fibrosis Trust is unclear why the committee was "unable to conclude if a severity modifier should be applied" (pg. 26) and the lack of detail in the draft guidance is frustrating to respond to. Cystic Fibrosis Trust has attended workshops for patient organisations hosted by NICE on the severity modifier to understand how patient organisations can provide specific evidence to enable NICE committee decision-making on the application of the modifier. The clear message from these workshops was that although the modifier is a numerical measure of the severity of disease, the exact qualification depends on the context as some diseases can be qualitatively severe, but not qualify for the severity modifier. In our evidence submission, and the submissions of other patient organisations, professional groups and clinicians, the impact of CF on quality and length of life is clear. The draft guidance clearly states that the committee acknowledged that *"CF is associated with considerable morbidity and can substantially shorten the lives of people with the condition"* (pg. 8) and it agreed that *"people with CF have a severely impaired quality of life"* (pg. 20).

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	Cystic Fibrosis Trust believes there is ample evidence from stakeholders that CF is a severe, multi-system disease which should qualify for the severity modifier, and that through patient expert testimony, the real-life impact of CF has been presented, and indeed subsequently acknowledged by the committee in the draft guidance. In fact, it is unclear what more would be required to qualify CF as a severe disease and could set a concerning precedent. We strongly encourage NICE to ensure the patient experts have a voice at the second committee meeting, and that the committee makes full use of their experiences to decide on whether the severity modifier should be applied to this appraisal.
6	Whilst we appreciate the NICE health technology evaluations manual states EQ-5D is the preferred method to measure health-related quality of life, we remain concerned about its applicability to CF. The NICE methods manual states: • *"to make a case that EQ-5D is inappropriate, provide qualitative empirical evidence showing that key dimensions of health are missing"* (pg. 74) • *"in circumstances where evidence generation is difficult (for example, rare diseases) when there is insufficient data to assess whether EQ-5D adequately reflects changes in quality of life, evidence other than psychometric measures may be presented and considered to establish whether the E5-QD is appropriate"* (pg. 75). As per our EAG report consultation response, we reiterate our call for the committee to recognise the CFQ-R data collected during the interim access period as this will accurately reflect the experiences of people with CF. It is a life-long condition and people with CF have never known life without it, making it difficult for an accurate assessment of the impact on their quality of life. We remain concerned that EQ-5D is too blunt an instrument to recognise this. The numerous physical, mental, financial, and social impacts of CF – such as the treatment burden, health perceptions, respiratory and digestive symptoms as well as physical and emotional functioning – must be part of the committee's decision-making.
7	The powerful patient expert testimonies at the committee meeting clearly articulated how challenging life with CF can be, particularly before access to these transformative treatments, and remains so for those unable to benefit from CFTR modulators. The severity of disease, and the benefits they have on physical health and quality of life is highlighted through some quotes below: *"We did not realise how much of an impact it would have on all our lives. [My child] was constantly coughing, had at least 30 lots of oral antibiotics each year. Had 3 stays in hospital with a bronchoscopy and intravenous antibiotics for 2-3 weeks at a time. [They] needed lots of physiotherapy, exercise, and nebulisers to keep her as well as possible. Sometimes [they] would go blue from lack of oxygen getting into her body, [they] were so thin as could not eat what is needed to keep [them] healthy, constantly [they] would have mucus in her lungs and faeces. Life could be very dark."* The draft guidance also states there are *"several important uncaptured benefits of treatments with CFTR modulators"* (pg. 27), highlighting the impact of pancreatic recovery in children, improved glycaemic control and reductions in CF-related diabetes and

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	reduced bacterial colonisation (and the potential for a reduction in antibiotic use), alongside the impact on carers and family members of people with CF. The CF community have commented on their experiences, and we wish to highlight some of the areas above the committee have identified in the draft guidance. *"At the age of 2 my daughter started Orkambi. This had a huge impact on her pancreas, and she was able to stop Creon® [a pancreatic enzyme replacement therapy] as her pancreas fully functions".* *"Since taking Kaftrio, our daughter has been able to stop taking Creon®. She has not grown any infections which require treatment since October 2021. She started taking it in April 2021."* *"…My daughter was needing 25 scoops of Creon® per day, and now is on 10 scoops maximum sometimes it's less, if any needed at all! Which is absolutely incredible…"* *"It has changed my daughter's life! She no longer needs Creon® ...Her mucus is so much thinner, and she moves everything off her chest so much easier. It is the best thing that has ever happened to her, and we are so grateful!"* *"Abdominal issues have improved and the need of Creon® has drastically reduced."* *"No infections requiring extra antibiotics or hospital admissions requiring IV antibiotics for three years. She has pseudomonas, staphylococcus and B.Cepacia. None of which have grown on cough swabs since starting. Hospital admissions were annually prior. Lung function increased from 60ish% to 98-100%. Less Creon® with food required. Life is generally better, more normal and future looks positive."* *"It has reduced the burden of hospitalisation and chronic exacerbations. It's given us some hope for the future, when before the trajectory looked very bleak."* *"Feel like I can plan my life again. I have more energy to work, more focus, more dedication…My diabetes is better managed, my GI issues have resolved and my lungs clear mucus in a way they never did before".* *"[His life] has improved because I can let him do more things... Pseudomonas is not a death sentence... [My child] ...had a lengthy period of bacterial colonisation Haemophilus influenzae prior to modulators and now he has a couple of infections a year that are easily treatable with antibiotics (so far) – massive quality of life improvement – more activities, allowed to do more things, like a child without CF (less the treatments). Happier parents and sibling because less time is spent on him and his care."*
8	Cystic Fibrosis Trust have presented clear and compelling testimony in our submission which demonstrates the significant indirect benefits of treatment which have not been captured in the committee's discussions. This includes how people with CF feel about their future, how parents of children with CF feel and how access to Orkambi, Symkevi and Kaftrio has changed their lives. It is difficult to quantify this impact, but it does not

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	mean it should be overlooked. Some of these uncaptured benefits have truly transformative effects on individuals and families, and their quality of life. Cystic Fibrosis Trust ran an online survey between February 2023 and March 2023, receiving 1,179 unique responses. Some of these responses were detailed in our evidence submission, and we highlight more experiences below to demonstrate the depth of the uncaptured benefits of these life-changing treatments. For example, the impact of reduced coughing: *"I don't cough constantly anymore and feel much clearer. I don't feel constantly tired like I used to. I'm able to be in work without needed weeks off for treatment and I have far less travel time and cost due to not needing to see my clinical team as frequently as before."* Adults with CF have told us how they can do the same activities as their friends without paying a huge exhaustion penalty afterwards. An adult with CF highlights the significance of this: *"I have far more energy than I've ever had, improving motivation to get active and work out, not feel the dread of the day after effects from a day out and just being able to be present in the moment not worrying about if you're going to be coughing your lungs up because you walked briskly for half an hour. You don't realise how tired you are when your constant is just always tired. I feel far more normal in how I breathe, I don't cough regularly, I'm no longer wheezy, my recovery from other sickness is quicker and easier. Mentally, it's opened so many doors and made me realise that even though I wasn't confined daily by negative thoughts, the pessimism and cynicism significantly reduced as there's no longer this thought of 'I won't be this healthy in 5 years anyway' now I can confidently say 'who knows what I'll be like in 5 years".* Health stability is also a key uncaptured benefit. An adult with CF described how before Kaftrio, they were on IVs every three months: *"With Kaftrio, I have much longer gaps, often years and the exacerbation are milder and easier to recover from. My quality of life has improved out of all recognition: I have much more energy, can play with my kids, do my share of parenting and even play sport. I can be fully engaged at work without having to worry that I'll need to disappear for weeks or months with zero notice. I can breathe more easily, don't need to cough up sputum every day or constantly feel like I'm fighting infection. I was starting to feel like I was down to my last few years - now I am able to think about and plan for the future. It has truly been life changing."* *"Infections are easier to handle. Before Kaftrio I would know I was getting ill and I would have to make sure I worked harder at my job, so that when the inevitable hospital stay came along, I would know that I wouldn't be missed for 2 weeks. Or I would wait until I had got my work to a point that could be left before admitting myself into hospital, with the possibility of a longer stay because I'd not admitted myself earlier. Now infections are so much easier to deal with, and they can be dealt with using tablets."* *"[My] confidence is something that has increased as my health has improved."* The life-changing nature of these treatments must be appreciated. The CF community told us: *"A life saver...Years of daughter coughing constantly, particularly if she laughed, then wet herself as a consequence. Unrecognisable spending time with her so improved…cannot*

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	begin to describe our relief after over 30 years of worry over her life expectancy, particularly as she has an 8 year old son now. Thank you, thank you, thank you!!!" *"My son's health immediately improved beyond any expectations. His lung function rocketed, he now has strength and stamina and can look to the future in a way he could not do before taking this marvellous medicine. It is like he has been given a completely new and much better life".* *"Since taking Kaftrio, there have been no more hospital admissions. Very few infections grown. Weight and height have been greatly improved, along with fat absorption. It literally has changed the life of my child".* *"Before taking Kaftrio, I was unable to work, depressed and had no long term future. It is impossible to comprehend how psychologically difficult it is to cope with CF and the opportunities in life you must give up. Since taking Kaftrio, I have my life back. I feel much healthier, and I am unbelievably grateful for what the NHS has done for me. I am only 32 but now believe I have my whole life ahead of me again."* *"Since going onto Kaftrio the past 3 years have been life changing!! I've managed to get full time employment, play football 3 to 4 times a week keeping up with all my peers. Life is absolutely fantastic I can't explain how amazing it is. I'm only 25 years old and it feels like life has only just started in the past 3⁄4 years."*
9	As well as the significant uncaptured treatment benefits highlighted above, the committee *"agreed the impact of CF on carers is large"* and that the beneficial effects of treatment *"may extend to multiple carers and to the families of people with CF"* (pg. 24). We are concerned that the draft guidance has assumed caregiver utility for those up to 11 when in the meeting, the committee indicated greater flexibility, after listening to patient experts. Parents and people with CF told us: "*I as a mum have been able to return to work and contribute to the household and the economy (I no longer need carer's allowance). My son is missing far less school, and he is enjoying participating in activities he would have been restricted from doing previously due to risks. Overall, we all feel a lot more positive about the future and our lives have returned to what we would consider pretty normal."* *As [a] mum, I am also able to work more hours which increases our household income substantially. It now seems feasible that [my child with CF] will have a wonderful future which won't require me to look after her and to be restricted by her health requirements."* *"It almost feels like we are a normal family, or at least that we have a "normal" of sorts, in that things are so much steadier!! I still have moments of complete amazement at how different things are. We have so much more freedom not having CF dictate what we can and cannot do…We no longer have the fear that her quality of life, and her ability to be a child, is being taken away. Being able to enjoy the good times, because they no longer feel like they are being ripped away."*

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	"[My child's] life is much better but the impact on parent's mental health has improved massively. Just imagine at the back of your mind your child may become unwell and this infection would dramatically reduce his quality of life and life span – that is quite lot for a parent who is here to protect their child to come to terms with daily. The new found hope makes these thoughts much fewer and further between – surely the impact of these drugs on the whole family for an illness that a child has through no fault of their own is worth the investment?" *"My husband has been taking Kaftrio since September 2020. This drug has been quite literally lifesaving and life changing for him and us as a family. We have two young children, and I was parenting them solo for a long time as he was just so ill and exhausted. Now you would never know that there was anything wrong with him. I cannot underestimate the positive impact it has had."* *"This has had a massive impact on the whole family as she doesn't miss any school for PICC line and IV admissions. Her parents no longer need to take regular time off work to cover 2 week hospital admissions/ school journeys to and from hospital whilst on IVs etc. The other children in the family no longer have to be juggled for hospital stays. No holidays have been cancelled and no school missed. Travel is easier as having gone off other nebulisers, the treatment and physical equipment burden is much reduced and manageable. She is much more able to be independent with less cumbersome treatment plan. Huge impact on the whole family."* A parent told us: *"You always worry about your children and their lives but now I don't have to worry every day about everything. [He] has a future, which is something we have dreamt about for many years."* *"We were a family where our lives were consumed by CF which with constant hospital visits, investigations, IVs as in-patient and home IVs and now it feels like we are hardly ever at the hospital other than routine reviews".* *"Massive- total change to family life. No IVs for a year now reduced hospital trips. Emotional impact of seeing my child so well in himself."* *"As we have managed to cut out saline and extra physio, it means I get time to play with them. Sadly, I almost never played them before, because there were so many jobs caused by the enormous treatment burden and by the frequency of their infections".* *"We save up to two hours a day by no longer needing to do formal physiotherapy…I am no longer constantly travelling back and forth to the hospital".*
10	Given the nature of the outstanding issues identified by the draft guidance, it is imperative patient and clinical experts are present at the second committee meeting.
11	Cystic Fibrosis Trust can facilitate requests for additional data through the UK CF Registry to further support the NICE appraisal process and if the committee believes additional data will enable their decision-making. Any requests will need to be made as

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	per the established data request protocol and considered by the Registry Research Committee[2].
12	As with other appraisals for rare and complex conditions, we recognise the difficult role of the committee and NICE more broadly around access to treatments. We recognise that this appraisal is particularly unique, and we strongly encourage NICE, NHS England and Vertex Pharmaceuticals to work together to resolve any uncertainties to meet what the committee have acknowledged as *"high unmet need for treatments in routine commissioning"* (pg. 28). Additionally, we hope all stakeholders will carefully consider how they communicate the next steps of this appraisal to the CF community.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[2] https://www.cysticfibrosis.org.uk/about-us/uk-cf-registry/apply-for-data-from-the-uk-cf-registry

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	CF Voices

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NONE
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned overall that the draft guidance fails to capture the entirety of, and severity with which CF, before/without modulator treatment, impacts patients for the whole of their lives. The impact on carers and families throughout, and beyond in the case of death of the patient, has also not

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	been fully captured. In addition, we believe the medium term and potential long-term effects of CFTR modulators to be underestimated and some key clinical benefits to be uncaptured in modelling. To provide more relevant evidence, CF Voices collated research which we believe to have been published after the initial submission date for the appraisal. We also collected further community lived experiences in order to inform the summaries of clinical and cost effectiveness. During November 2023 we widened our group membership from CF carers to invite patients and other affected family members to join. We also asked Quest for a CF Cure to join us and they helped in promoting an online survey, to ensure representation from the Scottish CF community. A full copy of the methodology used, the data and a summary report has been provided to NICE, as pre-agreed. Survey responses from 175 families were received, including patients and carers, representing those with and without access to modulator treatments. Despite being managed by multi-disciplinary teams in the NHS the evidence base for CF does still not reflect the whole effect of the disease or the drugs. CF becomes measured by narrow parameters e.g. Fev1, Pex and weight-for-age z scores in clinical trials and Orkambi and Symkevi, which provided life-changing impacts for many and life-stabilising effects for most patients, becomes 'modest effectiveness'. While the lived experience is '*treatment with Ivacaftor/lumacaftor brought stabilisation and a near normal life for my child.'* Kaftrio is noted as having 'substantial effectiveness' but this must be overlaid with lived experience for the whole picture '*Kaftrio has been truly life changing and nothing short of miraculous'*. Please take time to read the Full Stories at the end of our report where impacts of modulators were so transformational, and had such a profound impact on the whole life of the patient, that we have included them in full, rather than attempting to segment them. Finally, the provisional recommendations do not recognise the accumulating evidence that modulators are generating to show that patients can attain the goal of 'primary prevention' of CF and the associated implications for NHS services of this. If treated young enough, there is a window of opportunity to stop CF before any real damage is done to most people born now and in the future with CF. This opportunity cannot be lost.
2	**Section 3.3 – CFTR Modulators** - In our survey responses, reported impacts of CF on participants were common and severe and – unsurprisingly – all respondents with access to modulator therapy reported an improvement in some aspect of their life (128/128 respondents that had been given access to modulator therapy). Most commented on improvements to physical symptoms (107/128 respondents). Within this group, clearing or reducing bacterial infection (55/128), reduced antibiotic treatment (46/128), increased energy (44/128), and decreased intestinal and digestive problems (39/128) were the most commonly mentioned. *"My child has cultured pseudomonas aeruginosa (PA) since shortly before they were two years old. At six years old.. my child began Kaftrio. The chest x-ray taken on this day showed an improvement from that of the one taken two years earlier. Within two weeks my child no longer needed to be admitted for IVs. Since this time there has been no PA, or indeed any other damaging bacteria, in my child's sputum. In addition to this, from spring of this year they have required no oral antibiotics (previously used frequently), no steroid or ventolin inhalers (often used multiple times a day), no nebulized ventolin (previously used throughout exacerbations, of which there were many), no nasal spray (previously used daily), no laxatives (used daily prior to Orkambi), they have used hypertonic saline only for induced sputum collection (previously twice daily), have reduced the use of dornase alpha (seven-fourteen times a week to five times a week), and have had a reduction in creon from 24 tablets a day to 12 tablets a day. Physio has reduced from two-three times daily to once a day. They remain on inhaled antibiotics and will do so until they have had two years of sputum tests clear of PA."* *"My son's health, as evidenced above, has improved dramatically (beyond recognition since taking Kaftrio). His lung function has increased from 80% to over 100%. He has had zero hospital admissions*

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	since taking Kaftrio and has suffered zero lung infections (thus no need for IV antibiotics). There is now talk of slowly being brought off current drugs, such as DNASE thus will gain even more of his daily life back with reduced treatments. He has already reduced his need for nebulized treatments too. Reduced Creon requirements and Insulin requirements. Lung x-rays show improvement (lead consultant at Heartlands Adult CF Hospital commented that she had never seen this before in a CF adult)." *"My daughter is on Kaftrio and it has been life changing. She has gained weight and since starting the drug in October 2020, her lung function increased over a 6 week period from around 55% to 100% and has remained at 95-100% since. She would have had on average 8/9 changes in antibiotic annually and since 2020 she has had one. It has made such a difference to her quality of life and in fact our CF team has now taken her off her daily antibiotics given her state of health. She had colonised staphylococcus and that has now gone totally. After starting Kaftrio she told me that she had never realised how ill she felt before and she no longer has a feeling of weight in her chest holding her back."* *"I started Kaftrio in 2020.. Before Kaftrio I had a lung function of 22%. I also grew a resistant bug called B Capecia which also meant a lung transplant wasn't an option. I was therefore living on borrowed time. I couldn't keep up with my peers, I wasn't able to participate in most physical activities in school or beyond. I was on hospital every 3 months for IV antibiotics over a 2 week period just to sustain some of my lung function. I had to do physiotherapy twice a day and 3 nebulisers twice a day among countless medications. Since Kaftrio I have had NO IV antibiotics, my resistant bug B capecia hasn't grown in my lungs for 3 years [even though] we were always told I would never be able get rid of that bug. I have gone on to live a full life travelling and now I've welcomed a healthy baby boy who is now 1 year old. Something I was told I would never be able to have."* These improvements in physical symptoms were only a part of the story though. Impacts in both patients and carers were reported that affected respondents across a diverse range of quality of life components. 62 highlighted reduced visits to and admissions to hospital, and 49 reported reductions in the daily regime of care after modulator therapy. This reduced burden perhaps contributed to the positive impact of modulator therapy on their mental health, which was reported by 64/128 respondents. *"Since starting Kaftrio in Sept 2020, his (and our) lives have improved dramatically. He has had 1 hospital admission in 3 years, compared to the previous once to twice a year admissions. He has started volunteering twice a week at the local BHF charity shop and this year has felt well enough to secure his first ever employment at a retail cafe. This has enabled him to earn his own money for the first time ever and consequently has been thinking about being able to leave home and live in his own accommodation. His mental health is considerably better, as he feels as though he has a future. He used to think "what is the point of doing all of this treatment, or getting any qualifications, as he wasn't going to live long anyway". Kaftrio has changed that."* *"Being on Kaftrio also has a huge positive impact on my mental health. I can now see a full life ahead of me due to an increased life expectancy. I can look forward to having a family in the future which was uncertain before Kaftrio as patients with CF struggled to conceive (and also had a shorter life expectancy)."* The impact of CF on life attainment was also cited as a key issue, with 64/175 commenting on school, further education or work being impacted. Older patients commented on having to reduce or stop work due to CF related illness, or being able to increase their hours, go back to work or take on roles with higher responsibility once their treatment with modulators had begun. Other activities outside of work and education were also frequently mentioned (42/175), with themes including cancelled holidays and other plans because of CF, missing out on family occasions or activities because of illness and/or risk-mitigation, or conversely the ability to start participating in life experiences that had not previously been possible, some as profound as becoming parents, once modulator treatment had commenced.

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	"Once the new medications became available and his health improved dramatically, with no hospital admissions, he was able to take up full time work, remove his DLA payments and is now a Nuclear Reactor Physicist working full time, paying into the system, is a valued member of our society, doing a job he loves and he is good at etc. Without this medication, I am confident, he would now be on the lung transplant list and all that entails or worse." *"My son now in his words "has his life back" and "will need to think about a pension", he now works and is also the founder of a new exciting company. He can now do his own physio. He never thought about having a girlfriend as he felt he had too much going on with his health that he didn't think he could make time for one or that anyone would want him. Now he has started dating which is a huge deal."* *"It is as if someone has switched off CF. It is incredible. I can now breathe, laugh at jokes without a coughing fit. So many things that I thought was okay or "fine," I now realise was completely NOT. When thinking about the difference these modulators have made to my life, they have given me a life where I can live. I can hope. I can imagine a life without the huge burden of this disease. Since starting modulators, I have completed a university honours degree and have secured an enviable position as a solicitor in a prestigious law firm (something that I could never allow myself to have imagined back at my worst before any modulator treatments were available). I now am able to exercise, go to the gym and keep up with friends. I have so much more free time. I would not be alive today without these drugs, instead of being anxious of the inevitable doom and gloom of CF, I am looking forward to a future where I will live a long and fulfilled life and have a family of my own."* *"The biggest positive for me is the fact I have been able to have a daughter. Never in my wildest dreams did I think I would be able to become a Mum. I cannot explain how much of a positive impact this has had on my life!!"* **Other reported impacts include**: *"Removal of gastrostomy - no longer using night feeds - Stopping injecting lantus insulin for CFRD - Removal from the liver transplant waiting list - No longer using BIPAP breathing apparatus at night -No longer having 3 monthly IV courses - Reduction in Creon consumption"* *"Treatment with modulators has changed my life immeasurably. [Amongst other things] I can sit in a bath for more than 5 minutes, as my skin no longer shrivels so badly I physically cannot stand the pain."* *"3 days after my first Kaftrio tablets I stopped coughing and slept for a whole night, and have barely coughed since. My lung function has gone from 59% at its lowest to 120%."* *"The impact on my social/family life has also been immeasurable. I find it easy to maintain social relationships and after 6 months of treatment multiple friends commented 'wait you don't cough anymore'! I am now in a long-term relationship for which we have just celebrated our 3rd year anniversary. I started Kaftrio just over 3 years ago, and I can say there is no coincidence in this. I no longer worry about the burden of treatment on my partner or keeping him awake at night with my coughing. While we are not currently taking any steps in planning for a family, this is now a possibility and a genuine consideration for us - something I never thought to be possible. It has had a transformative effect on my physical and mental health and my ability to plan for the future."*
3	**Section 3.5** - CF Voices participated in the Interim Access Oversight Committee for the NICE data collection and we know that there is an (understandable) difference between what is feasible to collect through CF clinics and what patients/carers experience in real life. It's important to note the limitations of the data collection and the extent to which this impacts the relevant evidence the appraisal has taken into account to date.

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	Firstly, not all symptoms of CF are dealt with by CF clinics and are often accessed through GP's or other areas of NHS or privately e.g. mental health, ENT, MSD, Oncology, fertility. These issues were not always collected through CF clinics or reported by patients "Nearly all adults with CF have radiologic or endoscopic findings of sinus inflammation; however, only a minority report typical symptoms of chronic rhinosinusitis (CRS)..Because of minimal reporting, CF-related CRS (CF-CRS) is thought to be underdiagnosed and undertreated"[1] Patient comment: *"On commencing Kaftrio he was due to have sinus surgery as his sinus's were completely blocked despite constant sinus rinses and steroid drops as well as nebulising Dornase directly into his nose. This surgery was delayed however, due to covid. When the call finally came through to book his surgery appointment the hospital said as it had been a while a new CT scan would be needed. A week later they rang to say the surgery had been cancelled as his sinus's were now completely clear and it wasn't necessary. The doctor was so shocked she said she had needed to check that it was definitely his CT scan and there'd been no mix up. She said it was remarkable and could only be due to Kaftrio."* Loss of bowel or bladder control is found to be greater in people with CF due to persistent coughing. Research carried out before modulators were widely available based on the results of self-report questionnaires, found 105 patients (64.8%) had an overactive bladder, 91 (52%) had faecal incontinence, and 61 (34.3%) had stress urinary incontinence, or leakage of urine during moments of physical activity, including coughing or sneezing. And that "*The majority of people with [urinary or faecal incontinence] have never discussed their problems with their medical team despite the fact effective treatments and management strategies exist. It is probably considered too intimate or embarrassing to discuss, or secondary to other symptoms that are more directly related to the disease".*[2] Secondly, there are several impacts of CFTR modulators that were simply not predicted as they did not occur during short-term clinical trials e.g. changes to fertility. The likely combination of modulator induced hormonal changes plus the greater health of the CF community, has meant there has been a substantial increase in the number of women with CF now having babies, this rose from 58 in 2017 to 140 in 2022 [3]. No one could predict all the ways in which patients bodies and lives would be impacted over the long-term when the basic fault that caused their CF was corrected. This of course includes negative impacts as well as the positive. The NICE data collection period must be recognised as a relatively short period in which to assess long-term effects on chronic illness.
4	**Section 3.12 Economic model** – this is missing key elements including pseudomonas which is the most common cause of chronic respiratory infections and the leading cause of morbidity and mortality in patients [4], Aspergillus infections (affecting 15% of patients) [3] NTM infections, mental health, glycaemic index, gut health (beyond pancreatic sufficiency), pancreatitis, sinus disease and other later stage health impacts such as pancreatic scarring, liver failure (second highest cause of morbidity), lung transplants and colorectal cancer**.** Also, the model has pancreatic sufficiency and baseline infections as unchanging elements. However, there is both emerging clinical trial data and community testimony to question the validity of this. Stephenson et al. (2023) [5] found that "Most pwCF experienced an increase in FE-1 (faecal elastase) while receiving CFTR modulator treatment and a small percentage demonstrated values reflective of PS" (21% received pancreatic sufficiency) Chan at al (2022) found that "Treatment with Trikafta improved insulin secretion and body weight within one year in people with cystic fibrosis (CF), according to a small analysis" [6]. Of CF Voices respondents to consultation 27/128 reported improvements in pancreatic function and 19/128 in blood sugar management.

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5	**Section 3.15 Discount rate** – on this point we note that committee considers condition one is met. With regard to condition three, we would point out that this can be afforded a greater degree of certainty because of the BD dosing of CFTR modulators, ensuring the biochemical effect on the body is maintained. With regard to condition two, the committee view is that treatment 'does not restore people with CF to full health, but rather prevents decline'. However the criteria for a 1.5% discount rate refers also to 'near-full health' and we ask how 'near-full health' is defined. If this were to be from a patient's ability to live life to its full capacity with the same functioning and resilience as if they no longer had CF, then according to lived experience, evidenced through our research, the majority of currently treated patients would claim this. One stated *"I felt all the benefits of Kaftrio within 24 hours of taking my first dose. I compared it to the feeling you have the first day after a cold or virus has cleared. That feeling of being able to breathe better, not coughing up mucus or feeling that blocked feeling in your nose. Now imagine you had that cold for your entire lifetime, 30+ years in my case, then one day you woke up and it was gone. The modulators have essentially allowed my body to function in a more normal way. Being able to breathe properly, sleeping better, absorbing food more efficiently, no periods of sickness, no exacerbations, better mental health, more energy, ZERO hospital admissions and a reduction of almost 75% of all other medications as a DIRECT result of being on Kaftrio. It has been beyond life changing."* And another *"Since starting Kaftrio, I am pancreatic sufficient, my blood sugars are normal and require no intervention, I have gotten rid of all colonised bacteria that I previously had."* Another said *"It is like the clock has been turned back 30 years to the health I had before I was diagnosed at age 16. My overall energy levels are so much higher. My lung function numbers have not changed that much, so do not fully tell the picture of just how my life has changed."* *"Modulator treatment has changed everything for me. My lung function has improved to near normal levels and I have even managed to stop airway clearance and many of my other medications. I can exercise, play tennis, play golf and lead a healthy, happy and fulfilling life. I now work full time and will be joining a US law firm in January as a Partner. Something I could only have dreamed of before starting modulator treatment. I have not required any hospital treatment or antibiotics since commencing treatment. I can now also look at the long term as I hope I can now live a life with a near normal life expectancy (in fact, my lung function just keeps improving). My wife and I are even starting IVF treatment so we can start a family, with the knowledge that I should be around to bring a child up to adulthood. I cannot emphasise enough how much of a benefit modulator treatment has been for me. I have gone from being sick, depressed and resigned to death to being healthy, active, working full time and ready to start a family. All of this is entirely down to modulator treatment."* Sweat tests, which indicate whether the root cause fault in CF is present, are either improved to near normal or in many cases are now within normal range with CFTR modulator treatment – as if the patient no longer has CF. The currently treated cohort in the UK is considered largely to have a degree of existing CF damage (the majority has moderate or severe) and it is clinically accepted that beyond a certain point pancreatic and structural lung damage is irreversible. However, how important is that reversal to achieve 'near full health' in reality, when common patient experience is: *"Since Kaftrio- I work full time, in a physical occupation, I don't cough, I can laugh all day long, my mental health no longer requires intervention with drugs or therapy, my lung Functions are normal, I only take supplements such as vitamins, no other medication. My liver function is normal, I no longer have gut issues. I don't do any chest physio, I don't need to. I don't have any peg feeds anymore. My liver function is normal and no longer enlarged. I no longer required extra calories via my PEG. I have a full time very physical job and run daily, I do not tire! I no longer take any nebulised medication. I do not require sodium supplements anymore. I haven't had an antibiotic for a bacterial infection in 2 1/2 years. I have a new lease of life. Before Kaftrio I was heading towards the transplant list. I was sick all the time. I needed new lungs and a liver. I coughed all the time. I had no energy. I had suicidal thoughts*

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	as I had no quality of life and felt like I was a burden to my parents and younger siblings. Now I work full time, my job is physical demanding, I enjoy life. I no longer rely on anyone. I went from weekly review appts to 6/7 monthly reviews by phone or very occasionally at clinic. I no longer have to be fed via a gastrostomy to ensure I have enough calories. My toilet [behaviour is] normal. My life is amazing and I am so thankful. From what was a death sentence to a new life. It can only be described as amazing. I am enjoying this new life. I am a new person. My parents have a new life also. Most importantly I don't worry about my parents out living me anymore. I will be here long after them." In the younger patients, the committee stated that while it 'acknowledged the potential additional benefits of IVA-TEX-ELX in young children..it had not seen any evidence to support this'. We understand that the company will be providing further data by way of the now published Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2–5 Years with Cystic Fibrosis and at Least One *F508del* Allele. We have included other recent research which we believe addresses further uncertainty about this in our comments on uncaptured benefits, where e.g. 'Patients who started CFTR modulators at an earlier age tended to see the greatest benefits on pancreatic function.' A Vertex model has projected survival and long-term health outcomes in people with CF homozygous for *F508del* https://www.sciencedirect.com/science/article/pii/S1569199323000486 which we expect the company to present in greater detail for committee consideration. We wonder if the author could provide a further analysis of the data used in this study to aid with future costs modelling, on the basis that if the proportion of time spent in a more debilitated state (e.g. the 40%-70% ppFEV1, or <40% ppFEV1 states shown in Table 2) is reduced enough, then the average annual cost is likely to reduce, particularly when discounting is allowed for, noting that time spent in debilitated states would be expected to fall further into the future under the ELX/TEZ/IVA Tx than under other Tx's and thus costs under those states would be discounted by more. This could potentially be illustrated by estimating non-modulator cost for each state (>70, 40-70, <40) under each of the Tx's. This would then allow both for lower cost because of lower debilitation, but also lower cost because of variations in PEx / Tx event frequency and severity (and cause) under each type of modulator. Table 1 would seem to consider many of the same issues that underly annual costs, but presents them slightly differently. If effectiveness of each Tx was also shown separately for each state (at Tx initiation) for the 12+ cohort (e.g. by cutting the data into 3 groups), it should then be possible to determine years spent in each debilitation state for each Tx for a cohort of exact age 2 (given known distribution into the equivalent of >70, 40-70, and <40 at age 2), overlay the costs by debilitation state and Tx, and give rise to a comparison that better reflects the question in hand (i.e. what drugs to give from age 2 onwards).
6	**Section 3.16 Health-state utility values** - we strongly assert that use of EQ-5D questionnaires for CF is not fully valid and hope that Vertex will present the CFR-Q mapped to EQ-5D data that NICE invited it to submit. Failing this, we note that there is some published CFR-Q data for children aged 6-11 before and after Kaftrio, showing an average of a 6.2% increase in quality of life after Kaftrio. McGary et al (2020) [7] enrolled people with CF >=14yrs. Average utility was 0.81 (on a 0-1 scale) before Kaftrio, and increased by 0.07 after 4 weeks of Kaftrio and increased by 0.079 including ppFEV utility benefits too. However, as discussed at the first Committee meeting, all HRQoL questionnaires deal with perception and as people with CF have not known a different way of living any tool has limited validity. Patients grow resilient to be able to carry out their usual activities, take care of themselves, move around, deal with the emotional and physical pain of CF as part of their day-day life (the questions in EQ-5D). These 'ceiling effects' as they were referred to by Vertex, exist because patients are naturally unaware of how their bodies would be different after treatment e.g. *"I can feel air in my lungs for the first time. Before Kaftrio I didn't know what it felt like to have clear lungs. I thought what I was feeling before was normal and didn't realise what it was like to breathe. I spent months telling friends and family I could feel air on my lungs."* Patients were also unaware how burdensome and

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	distressing the nature of their day-day regime would be to a once healthy person. *'In the last few years before I received kaftrio. I had no real quality of life. I was in hospital every other month for 2-3 weeks at a time. I was depressed and just exhausted with trying to stay alive. I was hours from death in 2019 in icu for 9 weeks. I had no chance of coming back to health But then I received kaftrio. Within 72 hours I was back on a ward on only 2 litres of 02. 2 weeks later I was home. The years after that I got stronger and stronger. Nearly 4 years on I am the healthiest I've been and I'm now a mother !!! Something I never ever thought I would be. I never thought my body would hold out to do. I had the best pregnancy ever. And the most Perfect natural delivery! Breathing was not even an issue!!!!'* We attest that the EQ-5D asks the wrong questions to be sensitive for CF and cannot capture all the effort required to achieve the metrics e.g. usual activities, nor all the side effects, sequelae and comorbidities. Specifically, it is unlikely that the EQ-5D data adequately reflect the negative impacts of infertility on people with CF. Skedgel et al (2022) [8] state the case that "health-related quality of life is not broad enough to understand the full range of impacts associated with unmet parenthood goals. It is also likely that the impacts on individuals will vary significantly over time, and therefore will be hard to capture in shorter-term clinical trial data collection." We can also note evidence of 'ceiling effects' in carers of CF patients in our research, only realising the impact CF had on their lives when is reduced: *"We had more time than we've had in many years. When you care and worry for a loved one you forget what your life was like before. Even the smallest things like being able to go for a walk or laugh. Only when you start to feel the effects of the reassurance that slowly creeps in over time, do you realise how long it's been since you had relief or peace of mind. When you laugh and realise you can't remember the last time you had laughed or not had to fake a smile. You have time that you never had before. Illnesses that you just assumed were part of life are no longer there, backache, headaches and palpitations. Ask a stressed carer if they are stressed, most of the time they would say no because it's become part of their life and who they are just like CF. When Kaftrio came it not only changed the lives of the patients; the changes to the parents, families and carers is immeasurable."* As the committee identified it lacks any face validity that the quality of life for someone with untreated CF could be comparable to or higher than that of a healthy individual or that improvements with CFTR modulators would create marginal improvements. There must be recognition that solely relying on any tool for such a complex condition has limitations and we believe that this should inform committee flexibilities on both Treatment-specific utility benefit (3.17) and severity modifier (3.20).
7	**Section 3.17 Treatment-specific utility** See above. Here, the measured outcomes are narrowly reduced to Fev1 changes and Pex, with everything else considered as covered with HRQoL tools. Yet as apparent in the patient voice and expressed in the above comments, the outcomes of modulators treatment are far more extensive and HRQoL tools have limited capacity to measure them in CF. To go, for example, from 20-60 tablets per day, spending 2-3 hours on daily treatments, being frequently admitted to hospital, having sinus issues, potentially undergoing a lung transplant, contracting liver failure, CFRD, bowel cancer, and living with the understanding that you are infertile and will die in early adulthood - to a life where your health is largely unaffected by CF and 'CF is in the background' enabling you to live a largely 'normal' life with full utility and opportunity, including much greater potential for parenthood - just so long as you take the twice daily tablets, is not reflected solely through the other outcome measures and we believe should be considered for a treatment-specific utility. We do note that this depends on the company re-running the regression model.
8	**Section 3.18 Caregiver utility** – we strongly assert that caregiver utility benefit should apply without an upper age limit and refer to the CF Voices study March 2020 and to the November 2023 survey results. The impact on carers was demonstrated strongly, with themes of mental health, impact on work/careers and extended family impact being demonstrated. 76 of the 140 carers that responded

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	mentioned mental health. Mental health improvements in carers after patients received modulator therapy emerged as an important theme with 50 out of the 94 respondents in this category reporting improvements. 10 carers reported mental health problems that had required formal treatment and 8 of these – whose patients had received modulator therapy – reported improvements with treatment being no longer necessary. We separated carers into two groups; those caring for patients under 12 years of age (96 submissions) and those caring for patients over 12 years of age (44 submissions). Similar themes were identified in both groups, and were either present to similar levels, or were identified more strongly in the 12+ carer group. Mental health impacts on carers were very similar, with 24/44 submissions identifying this in the 12+ group and 52/96 submissions identifying this in the <12 age group. Impacts on the whole, or extended family, were more frequently mentioned in the 12+ age group with 19/44 submissions identifying this in the 12+ age group and 27/96 mentioning this in the <12 age group. Impacts on carer's work or career were also identified more often in the 12+ age group, with 17/44 submissions citing this in the 12+ age group and 27/44 submissions mentioning this in the <12 age group. As the committee recognised, logically for a progressive condition there is no cut-off of the carer impact and as patient health states decline towards early morbidity the emotional burden and practical support needed by patients is seen to increase. *"Over time, the effects of caring for someone with CF become more devastating as the disease progresses and the symptoms, complications and burden of care increases. Whilst other parents around you are looking forward to their children's futures you are living in fear of what is around the corner, and that gets worse as time passes and as they get older."* *"The burden of my treatment and disease was a huge struggle with both time and emotional energy for my Mum. I could see my Mum's heart break every time she would have to take me to hospital for another round of IVs as a teenager. Her heart break as she would watch my lung function and my functional baseline decrease year on year as a teenager, despite spending hours a day on my treatments and exercise. It had a profound affect on my Mum's physical and mental wellbeing. It also affected my sisters who had less of my Mum's time and attention as she was so busy trying to keep me well."* Equally, it can be imagined by anyone that coaxing a teenager to carry out 2-3 hours of medical regime around educational demands, is often more challenging than with a pre-schooler for whom play strategies can be employed and free time is greater. *"As a carer of someone with CF who as a teenager and young adult spent most of his time in hospital, I can say that it's is not only a huge burden but also very traumatic, depressing and impacts the whole family of the main carer (spouse, children, parents etc). As a main carer I was unable to progress in my career. I have missed many promotion opportunities. I haven't been able to achieve my potential in my job and have had to give up all hobbies. It is very depressing. I have had counselling and am prescribed anti - depressant drugs. Carers of those with CF are very isolated due to not being able to mix through fear of cross infection. Many of my 'friends' who I knew when my son was younger in hospital have since lost their children to this horrible disease."* The committee recognised that CF affects the wider family and certainly more than just one carer, and hence we point out that its current allowance for care utility is very conservative: *"[Pre modulators] My child is 13 years old. I am her main carer. I have stopped work as a medical professional in order to care for her. In addition to help from my husband we also require the support of my child's grandparents 3-4 days a week. Due to the physical and emotional impact of recurrent acute pancreatitis and chronic pain due to CF my daughter has significant care needs when recurrent pancreatitis and chronic pain is uncontrolled. She is fully NG fed, has severe acute and chronic pain, is anxious, has poor sleep and has reduced mobility. I care for her physically by lifting her, carrying her,*

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	washing and dressing her. I administer medication and NG feeds and support her to do physical therapies and rehabilitation. I support her emotionally with pain, anxiety and difficulty sleeping. I support her with accessing education via hospital education service at home. It has a huge impact on my and my families lives, physically from lifting and being largely housebound, financially from not working, emotionally seeing the effect on your loved one. When my child has periods of frequent flares requiring acute admission every 1-2 months it can cause huge disruption to our lives. Things are uncertain. It is very difficult to plan ahead or make commitments with family or friends. Holidays, Special days are often cancelled. It is hard emotionally for all the family to be apart. • *23 acute/unplanned admissions for pancreatitis over lifetime.* • *Total time out of mainstream education in lifetime approximately 4 years.* • *Total time fully NG fed 2-3 years.* • *Total time housebound and immobile 2.5 years* • *Total time main carer unable to work 4 years"* *"My mental health suffered hugely. I became very anxious. His sister also became very anxious about his health and understood that his life expectancy was reduced because of CF. It created huge anxiety within the family is a whole and put an enormous strain on our marriage for many years. It is difficult to overstate how pervasive CF is. You never escape it either emotionally or physically, and so much of the day was spent battling the condition, but it's like trying to hold back the tide."* *"CF has had a devastating impact on our family. My son with CF was one of our younger children. The older children were not given as much time and attention as they should have been able to get. When my son was diagnosed and he was very poorly in hospital all the time. One and sometimes both parents were absent a lot. Plans could not be made; family time was difficult and holidays were almost non-existent. The other children haven't achieved as well as they should have in school, they have a low self-esteem, their confidence is affected and as a result have had psychological problems. They have had drug and alcohol problems and are now on anti-depressant medication."* Loss of a loved one through CF must also be accounted for. A quote emailed by a CF parent indicates the ongoing devastation of loss of a child: *"(CF patient) was 16yrs and passed suddenly due to internal bleeding! She won gold medals the previous week in the Kelvin hall Glasgow for trampolining. She was buried on Christmas Eve. 1984.I will never get over it, but have learned with great difficulty to live with it*." Burying a child / grandchild / loved one is of course the greatest fear of any family has and this had been perhaps the greatest gift of CFTR modulators. Now most families can hope that their CF children / loved one has a chance to pass in the 'natural order' of age. According to CF Registry, the number of deaths in the CF community decreased from 143 in 2017 to 68 in 2021. The median age of people with CF has increased from 20 in 2017 to 22 in 2022. 63% of the CF population are now over 16. The predicted survival age of someone born today with CF has reached 56 compared to 47 in 2017. [3] *"Before our son started on Kaftrio age 14 we were watching him slowly die. That is no exaggeration. Our son's lung function dramatically declined and age 14 he had 50% lung function. He was constantly in and out of hospital with increasing frequency. He had allergic reactions to the antibiotics he was on, causing emergency dashes to A&E. he started to culture a drug-resistant bug. It was indescribably traumatic as a parent to watch this happen, and as a teenager he was becoming increasingly aware of how life-threatening the situation was. Despite being meticulous with physiotherapy, treatments and*

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	diet, there was nothing to halt the progression of the disease, and the steady decline of his health once he hit his teens. Just acknowledging this is very upsetting. As a carer, you try to put a brave face on it all the time, unlike when they are very young, this no longer fools them. A friend asked him if he was going to die before he was 30. The truth is he would have without Kaftrio; I have absolutely no doubt that. They were very dark days."
9	**Section 3.19 Disease Management:** while we understand these are figures taken from sources submitted by either the EAG or the company, chosen by the committee, we would like to take the opportunity to point out how clinical guidelines at CF centres are changing already. For example, at the Royal Brompton there have been many changes made to guidelines in the latest release (2023) that are specific to the children on Kaftrio [9]: - DNase - "We will no longer offer it routinely to a 6 year old child on Kaftrio or ivacaftor, assuming they have minimal lung disease" - Vitamins. We are getting high levels of vitamins A, D and E in some patients on Kaftrio so annual review results are being checked by the dietitians and pharmacists and dose adjustments made. - Hypertonic saline. We have now decided to offer 7% H/S twice daily routinely at 1 year of age unless they are already on ivacaftor. It is likely we will stop it if they start on Kaftrio. Also to point out that while CFTR modulators may have been an addition to ECM to date, they will increasingly replace it, particularly when prescribed to patients aged 2-5 who have minimal CF damage. Where these children have already been taking Kalydeco (from 1 month) or Orkambi (from 1 year) they may have essentially full-health preserved. As was stated at the North American Conference for CF this month, modulators are showing evidence that we are nearing the goal of 'primary prevention' of CF. That there is a 'window of opportunity to stop pulmonary damage before it occurs' and that 'improvements in fecal elastase..show in some patients..a possible window to rescue pancreatic function'. Primary prevention is the future driver for NHS cost savings with modulators.
10	**Section 3.20 Severity Modifier** Recent NICE review stated that "we proposed a quantitative modifier that gives additional weight to health benefits in the most severe conditions". Severity modifiers can only be applied to a relatively small number of severe diseases and we ask – if not CF, which? In the words of patients/carers: "*I was told I wouldn't live beyond my thirties. I spent weeks and weeks in hospital every year, sometimes there due to emergencies. I was airlifted to hospital in New Zealand due to a DIOS emergency. 3 x a year at least I was on IV antibiotics. I have had 3 portacaths in my lifetime, as well as other operations including embolisations. I missed weeks and weeks of school, I lost friends at a young age. Whilst I do work, I had days I couldn't get into the office due to my health. I couldn't get out of bed or walk up the stairs. I would cough CONSTANTLY, which resulted in voice loss, back issues and regular hymoptysis. My bones were thinning, my weight(s) was drastically low. Life was hard. And the impact on mental health is impossible to quantify. I have always had therapy throughout my life, because of the prognosis of CF, the burden it puts on your loved ones, the impact on relationships, work, school, friendships - every aspect of life - is hard to process and handle."* *'As I grew up, my LF declined. Rapidly from the age of 18. Everyday activities became more and more difficult. During my final year of university, I was admitted to hospital around 10 times. Each time for 2 weeks (at least) iv antibiotics. As my LF declined, I had to drop my work to 3 days a week, in order to enable me to continue working. I could no longer exercise like I wanted, and I tried to make the most of what time I had left, with my new born son. Physically and mentally I was broken.*

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	During COVID, I spent almost 2 years at home. If I had not started kaftrio at this time. I genuinely believe I would no longer be alive.' Statistics tell how in CF severity starts at birth: one in ten CF babies are born with or develop meconium ileus within the first few days of birth because of the clogging of the ileum by the thickened mucus. This will necessitate treatment with an NG tube and IV fluids. BMJ (Schluter 2019). Meconium peritonitis can develop as a complication and require emergency surgery. CF babies are 6.8 times more likely to suffer infant death (1.7% of CF babies compared to 0.32% of healthy babies). Ramos et al 2018 - CF babies are more likely to be born preterm and with low weight. During the first six months of life 30% of CF babies will suffer with Staphylococcus Aureus, Haemophilus Influenzae or Pseudomonas Aeruginosa infection, all requiring medical intervention (Ranganthan, 2017) [10]. Pseudomonas being most linked to infant mortality, the median age of contracting Pseudomonas being 2yrs but has been found as early as 3 months old. By the age of 3 years, one third of CF children will have signs of bronchiectasis as seen on CT scans. This deteriorates over the life of the CF sufferer. G-tubes are commonplace in CF children and severely impact their quality of life. CF sufferers are at a much higher risk of developing osteoporosis (Stalvey and Clines, 2013) [11], nasal polyps and sinus infections (Miller et al, 2023) [1], Liver disease is recognized in 4.5% to 20%, depending on age and the definition of significant liver disease (Kelly, 2014) [12], CFRD has an age-dependent incidence that ranges from 5% in 10–14 year olds to 13% in 15–19 year olds and near to 50% in patients 30-50 years of age (Kendig and Wilmott) [13] and the 2022 CF registry report showed 2315 people with CFRD. People with CF are 5-10 times more likely to develop adenomas earlier and have more aggressive types, with 50% having adenomas by the age of 40yrs, if they have lived to that age with 25% having progressed to adenocarcinomas (Scott et al, 2020) [14]. This risk increases further following lung transplants (Bhattacharya, 2022) [15] CF is declared as a indicative of hereditary colon cancer syndrome (Scott et al, 2020) and is being seen more in CF clinics as the patient population ages. If CFTR modulators are taken from a young enough age, this risk can be significantly reduced Scott et al, 2023 [16] state that the CFTR gene is a tumour suppressor in colorectal cancer, and therefore those with CF are at an increased risk of colorectal cancer 10. From this, it is also possible to deduce that by increasing the presence of CFTR, we reduce the risk of colorectal cancer. They conclude that "molecular therapies developed to treat cystic fibrosis by increasing CFTR activity may be applicable for colorectal caner tumours expressing low levels of CFTR". It should be noted that in NICE appraisal TA866 a treatment for Advanced colorectal cancer was given a severity modifier of 1.7. The 2022 UK CF registry data also shows an increased risk of Pneumothorax and haemotypsis, 246 people with CF with Gall bladder disease requiring surgery, Pancreatitis in 66 people, of which 8 were children, DIOS in 453 people with CF, 1065 people with CF had osteopenia, 505 suffered with depression and 376 with hearing loss. These figures are all considerably above that of a healthy population. NICE (2020) [17] state "a potential concern for rarer diseases is that there may be insufficient EQ-5D data to assess whether it adequately reflects changes to quality of life. evidence other than psychometric measures could be presented and considered in these specific circumstances…. EQ5-D is to be used in most circumstances unless there is strong evidence that it is inappropriate". We propose (as explained above in reference to section 3.16) that there is strong evidence to show EQ-5D as not fully valid for CF and ask the committee to hear the patient/carer voice with regard to the

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	matter of severity. It is clear that the modelling has not fully captured HR-QoL losses. We suggest that the highest severity modifier of 1.7 should apply.
11	**3.23 Uncaptured benefits** – CF patients evaluated as requiring a **transplant** (most commonly a double lung transplant) has reduced from 235 in 2017 to 41 in 2022, according to CF Registry.[3] **Improved pancreatic function (recently published research):** https://cysticfibrosisnewstoday.com/news/cftr-modulators-improved-pancreatic-function-cf-study/ https://www.sciencedirect.com/science/article/abs/pii/S1569199323009098 https://www.sciencedirect.com/science/article/abs/pii/S1526054220300737 A small subset of patients achieved FE-1 levels high enough that they were no longer considered to have pancreatic insufficiency (PI).. (21% received pancreatic sufficiency). Patients who started CFTR modulators at an earlier age tended to see the greatest benefits on pancreatic function. **Comments from CF Voices research** provides examples of lived experience – 27/128 reported improvements in pancreatic function: *"My 22 month old daughter was pancreatic insufficient - her faecal elastase score was 29 when tested at 1 month old. She commenced Orkambi in May 2023, and had her faecal elastase re-tested after 3 months of being on Orkambi. Her score was in the mid 300's deeming her pancreatic sufficient. She has been off creon with immediate effect from August 2023 with no issues."* *"Pancreatic Recovery: faecal elastase improved from <15ug/g to >500ug/g"* in 13 year-old patient with history "*of recurrent acute pancreatitis"* **Improved glycaemic control / CFRD (recently published research):** https://cysticfibrosisnewstoday.com/news/trikafta-improves-insulin-secretion-body-weight-cf-patients/ https://www.sciencedirect.com/science/article/pii/S2214623722000199 Treatment with Trikafta improved insulin secretion and body weight within one year in people with cystic fibrosis (CF), according to a small analysis. "This is the first report, to our knowledge, examining measures of insulin secretion and resistance in pediatric and adult patients, before and after initiation of the highly effective CFTR modulator [Trikafta]," the researchers wrote. **Comments from CF Voices research**: reported by 19/128 respondents to CF Voices survey including "*Stopping injecting lantus insulin for CFRD" "blood sugars are (also) much better controlled"* **Reduced bacterial colonisation:** According to **CF Registry** the number of Chronic P. Aeruginosa infections in paediatrics decreased from 209 in 2017 to 108 in 2022. The number of NTM infections in paediatrics decreased from 113 in 2017 to 65 in 2022, with NTM prevalence in the community dropping from 592(6.0%) to 289(3.1%). The number of CF patients prescribed IV Antibiotics has decreased from 4450 (45%) in 2017 to 2285 (23.3%) in 2022. CF Voices respondents on modulator treatments, mentions of clearing or reducing bacterial infection (55/128), reduced antibiotic treatment (46/128) **Comments from CF Voices research**:

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	"My daughter was chronically infected with NTM Abscessus which first appeared in her sputum samples in February 2015, aged 11. Her health deteriorated steadily from this point and she was put on 3 long-term oral antibiotics daily plus a nebulised antibiotic on top of nebulised Pulmozyme and saline (5 nebulisers per day). She was also admitted to hospital for 2 weeks of IV antibiotics every three months without fail (at least 8 weeks in hospital per year). She started taking Kaftrio on 7th July 2020 (on 'compassionate use' grounds). A sputum sample from 4th August 2020 was positive for NTM. The next sputum sample from 28th September 2020 was negative for NTM. Her sputum has never cultured NTM again from August 2020 until now. A CT scan in July 2021 showed a "radical improvement over that obtained in 2017". At this point she was allowed to stop all treatment for NTM (oral & nebulised antibiotics) and her health has remained stable. In fact, her lung function (FEV1) has increased from 37% when she first started Kaftrio to 62% this year. She has not been admitted to hospital for IVs since she started taking Kaftrio in 2020. In September this year, she had an operation to have her portacath removed as it had not been used for IV antibiotics for 3.5 years, since before starting Kaftrio. (She'd had her portacath for 10 years and the sense of liberation has been amazing)." *"My child has cultured pseudomonas aeruginosa (PA) since shortly before they were two years old. At six years old, whilst waiting for a hospital bed for an admission for IV antibiotics, my child began Kaftrio. The chest x-ray taken on this day showed an improvement from that of the one taken two years earlier. Within two weeks my child no longer needed to be admitted for IVs. Since this time there has been no PA, or indeed any other damaging bacteria, in my child's sputum. In addition to this, from spring of this year they have required no oral antibiotics (previously used frequently), no steroid or ventolin inhalers (often used multiple times a day), no nebulized ventolin (previously used throughout exacerbations, of which there were many), no nasal spray (previously used daily), no laxatives (used daily prior to Orkambi), they have used hypertonic saline only for induced sputum collection (previously twice daily), have reduced the use of dornase alpha (seven-fourteen times a week to five times a week), and have had a reduction in creon from 24 tablets a day to 12 tablets a day. Physio has reduced from two-three times daily to once a day. They remain on inhaled antibiotics and will do so until they have had two years of sputum tests clear of PA."* *"Prior to Kaftrio my daughter was not eligible for any modulators. She began Kaftrio 1 month after her 12th birthday in 2020 which coincided with the funding agreement. Prior to that she was colonised with pseudomonas (mucoid), aspergillus and regular staph growths. Almost all sputum samples were positive with a minimum of 1 set of IVs a year, regular posoconazole and ciprofloxacin, DNAse and alternating cayston/promixin nebs. She also underwent 15months of eradication treatment for NTM (abscessus) completed in 2018. Treatment burden was high. FEV1 still remained good at 100-102%. She had FESS sinus surgery in 2018 and also has been pancreatic insufficient since birth. After starting Kaftrio sweat test has reduced from 110 to 38. Lung function is consistently FEV1 115-120%. LCI on annual assessment has reduced from 13 to 7.6. No sputum growth or infection for 18months including more recently on induced sputum October 2023 after 5 months of no nebulised antibiotics. She no longer takes any nebulisers or prophylaxis. She has not had oral antibiotics for 2 years (last was when she had Covid and was given preventative Azithromycin)."* **Other new trial data that we don't believe the committee has been provided that adds to the weight of data of benefits not yet captured by the appraisal modelling:** **Improved GI symptoms - part of the RECOVER study (age >12)** https://cysticfibrosisnewstoday.com/news/kaftrio-eases-cf-gastrointestinal-symptoms-inflammation-study/ https://www.cysticfibrosisjournal.com/article/S1569-1993(23)00922-0/fulltext

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	One-year treatment with Kaftrio significantly improved the total CFAbd-Score — it was 15 at baseline versus 9.8 after a year — as well as its five domains, pain, gastroesophageal reflux disease (acid reflux), disorders of bowel movement, appetite, and impaired quality of life. A major improvement was seen in the first month, with symptoms reaching the minimum two months after treatment started. **Sinus disease -** published 14 October 2023 https://cysticfibrosisnewstoday.com/news/trikafta-lowers-p-aeruginosa-numbers-sinuses-cf-patients/ https://onlinelibrary.wiley.com/doi/10.1002/alr.23288 Treatment with ETI leads to a reduction in Pseudomonas abundance within the sinonasal microbiome of individuals with Pseudomonas at baseline. https://cysticfibrosisnewstoday.com/news/trikafta-eases-cf-sinus-disease-but-most-still-affected-study/ https://jamanetwork.com/journals/jamaotolaryngology/article-abstract/2808807?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jamaoto.2023.2701 **CF related liver disease** https://cysticfibrosisnewstoday.com/news/kaftrio-may-ease-fibrosis-severe-cf-related-liver-disease/ https://www.cysticfibrosisjournal.com/article/S1569-1993(23)00910-4/pdf **Real world study in Australia (adults)** https://cysticfibrosisnewstoday.com/news/adults-kalydeco-trikafta-show-lung-function-nutrition-gains/ https://www.sciencedirect.com/science/article/abs/pii/S1094553923000597#abs0010 **Other - Orkambi (limited benefit for small airways but unable to prevent the worsening of bronchiectasis)** https://cysticfibrosisnewstoday.com/news/trapped-air-children-ages-6-11-cleared-with-orkambi-over-2-years/ https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-023-02497-0 "This may suggest that LUM/IVA has some effect in relieving small airway obstruction caused by inflammation in small airways but is unable to prevent the worsening of bronchiectasis caused by established or persistent infection and associated inflammation." **Reduction in Treatment burden** https://www.sciencedirect.com/science/article/abs/pii/S1094553923000603 ETI therapy can reduce daily treatment burden in adult CF patients with at least one F508del mutation in real-life at 6 months of treatment while maintaining its effectiveness on respiratory symptoms and pulmonary exacerbations rate. In addition to the increase of a large number of lung function parameters, ETI improves airflow obstruction.

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

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	ETI Reducing bronchiectasis - published October 2023 https://onlinelibrary.wiley.com/doi/10.1002/jmri.29041 The study included 50 people with CF, ages 12 to 47 years, all of whom "were in a period of disease stability" at baseline, or the study's start. All had at least one F508del mutation, and 33 (66%) had previously been treated with Orkambi (lumacaftor/ivacaftor). After one year of treatment with Kaftrio, "there was a significant reduction in the main hallmarks of CF," the researchers wrote. These included reductions in abnormal thickening of the bronchi, mucus plugging, and bronchiectasis. The Bhalla scoring system was used to evaluate the severity of lung disease based on various hallmarks of CF. The total range for the Bhalla score is from 3 to 25, with a lower score indicating more severe radiological bronchiectasis. At baseline, the average Bhalla score was 12.8 points, increasing significantly to an average of 15.2 points after one year of treatment. At the same time, the average predicted forced expiratory volume in one second (FEV1), a measure of lung function, improved from 70% to 87%. In 18 patients, ultrashort echo-time MRI revealed narrower bronchi, indicating reversible bronchiectasis. Overall, there was a reduction in the severity and number of lung segments affected by bronchiectasis. Patients with reversible bronchiectasis were younger (mean 20.9 vs. 26.2 years) and had higher predicted FEV1 (mean 82.2% vs. 65.4%) and Bhalla scores (mean 14 vs. 12.2 points), indicating less severe lung disease compared with patients without reversible bronchiectasis. *From <https://cysticfibrosisnewstoday.com/news/kaftrio-ease-bronchiectasis-sensitive-mri-scans/>* **ETI impact on mental health - June 2023** Effective CFTR modulator use appears to ease depression with CF https://cysticfibrosisnewstoday.com/news/effective-cftr-modulator-mental-health-cystic-fibrosis/ https://www.sciencedirect.com/science/article/abs/pii/S1569199323008238 A long-term study on teenagers and young adults with cystic fibrosis (CF) suggests a higher likelihood of anxiety and depression in those with CF-related diabetes and more evident mental health challenges. The study, conducted over six years, found that individuals with reduced lung function and CF-related diabetes may need more mental health support. The study, published in the Journal of Cystic Fibrosis, involved routine mental health screenings for CF patients aged 12 and older. Results indicated that better access to more effective CF modulator therapies, particularly Trikafta, appeared to protect against depression. There is new evidence of successful treatment of fetuses with CF in utero. Including this study where a fetus with CF (F508del homozygous) and meconium ileus was born with no dilated bowel post-treatment. Prenatal Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy: A Promising Way to Change the Impact of Cystic Fibrosis https://pubmed.ncbi.nlm.nih.gov/36996799/
12	**3.25 Equality** – We note the Committee comment about the 10% untreated being more likely to be from minority ethnic backgrounds. While this may be outside the remit of NICE, we would like to propose the NHS carry out clinical trials to investigate the potential for patients among this group to establish if some could benefit, as studies globally suggest they might e.g. Hanger et al (Oct 2023)[18] '. It is also proven that socio-economic status impacts the family ability to care for CF patients. Therefore, CFTR modulators have a great potential for levelling inequality.

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	It should be noted that people with some neurological conditions (ADHD / Autism spectrum) and their carers may find the burdensome complex nature of managing CF on ECM alone disproportionately difficult, and hence modulator treatment has provided an additional important benefit for them that would be lost if final guidance is negative. There is an obvious and abhorrent inequality that would be caused by a final negative recommendation within the CF community. This may not technically fall under protected group legislation, but it would create an unethical and clearly unacceptable gap between the health and life chances of the treated cohort and the younger yet-to-be treated patients and future generations. Clearly, there is a moral responsibility on all parties here - on NICE to conclude a full and fair appraisal using all appropriate flexibilities. Vertex must offer fair pricing. NHS must prioritise negotiations to expedite the extension of treatment coverage beyond the current arrangements. The time-pressing nature of this is shown through this distressing CF parent comment: *"As a parent I've hugely struggled with mental health issues around CF and my son's potential health/quality of life issues. As a family it's taken us over 5 years to recover from our son's diagnosis and to be ready to have a much wanted second child. We are currently pregnant and awaiting NIPD test results for the baby, which has a 1/4 chance of also having CF. The only reason we finally felt ready for a second child, given the genetic risk factors, is due to the availability and incredible results of modulator drugs; it's is absolutely terrifying to me that my oldest son may continue to benefit from these but there is a potential that my future child may also need them and won't have access at 2, unlike my son who was born in 2018. The changes to the NICE guidelines were announced when I was 10 weeks pregnant and I am now considering a termination if this baby also has CF as I don't think I can cope with the inequality of having 2 children with such different treatment pathways and, as a consequence, drastically different qualities of health, treatment burden, and life expectancies."*
13	**Recommendations:** Given the vast amount of additional data likely to be made available to committee, we urge a recalculation taking all comments and recent research into account, before any further guidance is issued. There must be a recognition that the majority of data available now is from older patients with existing disease. Yet there is growing evidence of the very real potential for primary prevention of (any) CF damage through early initiation of modulators. This is fundamentally disease-changing, for such a severe disease with significant unmet need in routine commissioning. A way to model this future scenario must be used, particularly now that further information is available on the newly licensed Kaftrio for age 2-5 year-olds showing safety and efficacy equivalent to older age groups.
14	References: 1. Miller, J.E., Taylor-Cousar, J.L. and Beswick, D.M. (2023) '**Chronic rhinosinusitis with nasal polyposis in people with cystic fibrosis**', Sinusitis, 7(2), pp. 27–37. doi:10.3390/sinusitis7020004. 2. Katelyne Hubeaux, Laetitia Gueganton, Emmanuel Nowak, Baptiste Arnouat, Chantal Belleguic, Isabelle Danner,Boucher, Julie Mankikian, Annabelle Payet, Thierry Urban , Marion Buyse, Sophie Ramel (Oct 2023) **Prevalence and severity of functional urinary and anorectal disorders and their impact on quality of life in cystic fibrosis** 3. UK CF Registry report 4. *Christopher M. Waters and Joanna B. Goldberg (2019)* ***Pseudomonas aeruginosa*** **in cystic fibrosis: A chronic cheater** 5. Kimberly G. Stephenson, Abby J. Lingle, Kelly A. Baumberger, Charles R. Esther Jr., Ellen M. Meier, Christopher M. Oermann, Natalie Smith, Nicole S. Wimmer, Stephanie R. Duehlmeyer, Charissa W. Kam, Margaret O. Poisson, E. Claire Elson, (2023) **Changes in fecal elastase-1 following initiation of CFTR modulator therapy in pediatric patients with cystic fibrosis**

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	6. ChristineL. Chan, Andrea Granados, Amir Moheet, Sachinkumar Singh, Timothy Vigers, Ana Maria Arbeláez, Yaling Yi, Shanming Hu, Andrew W. Norris, Katie Larson Ode (2022) **Glycemia and β-cell function before and after elexacaftor/tezacaftor/ivacaftor in youth and adults with cystic fibrosis** *7.* McGarry, L. et al. (2020) 'PRS77 **application of the CFQ-R-8D to estimate utility benefit of elexacaftor/tezacaftor/ivacaftor (ELX/Tez/IVA) in people with cystic fibrosis (CF)**', Value in Health, 23. doi:10.1016/j.jval.2020.08.1957. *8.* Skedgel et al, 2022 "**considering severity in Health technology Assessment, can we do better**? Value in health journal, policy perspective volume 25. ***9.*** **Royal Brompton - Clinical Guidelines: Care of Children with Cystic Fibrosis** *10.* Ranganathan, S.C., Hall, G.L., Sly, P.D., Stick, S.M. and Douglas, T.A. (2017). **Early Lung Disease in Infants and Preschool Children with Cystic Fibrosis.** What Have We Learned and What Should We Do about It? American Journal of Respiratory and Critical Care Medicine, 195(12), pp.1567–1575. *11.* Stalvey and Clines (2013), **Cystic Fibrosis Related Bone Disease: insights into a growing problem, *Curr O[in Endocrinol Diabetes** Obes,* 20, 6, 547-552. *12.* Kendig, E.L. and Wilmott, R.W. (). Kendig and Chernick's **disorders of the respiratory tract in children**. Philadelphia, PA: Elsevier/Saunders. *13.* Kelly, D. (2014). **Liver Disease in the young adult with cystic fibrosis. Clinical Liver Disease**, 4(4), pp.84–85. *14.* Scott, P. et al. (2020) **'Cystic fibrosis, CFTR, and colorectal cancer**', International Journal of Molecular Sciences, 21(8), p. 2891. doi:10.3390/ijms21082891. *15.* Bhattacharya, R., Blankenheim, Z., Scott, P.M. and Cormier, R.T. (2022). **CFTR and Gastrointestinal Cancers**: An Update. Journal of Personalized Medicine, [online] 12(6), p.868. *16.* Scott, P.M., Wang, S., Onyeaghala, G.C., Pankratz, N., Starr, T.K. and Prizment, A.E. (2023). **Lower Expression of CFTR Is Associated with Higher Mortality in a Meta-Analysis of Individuals with Colorectal Cancer.** *Cancers*, 15(3), pp.989–989. doi:https://doi.org/10.3390/cancers15030989 *17.* **NICE, CHTE methods review**, health-related quality of live. Task and finish group report, July 2020. *18.* Hanger et al (Oct 2023) '**The effectiveness of CFTR modulators in people with CF and rare mutations: A real-world study'**

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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CF Voices Survey Analysis

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Introduction

Data was generated through an online survey conducted in November 2023. The survey responses were submitted anonymously but the survey was designed to determine whether the respondent was a patient or a carer and what life stage they were at. It contained questions about the impacts of CF that participants have experienced and, separately, the impacts of modulator therapy, which participants answered using free text responses. The survey was available through hyperlinks distributed by the CF Voices team to group members that opted in to the study following requests for participation in the CF Voices Facebook group. Quest for a CF Cure, a Scottish community group joined in promoting the survey to ensure representation from Scottish families. Participants were validated by the CF team to ensure that invitations were only sent to genuine UK-based members of the CF community. The online survey also utilised technology – through cookies and IP limitations – to ensure, as far as possible, that only one submission could be made by each registered participant.

In total, 175 survey responses were received from both patients and carers including those with and without access to modulator treatments. Each submission was examined in full, with keywords extracted from the free text answers that described the main themes in each submission. These were then coded into categories and an analysis performed of the number of submissions in each category, cross referenced against particular participant groups (such as patients, carers, and those with access to modulator treatment and without).

As expected, reported impacts of CF on participants were common and severe and – unsurprisingly – all respondents with access to modulator therapy reported an improvement in some aspect of their life (128/128 respondents that had been given access to modulator therapy). Most commented on improvements to physical symptoms (107/128 respondents). Within this group, clearing or reducing bacterial infection (55/128), reduced antibiotic treatment (46/128), increased energy (44/128), and decreased intestinal and digestive problems (39/128) were the most commonly mentioned.

These improvements in physical symptoms were only a part of the story though. Impacts in both patients and carers were reported that affected respondents across a diverse range of quality of life components. 62 highlighted reduced visits to and admissions to hospital, and 49 reported reductions in the daily regime of care after modulator therapy. This reduced burden perhaps contributed to the positive impact of modulator therapy on their mental health, which was reported by 64/128 respondents. Carers, as well as patients highlighted mental health as an issue, with 76 of the 140 carers that responded mentioning mental health. Mental health improvements in carers after patients received modulator therapy emerged as an important theme with 50 out of the 94 respondents in this category reporting improvements. 10 carers reported mental health problems that had required formal treatment and 8 of these – whose patients had received modulator therapy – reported improvements with treatment being no longer necessary.

The impact of CF on life attainment was also cited as a key issue, with 64/175 commenting on school, further education or work being impacted. Older patients commented on having to reduce or stop work due to CF related illness, or being able to increase their hours, go back to work or take on roles with higher responsibility once their treatment with modulators had begun. Other activities outside of work and education were also frequently mentioned (42/175), with themes including cancelled holidays and other plans because of CF, missing out on family occasions or activities because of illness and/or risk-mitigation, or conversely the ability to start participating in life experiences that had not previously been possible, some as profound as becoming parents, once modulator treatment had commenced.

The impact of CF on the whole, and extended family, came out very clearly in survey submissions, for both carers of patients under 12 and carers of patients over 12 years of age. Mental health problems experienced by carers were reported more frequently than mental health problems amongst patients (76/140 carer respondents as opposed to 71cases in patients reported by all 175 respondents). 57 of the 175 submissions cited an impact over the whole or extended family, such as the impact on (non-CF) siblings who felt ignored or sidelined, strains on marriages and friendships, or the impact on grandparents who were called upon for help. The work and careers of carers was also commonly cited, with 44/140 carers stating that they had reduced or given up work, or conversely had been able to increase or go back to work after their loved one had started modulator treatment.

This combination of improvements reported as a result of modulator therapy has created whole-life positive impacts which are transformational for both patients and carers. We have detailed below the impacts found under different themes, illustrating each one with selected quotes taken from the submissions.

Improvement in Patient Symptoms

Improvement in patient symptoms was the strongest theme we identified, with 107/128 respondents reporting improvements in this category. Within this group, clearing or reducing bacterial infection (55/128), reduced antibiotic treatment (46/128), increased energy (44/128), and decreased intestinal and digestive problems (39/128) were the most commonly cited. 38 highlighted improvements in lung function, 27 improvements in pancreatic function and 19 in blood sugar management.

"My daughter is on Kaftrio and it has been life changing. She has gained weight and since starting the drug in October 2020, her lung function increased over a 6 week period from around 55% to 100% and has remained at 95-100% since. She would have had on average 8/9 changes in antibiotic annually and since 2020 she has had one. It has made such a difference to her quality of life and in fact our CF team has now taken her off her daily antibiotics given her state of health. She had colonised staphylococcus and that has now gone totally. After starting Kaftrio she told me that she had never realised how ill she felt before and she no longer has a feeling of weight in her chest holding her back."

"On commencing Kaftrio he was due to have sinus surgery as his sinus's were completely blocked despite constant sinus rinses and steroid drops as well as nebulising Dornase directly into his nose. This surgery was delayed however, due to covid. When the call finally came through to book his surgery appointment the hospital said as it had been a while a new CT scan would be needed. A week later they rang to say the surgery had been cancelled as his sinus's were now completely clear and it wasn't necessary. The doctor was so shocked she said she had needed to check that it was definitely his CT scan and there'd been no mix up. She said it was remarkable and could only be due to Kaftrio."

"Prior to Kaftrio my daughter was not eligible for any modulators. She began Kaftrio 1 month after her 12th birthday in 2020 which coincided with the funding agreement. Prior to that she was colonised with pseudomonas (mucoid), aspergillus and regular staph growths. Almost all sputum samples were positive with a minimum of 1 set of IVs a year, regular posoconazole and ciprofloxacin, DNAse and alternating cayston/promixin nebs. She also underwent 15months of eradication treatment for NTM (abscessus) completed in 2018. Treatment burden was high. FEV1 still remained good at 100-102%. She had FESS sinus surgery in 2018 and also has been pancreatic insufficient since birth. After starting Kaftrio sweat test has reduced from 110 to 38. Lung function is consistently FEV1 115-120%. LCI on annual assessment has reduced from 13 to 7.6. No sputum growth or infection for 18months including more recently on induced sputum October 2023 after 5 months of no nebulised antibiotics. She no longer takes any nebulisers or prophylaxis. She has not had oral antibiotics for 2 years (last was when she had Covid and was given preventative Azithromycin)."

"My son's health, as evidenced above, has improved dramatically (beyond recognition since taking Kaftrio). His lung function has increased from 80% to over 100%. He has had zero hospital admissions since taking Kaftrio and has suffered zero lung infections (thus no need for IV antibiotics). There is now talk of slowly being brought off current drugs, such as DNASE thus will gain even more of his daily life back with reduced treatments. He has already reduced his need for nebulized treatments too. Reduced Creon requirements and Insulin requirements. Lung x-rays show improvement (lead consultant at Heartlands Adult CF Hospital commented that she had never seen this before in a CF adult)."

"My daughter was chronically infected with NTM Abscessus which first appeared in her sputum samples in February 2015, aged 11. Her health deteriorated steadily from this point and she was put on 3 long-term oral antibiotics daily plus a nebulised antibiotic on top of nebulised Pulmozyme and saline (5 nebulisers per day). She was also admitted to hospital for 2 weeks of IV antibiotics every three

months without fail (at least 8 weeks in hospital per year). She started taking Kaftrio on 7th July 2020 (on 'compassionate use' grounds). A sputum sample from 4th August 2020 was positive for NTM. The next sputum sample from 28th September 2020 was negative for NTM. Her sputum has never cultured NTM again from August 2020 until now. A CT scan in July 2021 showed a "radical improvement over that obtained in 2017". At this point she was allowed to stop all treatment for NTM (oral & nebulised antibiotics) and her health has remained stable. In fact, her lung function (FEV1) has increased from 37% when she first started Kaftrio to 62% this year. She has not been admitted to hospital for IVs since she started taking Kaftrio in 2020. In September this year, she had an operation to have her portacath removed as it had not been used for IV antibiotics for 3.5 years, since before starting Kaftrio. (She'd had her portacath for 10 years and the sense of liberation has been amazing)."

"My daughter's fecal elastase numbers have not changed on Kaftrio/Kaydeco, however her experience of needing to take creon have. Even though she has greatly reduced her creon intake, sometimes not taking it at all, she is no longer symptomatic. Her CF dietitian is monitoring this and and has said that others at our hospital are reporting the same."

"He has had no admissions to hospital or any courses of antibiotics since commencing Kaftrio. His lung function has gone from at its lowest 54% to 120%!"

"Removal of gastrostomy - no longer using night feeds - Stopping injecting lantus insulin for CFRD - Removal from the liver transplant waiting list - No longer using BIPAP breathing apparatus at night - No longer having 3 monthly IV courses - Reduction in Creon consumption"

"Treatment with modulators has changed my life immeasurably. [Amongst other things] I can sit in a bath for more than 5 minutes, as my skin no longer shrivels so badly I physically cannot stand the pain."

"3 days after my first Kaftrio tablets I stopped coughing and slept for a whole night, and have barely coughed since. My lung function has gone from 59% at its lowest to 120%."

"Since starting Kaftrio, I am pancreatic sufficient, my blood sugars are normal and require no intervention, I have gotten rid of all colonised bacteria that I previously had."

"I can feel air in my lungs for the first time. Before Kaftrio I didn't know what it felt like to have clear lungs. I thought what I was feeling before was normal and didn't realise what it was like to breathe. I spent months telling friends and family I could feel air on my lungs."

"I felt all the benefits of Kaftrio within 24 hours of taking my first dose. I compared it to the feeling you have the first day after a cold or virus has cleared. That feeling of being able to breathe better, not coughing up mucus or feeling that blocked feeling in your nose. Now imagine you had that cold for your entire lifetime, 30+ years in my case, then one day you woke up and it was gone. The modulators have essentially allowed my body to function in a more normal way. Being able to breathe properly, sleeping better, absorbing food more efficiently, no periods of sickness, no exacerbations, better mental health, more energy, ZERO hospital admissions and a reduction of almost 75% of all other medications as a DIRECT result of being on Kaftrio. It has been beyond life changing."

"My son aged 13 started Kaftrio March 2022 aged 11 as his lung function had plummeted from 97% to 54% he also had chronic lung infections and was constantly on extra antibiotics. In the past 18months we haven't had to put him on extra antibiotics and his lung function is now 87% which it rose to this within 6 weeks of starting the medication. He was being monitored for CF related diabetes prior to Kaftrio and now all levels are normal. He is able to play football 6 times per week - able to attend school even in the winter without suffering from chronic chest infections - better sleep due to not having breathing issues - weight gain - no extra antibiotics - no more stomach issues or leaking from his bottom

- increased energy - reduced headaches and sickness - no wheezing or crackling - no salty skin or excess sweating - no sore bones - able to stay warmer."

"My 22 month old daughter was pancreatic insufficient - her faecal elastase score was 29 when tested at 1 month old. She commenced Orkambi in May 2023, and had her faecal elastase re-tested after 3 months of being on Orkambi. Her score was in the mid 300's deeming her pancreatic sufficient. She has been off creon with immediate effect from August 2023 with no issues."

"I have cleared pseudo infection entirely, blood sugars are also much better controlled and I have reduced my reliance on Creon significantly."

"It is like the clock has been turned back 30 years to the health I had before I was diagnosed at age 16. My overall energy levels are so much higher. My lung function numbers have not changed that much, so do not fully tell the picture of just how my life has changed."

Treatment Burden and Daily Routines

A strong theme was the significant challenge of daily routine around treatments, which affects both patients and their carers, and the improvement in this following modulator treatment. 69 out of the 175 submissions mentioned the treatment burden and daily routine as a challenge, and 49 of the 128 submissions from respondents with access to modulator therapy specifically referenced an improvement in this.

"My child has cultured pseudomonas aeruginosa (PA) since shortly before they were two years old. At six years old, whilst waiting for a hospital bed for an admission for IV antibiotics, my child began Kaftrio. The chest x-ray taken on this day showed an improvement from that of the one taken two years earlier. Within two weeks my child no longer needed to be admitted for IVs. Since this time there has been no PA, or indeed any other damaging bacteria, in my child's sputum. In addition to this, from spring of this year they have required no oral antibiotics (previously used frequently), no steroid or ventolin inhalers (often used multiple times a day), no nebulized ventolin (previously used throughout exacerbations, of which there were many), no nasal spray (previously used daily), no laxatives (used daily prior to Orkambi), they have used hypertonic saline only for induced sputum collection (previously twice daily), have reduced the use of dornase alpha (seven-fourteen times a week to five times a week), and have had a reduction in creon from 24 tablets a day to 12 tablets a day. Physio has reduced from two-three times daily to once a day. They remain on inhaled antibiotics and will do so until they have had two years of sputum tests clear of PA."

"I have just 3 antibiotic nebulisers a day every other night and do DNASE 2 times a week (instead of 2 times a day) I don't have to do sinus nebs, drops or rinses anymore, and only do physio 2 x a week."

"Huge reduction in a very gruelling schedule."

Patient Mental Health

Patient mental health was a strong theme, and it was often tied up inextricably with declining physical health, the burden of daily treatments and knowledge of impending decline and life expectancy. 71 of the 175 submissions cited mental health as an issue, with 64 of the 128 submissions from respondents with access to modulator therapy citing an improvement in this.

"Since starting Kaftrio in Sept 2020, his (and our) lives have improved dramatically. He has had 1 hospital admission in 3 years, compared to the previous once to twice a year admissions. He has started volunteering twice a week at the local BHF charity shop and this year has felt well enough to secure his first ever employment at a retail cafe. This has enabled him to earn his own money for the first time ever and consequently has been thinking about being able to leave home and live in his own accommodation. His mental health is considerably better, as he feels as though he has a future. He used to think "what is the point of doing all of this treatment, or getting any qualifications, as he wasn't going to live long anyway". Kaftrio has changed that. It means he can walk into town, go and do some shopping, all things he could never do before. He could not carry heavy bags of shopping back from the shop, as he became too breathless. He is able to manage this much more now. He still suffers with breathlessness, fatigue, presumed infertility and low mood due to the daily treatment burden of CF, but these are all massively improved since being on Kaftrio. Every child deserves to have this chance of life."

"Being on Kaftrio also has a huge positive impact on my mental health. I can now see a full life ahead of me due to an increased life expectancy. I can look forward to having a family in the future which was uncertain before Kaftrio as patients with CF struggled to conceive (and also had a shorter life expectancy)."

"Since Kaftrio- I work full time, in a physical occupation, I don't cough, I can laugh all day long, my mental health no longer requires intervention with drugs or therapy, my lung Functions are normal, I only take supplements such as vitamins, no other medication. My liver function is normal, I no longer have gut issues. I don't do any chest physio, I don't need to. I don't have any peg feeds anymore. My liver function is normal and no longer enlarged. I no longer required extra calories via my PEG. I have a full time very physical job and run daily, I do not tire! I no longer take any nebulised medication. I do not require sodium supplements anymore. I haven't had an antibiotic for a bacterial infection in 2 1/2 years.

I have a new lease of life. Before Kaftrio I was heading towards the transplant list. I was sick all the time. I needed new lungs and a liver. I coughed all the time. I had no energy. I had suicidal thoughts as I had no quality of life and felt like I was a burden to my parents and younger siblings. Now I work full time, my job is physical demanding, I enjoy life. I no longer rely on anyone. I went from weekly review appts to 6/7 monthly reviews by phone or very occasionally at clinic. I no longer have to be fed via a gastrostomy to ensure I have enough calories. My toilet [behaviour is] normal. My life is amazing and I am so thankful. From what was a death sentence to a new life. It can only be described as amazing. I am enjoying this new life. I am a new person. My parents have a new life also. Most importantly I don't worry about my parents out living me anymore. I will be here long after them."

"The benefits of my improved lung function have been invaluable to my daily life. I no longer have a daily cough that stops me sleeping. I no longer struggle to maintain my weight. I no longer expectorate mucus, even with vigorous exercise. I do high intensity exercise 4 times a week with my friends and partner who do not have CF and I do not struggle any more than them. It allows me to spend more time with friends and family which has improved my mental well-being immeasurably."

Patient Independence and ability to progress goals including education, career, and parenthood, sports and other interests

Education and work/career was a strong theme, with 64/175 submissions referencing the impact on this. The ability to pursue other interests and even start a family was also present, with 32/128 respondents indicating an improvement in this following modulator treatment, and 16/128 respondents specifically mentioning fertility and/or parenthood.

"Once the new medications became available and his health improved dramatically, with no hospital admissions, he was able to take up full time work, remove his DLA payments and is now a Nuclear Reactor Physicist working full time, paying into the system, is a valued member of our society, doing a job he loves and he is good at etc. Without this medication, I am confident, he would now be on the lung transplant list and all that entails or worse."

"My son has been able to compete in sport at a higher level and even achieved a bronze medal in the national surf life saving championships since starting Kaftrio. Prior to that he was struggling with short distance swims and runs."

"My son now in his words "has his life back" and "will need to think about a pension", he now works and is also the founder of a new exciting company. He can now do his own physio. He never thought about having a girlfriend as he felt he had too much going on with his health that he didn't think he could make time for one or that anyone would want him. Now he has started dating which is a huge deal."

"The biggest positive for me is the fact I have been able to have a daughter. Never in my wildest dreams did I think I would be able to become a Mum. I cannot explain how much of a positive impact this has had on my life!!"

"It is as if someone has switched off CF. It is incredible. I can now breathe, laugh at jokes without a coughing fit. So many things that I thought was okay or "fine," I now realise was completely NOT. When thinking about the difference these modulators have made to my life, they have given me a life where I can live. I can hope. I can imagine a life without the huge burden of this disease. Since starting modulators, I have completed a university honours degree and have secured an enviable position as a solicitor in a prestigious law firm (something that I could never allow myself to have imagined back at my worst before any modulator treatments were available). I now am able to exercise, go to the gym and keep up with friends. I have so much more free time. I would not be alive today without these drugs, instead of being anxious of the inevitable doom and gloom of CF, I am looking forward to a future where I will live a long and fulfilled life and have a family of my own."

Carer Impact – Mental Health, work/career, reduced reliance on benefits, and extended family impact

The impact on carers was demonstrated strongly, with themes of mental health, impact on work/careers and extended family impact being demonstrated.

We separated carers into two groups; those caring for patients under 12 years of age (96 submissions) and those caring for patients over 12 years of age (44 submissions). Similar themes were identified in

both groups, and were either present to similar levels, or were identified more strongly in the 12+ carer group.

Mental health impacts on carers were very similar, with 24/44 submissions identifying this in the 12+ group and 52/96 submissions identifying this in the <12 age group.

Impacts on the whole, or extended family, were more frequently mentioned in the 12+ age group with 19/44 submissions identifying this in the 12+ age group and 27/96 mentioning this in the <12 age group. Impacts on carer's work or career were also identified more often in the 12+ age group, with 17/44 submissions citing this in the 12+ age group and 27/44 submissions mentioning this in the <12 age group.

"Over time, the effects of caring for someone with CF become more devastating as the disease progresses and the symptoms, complications and burden of care increases. Whilst other parents around you are looking forward to their children's futures you are living in fear of what is around the corner, and that gets worse as time passes and as they get older."

"My mental health suffered hugely. I became very anxious. His sister also became very anxious about his health and understood that his life expectancy was reduced because of CF. It created huge anxiety within the family is a whole and put an enormous strain on our marriage for many years. It is difficult to overstate how pervasive CF is. You never escape it either emotionally or physically, and so much of the day was spent battling the condition, but it's like trying to hold back the tide."

"As a parent I've hugely struggled with mental health issues around CF and my son's potential health/quality of life issues. As a family it's taken us over 5 years to recover from our son's diagnosis and to be ready to have a much wanted second child. We are currently pregnant and awaiting NIPD test results for the baby, which has a 1/4 chance of also having CF. The only reason we finally felt ready for a second child, given the genetic risk factors, is due to the availability and incredible results of modulator drugs; it's is absolutely terrifying to me that my oldest son may continue to benefit from these but there is a potential that my future child may also need them and won't have access at 2, unlike my son who was born in 2018. The changes to the NICE guidelines were announced when I was 10 weeks pregnant and I am now considering a termination if this baby also has CF as I don't think I can cope with the inequality of having 2 children with such different treatment pathways and, as a consequence, drastically different qualities of health, treatment burden, and life expectancies."

"Health is completely turned around for the entire family. Before it was a daily struggle to "keep afloat," now and for the first time since Kaftrio, CF is in the background."

"As a carer of someone with CF who as a teenager and young adult spent most of his time in hospital, I can say that it's is not only a huge burden but also very traumatic, depressing and impacts the whole family of the main carer (spouse, children, parents etc). As a main carer I was unable to progress in my career. I have missed many promotion opportunities. I haven't been able to achieve my potential in my job and have had to give up all hobbies. It is very depressing. I have had counselling and am prescribed anti - depressant drugs. Carers of those with CF are very isolated due to not being able to mix through fear of cross infection. Many of my 'friends' who I knew when my son was younger in hospital have since lost their children to this horrible disease."

"CF has had a devastating impact on our family. My son with CF was one of our younger children. The older children were not given as much time and attention as they should have been able to get. When my son was diagnosed and he was very poorly in hospital all the time. One and sometimes both parents were absent a lot. Plans could not be made; family time was difficult and holidays were almost non-

existent. The other children haven't achieved as well as they should have in school, they have a low self-esteem, their confidence is affected and as a result have had psychological problems. They have had drug and alcohol problems and are now on anti-depressant medication."

"I now sleep soundly with no disturbances from coughing or finding myself laying in bed wide awake listening out for him. I have returned to work and as he now attends hospital appointments on his own and has begun to socialise I actually have time on my hands and my mental health has drastically improved, I feel I am a wife and mother again running a normal family without the weight of CF care weighing me down."

"We had more time than we've had in many years. When you care and worry for a loved one you forget what your life was like before. Even the smallest things like being able to go for a walk or laugh. Only when you start to feel the effects of the reassurance that slowly creeps in over time, do you realise how long it's been since you had relief or peace of mind. When you laugh and realise you can't remember the last time you had laughed or not had to fake a smile. You have time that you never had before. Illnesses that you just assumed were part of life are no longer there, backache, headaches and palpitations. Ask a stressed carer if they are stressed, most of the time they would say no because it's become part of their life and who they are just like CF. When Kaftrio came it not only changed the lives of the patients; the changes to the parents, families and carers is immeasurable."

"CF has had a huge impact on my life being the mother of a child with CF and a mum to two other non-CF children. From the day he was diagnosed my life changed negatively and was getting worse every year as his health declined. I started getting panic attacks often and depression due to the regimen of medication and physio and hospital stays and visits and just making sure everything is clean and just being in a hyper vigilant state always. When he received the Kaftrio his life changed on that very day and so did mine. Ever since then I feel like the old me is coming back less anxiety and I feel able to enjoy life again with hope and dreams of having him with us always. The guilt I felt for my other children was huge always feeling like I wasn't there for them as I should have been but CF always took priority. I feel Kaftrio has enabled me to be a mum to all of my children not just my son with CF and the burden of the disease has been lifted. The only way I can describe it is if you ever imagined what a miracle looked like the. That's what we have been given."

Full Stories

Many stories suggested impacts of modulator treatments that were so transformational, and had such a profound impact on the whole life of the patient, that we have included them in full, rather than attempting to segment them into themes:

"I am a patient with CF who is now 29. The burden of my treatment and disease was a huge struggle with both time and emotional energy for my Mum. I could see my Mum's heart break every time she would have to take me to hospital for another round of IVs as a teenager. Her heart break as she would watch my lung function and my functional baseline decrease year on year as a teenager, despite spending hours a day on my treatments and exercise. It had a profound affect on my Mum's physical and mental wellbeing. It also affected my sisters who had less of my Mum's time and attention as she was so busy trying to keep me well.

Prior to starting Kaftrio, the trend of my FEV1 had been on a gradual downward decline since 2009, aged 15. In January of 2020 my FEV1 was 2.78L/s (69% of predicted). What that graph looked like in real life was a constant battle to try to maintain my health with an hour a day chest physio regime, 2 nebulisers, 2 inhaled treatments and 60+ tablets per day. I would force myself to exercise in order to

try to maintain my fitness. And despite that I would cough every day and my health was deteriorating every year. I would find it hard to sleep with the constant cough I had. This would worsen during exacerbations to the point where I would find it hard to leave the house, have to take time off work and miss out on social occasions. I would have to take time off exercising and increase the amount of time I spent doing chest physio. After all of that effort, I would then get back to 'normal' at a new, lower, FEV1 and functional baseline. It was extremely demotivating and upsetting.

As a teenager I spent around 1 week every year from 14-18 in the hospital having IVs, missing out on school and socialising with my friends. Once I started work I would average around 1 week off per year due to ill health. I required a half day off for routine hospital appointments every 6 weeks, or more during poorer health.

I had great relationships with friends but was often embarrassed as to how much I was coughing and was acutely aware of people who did not know me judging my decision to go to the gym, or be in the shops, assuming I had an infection that they were now going to catch. I avoided social situations when I was unwell as a result. This embarrassment extended to romantic relationships. I was 25 when I started Kaftrio and had never been in a romantic relationship or even tried to date as I was so embarrassed at the thought of someone having to see my treatment regime, be kept awake by my coughing, or having to care for me when I was unwell. I had certainly never considered having children, both because I knew this would be difficult from a fertility point of view and because I did not want my child to grow up without a Mother.

The trajectory I saw myself on was a steady decline in health and eventually earning myself a place on a list for a double lung transplant. By current estimations, dead by the time I was 40.

[Since starting Kaftrio] I work full time and have had to have no time off due to my health in the last 2.5 years. I work as a junior doctor in A&E. Since starting Kaftrio, I have completed my foundation training, a post-graduate certification in medical education and plan to start GP training next August. I no longer have to drag myself to work in the midst of an awful exacerbation, trying to speak to patients in between coughing fits.

The impact on my social/family life has also been immeasurable. I find it easy to maintain social relationships and after 6 months of treatment multiple friends commented 'wait you don't cough anymore'! I am now in a long-term relationship for which we have just celebrated our 3rd year anniversary. I started Kaftrio just over 3 years ago, and I can say there is no coincidence in this. I no longer worry about the burden of treatment on my partner or keeping him awake at night with my coughing. While we are not currently taking any steps in planning for a family, this is now a possibility and a genuine consideration for us- something I never thought to be possible. It has had a transformative effect on my physical and mental health and my ability to plan for the future."

"Before our son started on Kaftrio age 14 we were watching him slowly die. That is no exaggeration. Our son's lung function dramatically declined and age 14 he had 50% lung function. He was constantly in and out of hospital with increasing frequency. He had allergic reactions to the antibiotics he was on, causing emergency dashes to A&E. he started to culture a drug-resistant bug. It was indescribably traumatic as a parent to watch this happen, and as a teenager he was becoming increasingly aware of how life-threatening the situation was. Despite being meticulous with physiotherapy, treatments and diet, there was nothing to halt the progression of the disease, and the steady decline of his health once he hit his teens. Just acknowledging this is very upsetting. As a carer, you try to put a brave face on it all the time, unlike when they are very young, this no longer fools them. A friend asked him if he was going to die before he was 30. The truth is he would have without Kaftrio; I have absolutely no doubt that. They were very dark days.

The impact of Kaftrio was transformative. Within 48 hours our son's lung function went from 50% to 85% and has stayed there. He had been in hospital for IV antibiotics every 4-6 months all his life, and had regular courses of all antibiotics. He constantly had terrible tummy aches and diarrhoea as a consequence of all the antibiotics Since commencing Kaftrio in October 2020 he has not been to hospital for IV antibiotics AT ALL and has had only three courses of oral antibiotics. He has finally been able to put on weight, although he still remains smaller than his peers as his growth spurt started before he started Kaftrio. His blood sugars have stabilised. He has a future again. As parents, we don't feel frightened about the future but hopeful. He no longer misses chunks of school at a time. He's just done really well in GCSEs and is doing A levels and will go to university. He wants to be a lawyer. We have been able to increase our own work (we are professionals) as we have far fewer caring responsibilities, time spent in hospital with him et cetera. As a family we are immeasurably happier. His sister is no longer extremely anxious about his health. It has given us immeasurably more than I can write in words. He finally has a normal life and so do we."

"In the last few years before I received Kaftrio, I had no real quality of life. I was in hospital every other month for 2-3 weeks at a time. I was depressed and just exhausted with trying to stay alive. I was hours from death in 2019 in ICU for 9 weeks. I had no chance of coming back to health. But then I received Kaftrio. Within 72 hours I was back on a ward on only 2 litres of 02 [oxygen]. 2 weeks later I was home. The years after that I got stronger and stronger. Nearly 4 years on I am the healthiest I've been and I'm a mother!!! Something I never ever thought I would be. I never thought my body would hold out to do. I had the best pregnancy ever. And the most perfect natural delivery! Breathing was not even an issue!!!!"

"[Pre modulators] My child is 13 years old. I am her main carer. I have stopped work as a medical professional in order to care for her. In addition to help from my husband we also require the support of my child's grandparents 3-4 days a week. Due to the physical and emotional impact of recurrent acute pancreatitis and chronic pain due to CF my daughter has significant care needs when recurrent pancreatitis and chronic pain is uncontrolled. She is fully NG fed, has severe acute and chronic pain, is anxious, has poor sleep and has reduced mobility. I care for her physically by lifting her, carrying her, washing and dressing her. I administer medication and NG feeds and support her to do physical therapies and rehabilitation. I support her emotionally with pain, anxiety and difficulty sleeping. I support her with accessing education via hospital education service at home. It has a huge impact on my and my families lives, physically from lifting and being largely housebound, financially from not working, emotionally seeing the effect on your loved one. When my child has periods of frequent flares requiring acute admission every 1-2 months it can cause huge disruption to our lives. Things are uncertain. It is very difficult to plan ahead or make commitments with family or friends. Holidays, Special days are often cancelled. It is hard emotionally for all the family to be apart.

- *23 acute/unplanned admissions for pancreatitis over lifetime.*
- *Total time out of mainstream education in lifetime approximately 4 years.*
- *Total time fully NG fed 2-3 years.*
- *Total time housebound and immobile 2.5 years*
- *Total time main carer unable to work 4 years*

[Post Modulators] Previous treatment with Ivacaftor/lumacaftor brought stabilisation and a near normal life for my child. My child then had a period of instability and symptoms returned and faecal elastase dropped as her team worked to stabilise her on a new modulator. It is early days to know the full benefit but she has now been taking ivacaftor/tezacaftor/elexacaftor for 8 months.

- *Pancreatic Recovery: faecal elastase improved from <15ug/g to >500ug/g.*
- *Sweat test results are in the normal non-CF range.*
- *Only one short hospital admission for pancreatitis in 2 years instead of every 1-2 months.*

- *Modulator treatment improved quality of life by reducing flares and preventing hospital admission.*
- *Able to attend full time school.*
- *Mobility returned to normal and able to fully participate in sport.*
- *Stopped NG feeding and able to eat a full healthy diet.*
- *Enjoyed socialising with friends and family.*
- *Care requirements reduced so was able to return to flexible part time work.*
- *Less worry about my child's health.*
- *Able to look after myself better with more time to exercise/recharge emotionally.*
- *More time together as a family, feeling stable."*

"Kaftrio has been truly life changing and nothing short of miraculous. My daughter is back at work, happily married and has a son. Although her lung damage cannot be reversed she is well enough to manage everything - she has a social life again, has been on holidays abroad and is just having a happy 'near normal' life. My son, with the wellness and stability that Kaftrio has brought, has had the confidence to start his own business. His mental health problems and anxiety have been completely resolved. As a parent, for the first time in over 30 years, I am able to look forward positively instead of dreading the future."

"I started Kaftrio in 2020, I have been receiving the drug for just over 3 years. Before Kaftrio I had a lung function of 22%. I also grew a resistant bug called B Capecia which also meant a lung transplant wasn't an option. I was therefore living on borrowed time. I couldn't keep up with my peers, I wasn't able to participate in most physical activities in school or beyond. I was on hospital every 3 months for IV antibiotics over a 2 week period just to sustain some of my lung function. I had to do physiotherapy twice a day and 3 nebulisers twice a day among countless medications. Since Kaftrio I have had NO IV antibiotics, my resistant bug B capecia hasn't grown in my lungs for 3 years [even though] we were always told I would never be able get rid of that bug. I have gone on to live a full life travelling and now I've welcomed a healthy baby boy who is now 1 year old. Something I was told I would never be able to have."

"Before commencing modulator treatment, CF had a huge and devastating impact on my life. My lung function had gradually declined to a point where I was no longer able to exercise and even walks could be a challenge. My career (I am a qualified solicitor) also suffered as I was unable to work the hours required and concentrating on complex matters was almost impossible. I was also frequently in hospital for IV antibiotic treatment. My daily regime to try and prolong my life was arduous. I would require 4 sets of nebulised treatment a day (Dnase and antibiotics) and twice daily airway clearance. I would spend at least 2 hours every day just to get through my nebuliser and airway clearance requirements. Not to mention many, many tablets. My mental health suffered as a result too, of course. I had resigned myself to living a short life and was unable to even consider starting a family like many of my friends had already done.

Modulator treatment has changed everything for me. My lung function has improved to near normal levels and I have even managed to stop airway clearance and many of my other medications. I can exercise, play tennis, play golf and lead a healthy, happy and fulfilling life. I now work full time and will be joining a US law firm in January as a Partner. Something I could only have dreamed of before starting modulator treatment. I have not required any hospital treatment or antibiotics since commencing treatment. I can now also look at the long term as I hope I can now live a life with a near normal life expectancy (in fact, my lung function just keeps improving). My wife and I are even starting IVF treatment so we can start a family, with the knowledge that I should be around to bring a child up to

adulthood. I cannot emphasise enough how much of a benefit modulator treatment has been for me. I have gone from being sick, depressed and resigned to death to being healthy, active, working full time and ready to start a family. All of this is entirely down to modulator treatment."

"I am in no way exaggerating when I say Kaftrio has changed my life in ways I never thought imaginable. I am now 33, and have lived with Cystic Fibrosis for over 3 decades. I started Kaftrio in September 2020. At the time I was in and out of hospital, on a huge amount of treatment and with a lung function of below 50%. I had recently been diagnosed with a heart condition as a result of treatment for my CF. Life was different - the future was unpredictable, planning for life was hard. Since Kaftrio I have been able to achieve some stability. My lung function has improved and I was able to naturally conceive and carry my son.

I was told I wouldn't live beyond my thirties. I spent weeks and weeks in hospital every year, sometimes there due to emergencies. 3 x a year at least I was on IV antibiotics. I have had 3 portacaths in my lifetime, as well as other operations including embolisations. I missed weeks and weeks of school, I lost friends at a young age. Whilst I do work, I had days I couldn't get into the office due to my health. I couldn't get out of bed or walk up the stairs. I would cough CONSTANTLY, which resulted in voice loss, back issues and regular hymoptysis. My bones were thinning, my weights was drastically low. Life was hard. And the impact on mental health is impossible to quantify. I have always had therapy throughout my life, because the prognosis of CF, the burden it puts on your loved ones, the impact on relationships, work, school, friendships - every aspect of life - is hard to process and handle.

*My life *was* CF before Kaftrio. It was for my whole family. My mum left work to look after me because the treatment burden was so intense.*

Since Kaftrio, my life is so much more. I can contribute to society in a way I couldn't before & I look at my life & can only imagine what I would be if I had gotten access to the medication sooner. Whilst it isn't a cure, it's given me time. It's given me energy, and stability, and greater control. It's reducing my time off work and in hospital. It is no longer my identity."

"Orkambi and later Kaftrio have turned the life of our daughter around. From struggling to gain weight and grow pre treatment, being constantly exhausted and lethargic and pale, within a few weeks of starting treatment her weight was up, her energy levels were up, her concentration had improved she had colour in her cheeks and for the first time in her life I was able to say my daughter looked healthy.

Fast forward a few more months the benefits of her treatment continued. No more iron supplements required, less vitamins required therefore less tablets to take. Lung function improving. Recovering from colds and other illnesses as quickly as a normal healthy child would. The benefits of these medicines didn't stop there either, they continued. Due to her continued good health, with only one brief hospital admission to the CF ward since beginning treatment her clinic appointments were reduced from a 6 weekly face to face to a 12 weekly face to face with a telephone clinic in between.

This enabled my daughter to miss less school, attend more family and social events, gain more life experiences and catch up with her education and not be left behind worrying about catching up and what she had missed that her friends had learned without her. Less clinics also helped us as parents with less time off work reducing the financial burden and being able to provide more for our family, again improving everybody's stress and mental health.

Due to my daughter's vast improvement in health and wellbeing since starting Orkambi and later Kaftrio, me and my daughter both have the confidence to live life and not be limited, she has begun to take up horse riding, amongst other activities and experiences, something we were fearful to do pre Kaftrio due to risks of infection and recovery. Now with these medicines she is not limited. Yes we have to remain cautious they are not a cure, however the huge, massive improvement they make to her health is also complimented by the fact that we now have hope for the future, she has hope, I have

hope her family and friends have hope and with hope comes a will to live, a will to fight, a will to succeed. Its imperative these medicines are approved and made available to all who need them.

The future with these medicines is day and night to that of a future without them. Everybody benefits from these drugs being available that is plain to see. The patient benefits, better health, a future, an education, a career a family a chance to live to a normal age. The family and friends benefit less stress and anxiety better mental health, hope, confidence, fight all instilled with access to these medicines. The NHS benefits, less admissions, less clinics, less preventative medicines on prescription, less IVs and transplants, freeing up time for consultants, physios, dieticians etc, more bed spaces. The country as a whole benefits, with another 8,000 people, plus all future patients given a chance to contribute to life and the economy with access to these medicines. They must simply be approved, a way must be found a deal must be done. It would be a crime against humanity, a human rights violation not to approve these medicines given their benefit to all."

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 24 November 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Quest For a cf Cure Patient Interest Group]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	In response to the evaluation committee's request for comments the Quest For a cf Cure Patient Group would like to state the following:

Please return to: **NICE DOCS**

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

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	• All relevant evidence has not been taken in to account • That the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence • That the recommendations are not sound and suitable guidance for the NHS • The following aspects of the recommendation need particular consideration 1. **Price:**The patient group has concerns that the list price does not accurately reflect the price that is ultimately paid for these drugs (it does not take into account discounts and rebates gained by NHS Procurement) **2. Longer Term Data** 3.5 There is no mention of the increase in pregnancies & children born to cf Patients due to the increased health & quality of life. We believe that this data is now available and was published in September '23 **3. Annual Discount Rates** The patient group strongly disagrees that there is acknowledgement of the potential benefits in young children but there is no evidence to support this. We have spoken to clinicians, patients, parents and carers. This drug (IVA-TEZ-ELX) goes far beyond preventing decline in young children and greatly increases the quality of their lives. It makes no sense not to provide this drug to children when there is no evidence to suggest decline. If the patient will decline without this medicine and it is accepted the patient will decline, then the sooner the drug is given the greater the benefit and outcome will be. **4. Utility values Health state utility values** In relation to a treatment that is as transformational as this drug (IVA-TEZ-ELX), the EQ-5D falls far short of a useful and appropriate assessment of the benefits of the drug. It doesn't capture thee real life quality of life benefits. The patient group believes this based on our experience of talking with clinicians, patients and carers. Including the evidence taken from patient case studies: "*in relation to all this talk on health benefits vs quality of life, It is not just 43 years of extra life surviving cf, it is 43 years of living. And by living I mean LIVING my BEST life, I have now gone to university, (something I never allowed myself to think about!), I am a qualified solicitor, I have a good job in a law firm, I pay tax. I have hobbies, I play football, I have a future. One day I will have a family and my children will grow up and pay into the system too! Without these drugs I would not be here today – even my cf doctor says this"* 5. **Caregiver Utility Benefit** The patient group agrees that the care giver utility was conservative as it only applied to younger patients. The reality is that the older the patient is, the more care that is required. More so beyond the age of 18 where the lungs have declined and often end stage cf is present or close. End stage cf is hugely burdensome and requires not only one or two carers but sometimes more 24/ 7 and for quite some time depending on how 'stable' the patient is at end stage of the disease. The colossal amount of time spent on administering and carrying out treatments, then cleaning of equipment has a huge impact on the level of care. Case study quotes: Patient aged 29yrs without modulator drug*. "Some days I don't get dressed as it is too tiring. I suffer from severe pain from my reactive arthritis as a result of the continuous cf infections. If I have a shower, I cant wash my hair at the same time as it makes me too breathless and drained, I don't know what I would do without my mum and partner helping me"*

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

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	6. **Costs Disease-management costs** The patient group is surprised that no figure has been given for the reduced for the reduced need for treatments from standard care. There is emerging evidence to support reduction in prescribed medicines, treatments and hospital stays. The reduction in extra costs involved not only in cf (predominantly respiratory care) with diabetes care and hepatology care, along with other departments affected by symptoms related to cf. Other medicines, clinic visits and hospital stays are significant costs. Since 2020 in Scotland when the drug (IVA-TEZ-ELX) was prescribed, it was evident during the COVID pandemic that the respiratory hospital beds weren't taken up by chronically ill cf patients. Where there were normally waiting lists to be admitted (even for an ill cf patient) there was free beds available. By communicating within our patient group it is now rare (because of these drugs) for patients to be staying in hospital, or on home intravenous antibiotics. *7.* **Severity** The patient group disagree with this finding. It is patently obvious that if cf patients do not receive this drug, the disease is severe and even with standard care they will die. We cannot understand how a severity modifier has not been able to be established. We cannot understand how cf can be considered anything but severe. The recommendation here is unclear and difficult to understand. Quote from 15 year old patient (no modifying drug) "*For the majority of my short life, I have lived off machines, medication, treatment, inhalers, physiotherapy, nebulisers, antibiotics (oral and intravenous) and so much more.* *From the age of 2 and a half my veins were constantly punctured; my lungs were constantly tired, and I was used to sleeping in a hospital bed for 2 weeks every 3 months. Although I was nearly 3 I'd spend the day coughing until I was sick, being in pain until my body couldn't take anymore and getting out of breath just running to cuddle my mum.* *This was completely normal for me, little did I know that Cystic Fibrosis would deteriorate my tired small and weak body a little bit more every day.* *As years went on, I became dependant on oxygen and my lungs got to the point where holding my own body up became too much. Standing just simply brushing my teeth would feel like I'd ran a marathon and bathing myself was impossible.* *Cystic Fibrosis - my worst enemy.* *No matter how much medication I forced down myself, how much treatment I did the damage was irreversible.* *By the age of 15, cystic fibrosis was my life. Hospital was my home. And a hospice was next on the cards. Everyone had always been completely honest with me, so I knew I didn't have much time left on this earth.* *15 years of constant Cystic Fibrosis and now I was ready to die. The fight with this disease was over. I'd accepted it. I hadn't given up, but my body couldn't take anymore. Constant pain. Constant suffering. Constantly struggling to breathe.* *For anyone who doesn't know Cystic Fibrosis, this genetic disease is a killer."* 8. **Uncaptured benefits** in addition to those listed in the draft guidance there are the following uncaptured benefits that must hold a great deal of value and cost savings: **Fertility**. Female cf patients being able to fall pregnant easier and without treatment or intervention, Male and female cf patients having the confidence to

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		plan a family knowing they will be alive and well enough to be able to contribute to the upbringing of children. To be able to enjoy family life. Consideration must be given to reduction in costs for infertility treatment and the added value that the benefit a family life and as such the nourishing environment avails to patients. **Improved GI symptoms - part of the RECOVER study (age >12)** (Published Cystic Fibrosis News Today) One-year treatment with Kaftrio significantly improved the total CFAbd-Score — it was 15 at baseline versus 9.8 after a year — as well as its five domains, pain, gastroesophageal reflux disease (acid reflux), disorders of bowel movement, appetite, and impaired quality of life. A major improvement was seen in the first month, with symptoms reaching the minimum two months after treatment started. **Sinus disease** – published 30th October 2023 in Cystic Fibrosis News Today. Treatment with this drug (IVA-TEZ-ELX) leads to a reduction in Pseudomonas abundance within the sinonasal microbiome of individuals with Pseudomonas at baseline. **Cystic Fibrosis Liver Disease** However, patients with elevated markers of liver stiffness before starting on Kaftrio saw those fibrosis markers drop. While similar effects were not observed in liver fibrosis markers according to CF-related liver disease (CFLD) status, these findings suggest that the therapy — sold as Trikafta (IVA-TEZ-ELX) in the U.S. — might ease liver fibrosis in adults with severe CFLD. The study, "Effects of elexacaftor/tezacaftor/ivacaftor on liver fibrosis markers in adults with cystic fibrosis," was published in the journal of cystic fibrosis. **Reduction in Bronchiecstatsis published 20th October 2023** Treating with IVA-TEZ-ELX "MRI revealed a reduction in the severity and number of lung segments affected by bronchiectasis. **Reduction in Depression -19 July 2023** Published Cystic Fibrosis News Today. Treating with IVA-TEZ-ELX which address the disease's underlying cause, appears to help protect against depression, its researchers stated. They noted improvements in patients' physical health — including lung function and body mass — as more began modulator treatment. **Reduction of treatments as published by Royal Brompton Hospital 2023 Guidlines** Care of children with cystic fibrosis DNase - "We will no longer offer it routinely to a 6 year old child on Kaftrio or ivacaftor, assuming they have minimal lung disease" - Vitamins. We are getting high levels of vitamins A, D and E in some patients on Kaftrio so annual review results are being checked by the dietitians and pharmacists and dose adjustments made.
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Dietetic Association CF Specialist Group

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
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Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for your comments to our response submitted earlier this year. We believe that all the evidence has been reviewed yet may require further consideration and that all stakeholder and committee comments be considered in great depth.

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2	We appreciate the recognition of the impact the CFTR modulators have on co-adherence of other CF therapies. In real life experience it is noticeable that due to the nutritional improvements seen with the use of CFTR modulators – there is less requirements for ONS, Enteral tube feeding – admission, and placement of feeding tubes. Additionally, there is less reliance on admissions to support nutritional status support, for example - feeding, CF diabetes treatment support. Yet the evidence is limited at present.
3	Thank you for submitting/ highlighting the need for research to explore the rates of co-adherence to non CFTR modulator therapies and costs. However, we also need to highlight the QOL impact on these individuals who no longer require overnight enteral feeding or feeding tubes attached to their bodies. There is less pressure on them from a nutritional intake perspective and additionally opportunities to consider a reduction in treatment burden. In line with this is the cost saving on reduced calorie intake requirements, staff resources to change feeding tubes and the costs of ancillaries etc. It is difficult to capture the cost benefits across the expanding health outcomes but all of it does need to be considered.
4	Over and above the obvious health outcomes (shown in the studies), it is difficult to understand the future health benefits and social benefits for these individuals, who will ideally have significantly improved if not “normal”, nutritional, and clinical status. If we consider the data considering the Ivacaftor impact on pancreatic function in younger cohorts, this will have significant impact on costs, symptoms and QOL. However, it is too early to establish whether this will be feasible without any future data.
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Insert extra rows as needed

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CF Digicare submission

Context and background

This short document provides context around the NEEMO analysis also submitted on 24th November by CFDigicare.

CFDigicare have provided a summary of the analysis from 2 years of the NEEMO study (National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) programme: a prospective observational study - CFHealthHub.com) which is an NIHR portfolio study and CTAP study to understand the impact of co-adherence to inhaled therapy on FEV1 decline that CFDigicare (CFDigiCare - CFHealthHub.com) group have hosted.

CFDigicare are clinicians from >50% of Adult CF centres in England and consider that co-adherence is a critical issue in impacting the cost effectiveness of Kaftrio. In the case of the Ivacaftor HTA the optimistic scenario based on open label extension data delivered an ICER of ~ £335K per QALY but the pessimistic scenario suggested (FEV1 decline continued after introduction of Ivacaftor) an ICER of > £1 million per QALY. The assumptions under pinning the cost of Ivacaftor appeared to assume relatively stable FEV1 but the real world data showed that FEV1 decline continued and as adult clinicians we considered this to be due to non-adherence to inhaled therapy with adherence to Ivacaftor maintained as the Thorax Manchester data demonstrated.

We have accelerated our analysis of just over 1000 patients in the NEEMO study and demonstrated a significant difference in FEV1 decline between patients with high inhaled therapy adherence compared to those with lower inhaled therapy co-adherence. We are still completing the analysis of the MPR data for Kaftrio across this 1000 patients and final data checking is still ongoing and not yet ready for publication. However the MPR across the 1000+ patients in the NEEMO study is similar to the Thorax Manchester Ivacaftor data at > 80%.

We think therefore that if NICE recommendations do not take into account co-adherence to inhaled therapy in adults the cost effectiveness of Kaftrio will be diminished in a similar way that was observed with Ivacaftor. It is noteworthy that asthma biologics have also had cost-effectiveness impacted by co-adherence to inhaled therapies and we would ask that NICE recommendations signpost the possibility that the cost effectiveness of Kaftrio may be impacted by co-adherence to inhaled therapy such that any implementation of Kaftrio should include measurement of co-adherence. This is worthwhile since the ACTif RCT (the largest Cystic Fibrosis RCT carried out in the UK) demonstrated that an intervention exists that is proven to significantly increase inhaled therapy in adults with CF.

Unfortunately, the precision of the MPR analysis is not yet available. MPR data is somewhat complex and our clinical teams have been impacted by strikes and winter pressures so that data cleaning was not finished. However, in terms of broad brush strokes the MPR across all 1000+ patients included in the NEEMO 2 year data had MPR over the 2 years in excess of 80% which is similar to the MPR in the Manchester Ivacaftor study that demonstrated FEV1 decline over the 5 years since Ivacaftor was

introduced. There was no difference in MPR between patients with high inhaled therapy adherence and those with the lower inhaled adherence and this analysis suggests that the difference in FEV1 trajectory between patients with high inhaled adherence and those with lower inhaled therapy adherence was explained by inhaled therapy rather than by Kaftrio use.

The MPR data final analysis is expected within the next month.

Background

Elexacaftor-Tezacaftor-Ivacaftor (ETI), a triple combination CFTR modulator which is highly efficacious for around 80% of the CF population [1-3], has been widely available for adults with CF in the UK since August 2020. With a list price exceeding USD325k per patient per year [4], optimising the real-world benefits of ETI would be important to maximise its cost-effectiveness.

It is worth noting the experience with Ivacaftor, which is the first available highly efficacious CFTR modulator from 2012-2013. Health technology assessment by NICE estimated an incremental cost-effectiveness ratio (ICER) of £335k per QALY gained if there was no FEV_1 decline and £1.3M per QALY gained if FEV_1 declined at the same annual rate as standard care after 90 weeks [5]. Whilst the Ivacaftor open-label study showed a 47% reduction in FEV_1 decline three years post-Ivacaftor [6], a systematic review of real-world data found unabated FEV_1 decline (such that FEV_1 returned to pre-Ivacaftor levels in 5-6 years [7]) despite persistent BMI increase [8]. Persistent BMI increase may point towards on-going efficacy of Ivacaftor. Therefore, a potential explanation for the difference in the efficacy and effectiveness of Ivacaftor in terms of lung health is co-adherence to inhaled therapies. Inhaled therapies were continued during the RCT [4] whereas there is real-world evidence of declining inhaled therapy use following the initiation of Ivacaftor [9,10].

There are also data showing declining inhaled therapy use following the initiation of ETI [11]. The 2-year results for the ETI open-label study may suggest a lack of FEV_1 decline following the initiation of ETI [12]. However, the results were confounded by ETI participants being exposed to the Covid-19 lockdown / shielding [13] and a recent Australian registry analysis showed improvement in annual $ppFEV_1$ trend from –0.13 (95% CI –0.36 to +0.11) to +1.76 (95% CI +1.46 to +2.05) during the Covid-19 pandemic among a largely CFTR modulator naïve population (only 0.4% on ETI) [14]. Therefore, it remains uncertain if the efficacy of ETI would be fully realised in the real-world.

To better understand how to optimise the real-world benefits of ETI, we undertook the National Efficacy Effectiveness CFTR Modulators Optimisation (NEEMO) program (NCT05519020). This is a 5-year multi-centre prospective observational study embedded within the CFHealthHub digital Learning Health System (ISRCTN14464661), designed to determine the nature of effective and efficient care in the post-ETI era. Over 50% of the adult CF centres in England are part of CFHealthHub and around 1,400 participants using data-logging nebulisers (such as eTrack®) have been recruited. The NEEMO program is an NIHR portfolio study supported by the NIHR Clinical Research Network in England and a UK CF Clinical Trials Accelerator Platform (CTAP) badged study.

Preliminary results from NEEMO

There are currently around 1,400 adults with CF participating in the CFHealthHub digital Learning Health System. Participant recruitment is on-going, though most centres have utilised all available E-track nebulisers. As of September 2023, the NEEMO study consisted of 1,182 adults prescribed ETI of whom 898 (76%) have been prescribed ETI for ≥2 years.

The NEEMO study has a number of strengths since it is embedded within the CFHealthHub digital learning health system that was established in 2017, such that the dataset includes both lung function and objective electronic data capture of co-adherence to inhaled therapies from 2017 onwards. As such, even though ETI

was commenced in the UK during the fall of 2020 and FEV_1 availability was impacted during the period of Covid-19 lockdown / shielding, preliminary analysis of the NEEMO data was able to include 642 participants with complete adherence data for ≥2 years after the initiation of ETI and ≥3 FEV_1 readings during the same period. Results from mixed-effect modelling showed a similar annual $ppFEV_1$ trend in Year 1 for those with consistently high inhaled therapy co-adherence, in comparison to those with lower levels of co-adherence (see Table 1). However, the difference in annual $ppFEV_1$ trend in Year 2 was +2.18 percentage points (95% CI +0.01 to +4.34) in favour of those with consistently high inhaled therapy co-adherence. This result suggests that the cost-effectiveness of ETI may be influenced by co-adherence to inhaled therapies.

Table 1: preliminary analysis of annual $ppFEV_1$ trend among adults prescribed ETI, according to the levels of inhaled therapy co-adherence†

	Year 1		Year 2	
Levels of co-adherence to inhaled therapies	*N*	Annual $ppFEV_1$ trend, mean (95% CI)	*N*	Annual $ppFEV_1$ trend, mean (95% CI)
Participants with consistently high levels of co-adherence to inhaled therapies‡	137	+1.62 (–1.46 to +4.69)	110	+1.67 (–1.38 to +4.72)
Participants with lower levels of co-adherence to inhaled therapies‡	505	+2.26 (+1.27 to +3.27)	532	–0.51 (–1.39 to +0.38)
The between-group difference in annual $ppFEV_1$ trend (lower levels of co-adherence as reference)		–0.64 (–2.70 to +1.42)		+2.18 (+0.01 to +4.34)

†Mixed effect modelling would account for between-group differences in baseline FEV_1. For the preliminary analysis, no adjustments for other covariates were made as the data-cleaning process is on-going.

‡Co-adherence to inhaled therapies was categorized according to previously described methods, taking into account both the magnitude and variability of adherence [15]. Participants with consistently high levels of co-adherence had 3-monthly adherence levels ≥75% throughout the 1-year period.

The lack of a difference in Year 1 is likely due to inhaled therapies being less critical during the Covid-19 lockdown when reduced exposure to respiratory viruses in itself could lower the risk of pulmonary exacerbations. Australian registry data where only 0.4% of the participants were on ETI showed no FEV_1 decline during the Covid-19 shielding / lockdown period with commentators hypothesising that viral shielding was an important aetiological factor [14], which might also explain our Year 1 data. A substantial decrease in exacerbation rates was also observed in other chronic respiratory conditions such as asthma [16-18] and COPD [19-21]. However, exacerbation rates in other chronic respiratory conditions have since rebounded with the relaxation of Covid-19 restrictions [22] and this may explain the difference observed in Year 2.

Though the results in Year 2 are somewhat lacking in precision, it should be noted that the sample size estimation for NEEMO is on the basis of a 5-year study. Assuming a 2 percentage points difference in the annual $ppFEV_1$ trend from Year 2 to Year 5 (i.e. 8 percentage points difference in $ppFEV_1$ at Year 5 between those with consistently high inhaled therapy co-adherence and those with lower co-adherence levels), a sample size of 326 (62 with consistently high co-adherence, 264 with lower levels of co-adherence) should have 90% power to detect a between-group difference at a type 1 error rate of 0.05 and a standard deviation of 25 percentage points for both groups (based on a recent UK CF registry analysis of FEV1 data [23]). Based on the results in Year 1 and Year 2, the difference in annual $ppFEV_1$ trend according to inhaled therapy co-adherence levels among people prescribed ETI may even continue to diverge further over time. Therefore, longer-term follow-up in the post-Covid epoch is important to better understand the role of inhaled therapy co-adherence in the post-ETI era.

Other publications highlighting the scale of the adherence problem and an evidence-based adherence intervention

A multi-centre observational study using data from the CFHealthHub digital Learning Health System prior to the introduction of ETI found generally low levels of adherence to inhaled therapies, with 50% of the adults had objective adherence <1/3, despite a universal health care system that provides nebulised medications free at the point-of-care [24].

One of the consequences of low adherence is the accumulation of unused medicines, which potentially results in waste since medicines have limited shelf-lives. A conservative estimate using multi-centre data from the CFHealthHub digital Learning Health System for the cost of excess medicines supply among adults with CF was £822/person/year (95% CI £587 to £1,057) [25]. There are currently around 6,500 adults with CF in the UK with ≥70% of them on inhaled therapy [26]. Extrapolating from the mean excess supply cost observed in this study sample gives a potential annual waste of around £3.7M. However, if we consider that the overall real-world adherence level to be closer to 30-40% [25] where excess supply cost was £1,540/person/year, then the potential annual waste may exceed £7M.

Given the widespread problem of low adherence and the dire consequences of low adherence, The CFHealthHub team developed a multi-component (complex) self-management intervention to support sustained treatment adherence [27], incorporating objective adherence measurement, underpinned by behavioural science theory and with extensive input from people with CF. This intervention was evaluated in a 608-patient two-arm, open-label, parallel-group, usual care-controlled randomised clinical trial with 12-month follow-up at 19 UK CF centres (trial registration ISRCTN55504164). This is the largest self-management intervention trial in CF and the largest UK CF trial. Compared with usual care, the intervention achieved higher objectively measured effective adherence, higher BMI and lower perceived CF treatment burden [28]. This is the first iteration of a self-management intervention that may have the potential to be improved by continual iteration in a digital learning health system. Analogous to the overwhelming success in the CF drug pipeline of building on early signals with ongoing developments and trials, we plan to continue iterating and evaluating the CFHealthHub-based intervention by building on signals we have observed to further improve the intervention. In our subsequent trials, we plan to nest the evaluation of adherence interventions within the CFHealthHub digital Learning Health System so that baseline adherence can be understood prior to randomisation. This has a number of benefits, including recruiting participants in whom adherence can be seen to improve from baseline (effectively removing the impact of whitecoat adherence) and greater efficiency by avoiding the recruitment of potential participants with maximal adherence at baseline.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cystic Fibrosis Nursing Association (CFNA)

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Name of commentator person completing form:	[redacted]

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	We thank the AEG for their response within the appraisal document, however, although they have acknowledged the feedback, the points raised within it do not seem to have been fully appreciated or integrated within the decision-making process. We appreciate the limitations of the health economic modelling process and adapting this to include these points, however, multiple stakeholders have provided data, and real-world evidence which does not appear to have been considered.

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	We would also like to express further disappointment in the appraisal process with the timing of the release of this document. Releasing this on a Friday afternoon with little/no support for patients and their families over the weekend caused significant emotional distress to a vulnerable cohort of people, with wider impact on clinical teams leading to a significant increase in workload in the subsequent week.
1	Despite emotive patient representation and stakeholder feedback, the impact of the disease does still not appear to be fully appreciated. This patient group have huge burdens of care and multi-system complications. Focus on pulmonary complications is understandable, however this is a multi-system disease and other complications equate to significant burden of care and costs to the NHS (diabetes, pancreatic insufficiency and gastrointestinal particularly). As per our original response there have been reduction in pancreatic supplements and insulin use and central lines/Totally implantable venous access devices (TIVAD's). Also previously highlighted the increase in pregnancy rates, leading to a reduction in fertility/IVF referrals.
2	Due to the high burden of care (as highlighted above) the burden of care on parents, partners/spouses and carers is also significant. Despite lengthy conversations and recognition of this within the committee meeting the carers utility is only being applied to 11 years? This does not reflect real world experience, where it is acknowledged that burden of care increases with age/disease severity. This again highlights a lack of recognition of the severity of the disease and therefore the CFNA would ask the EAG to review these points simultaneously.
3	The CFNA thanks the AEG for highlighting the employment rates to NICE (as previously discussed). We would again urge that the wider impact of employment rate of both those with CF, and their parents/spouses/families is considered (linking into point 2 and 3) as this has huge cost implications on government funding.
4	In agreement with the company, the annual discount rate of 1.5% for health outcomes is justified under the specialist criteria. Failure to apply this implies a lack of recognition of the severity of the disease and impact of the modulators.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Royal College of Paediatrics and Child Healht (RCPCH)**

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Name of commentator person completing form:	[redacted]

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1	**Has all the relevant evidence been taken into account?** The RCPCH is concerned that not all the relevant evidence has been fully considered. This raises critical issues on the chosen parameters crucial on the decision- making process when commissioning treatments. The lack of inclusion of adequate data in this topic results in age discrimination of the younger paediatric population. The RCPCH fully supports the views of our colleagues at the British Paediatrics Respiratory Society (BPRS) that have raised critical views that

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	the evidence considered is only looking at the benefits to children and adults already taking CFTR modulator treatment. The RCPCH would recommend NICE to carefully consider the additional evidence submitted by BPRS that clearly contradicts recommendations presented in section 3.15 of the guideline and points to the clinical effectiveness of IVA-TEX-ELX. Those are: - Data in improvements in Lung Clearance Index (LCI) and reduction in sweat chloride for children aged 2-5 [1:] - Approval of IVA-TEZ-ELX for children aged 2-5 years by the Food and Drug Administration (FDA) - Extended licence of IVA-TEZ-ELX for children aged 2–5 years by the Medicines and Healthcare products Regulatory Agency (MHRA). (1) Goralski JL, Hoppe JE, Mall MA, McColley SA, McKone E, Ramsey B, *et al.* Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2–5 Years with Cystic Fibrosis and at Least One *F508del* Allele. *Am J Respir Crit Care Med.* 2023 Jul 1;208(1):59–67.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The RCPCH fully supports the disagreement raised by BPRS with the NICE statement that IVA-TEZ-ELX does not restore people with Cystic Fibrosis to full health. It is paramount that the cost effectiveness interpretations are carefully reconsidered to include: - a review of the calculation of annual discount rate. - a formal consideration of other elements not included in the economic model such as the societal cost of CF to patients and parents, the complex NHS costs of CF treatment and the direct wider benefits to the NHS with the use of CFTR modulators[2,3] and a notable improvement in the mental well-being of both patients and their families[3] . [2] Walter E, Bass JL. 'The Effect of Elexacaftor/Tezacaftor/Ivacaftor on Hospitalizations and Intravenous Antibiotic Use.' TPJ. 2022 Mar;26(1):73–9. [3] Majoor C, Van Brunt K, Daines C, et alS66 Impact of elexacaftor/tezacaftor/ivacaftor triple combination therapy on health-related quality of life in people with cystic fibrosis

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	homozygous for F508del (F/F): results from a Phase 3 clinical studyThorax 2021;76:A41-A42.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The RCPCH fully support the views of the BPRS that strongly oppose the draft recommendations by NICE that proposes the discontinuation of CFTR modulator treatments for patients not currently undergoing treatment. The RCPCH is extremely concerned about the discrimination this guidance will bring to the younger paediatric population and the consequences that will affect younger children longer term if the treatment is delayed taking into consideration their worsening of the condition over time and its associated irreversible organ damage and potential need for lung transplants. Withholding these treatments from young children discriminates against those who are likely to benefit the most. In addition, young children will be unlikely to achieve maximum benefit of CFTR modulator treatments if their access is delayed. The RCPCH joins our colleagues at BPRS to request that NICE reconsider the proposal of access restriction to CFTR modulators to ensure these effective treatments are available to all ages through the NHS.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** The RCPCH would strongly recommend re-considering the proposed recommendations and takes the opportunity to highlight the unacceptable age-based discrimination to the younger paediatric groups. The RCPCH fully supports the statements submitted by BPRS denouncing the contradicting messages by NICE that: - recognises the potential of IVA-TEZ-ELX in preventing health decline but deny treatment to younger children. -acknowledges the benefits to the physical and mental health of patients and parents/family but denying treatment to younger children

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	We have been made aware by our members and different parent groups[4,5] who have expressed their dismissal on the changes proposed and the expected impact that these recommendations will have in clinical management and in families due including: - progressively worsening over time due to irreversible lung damage and bacterial colonisation, liver fibrosis and pancreatic dysfunction - complex NHS costs and burden of time-intensive treatments - inpatient treatment including lung transplantation - contribution to antibiotic resistance - impact on loss of education and earnings for patients and caregivers - daily laborious home treatments - worsening in mental well-being of patients and their families - inconsistent access to treatment on siblings - planned pregnancies with expectation of access to treatment… The RCPCH is overly concerned about the inequity in the application of CFTR therapies which specifically disadvantages children and especially younger children and request NICE to carefully consider the lack of priority to early intervention that will have clear consequent long-term effects for children and their families. [4]Phipps, A, Royce, R (2023) 'Kaftrio: Patients fear loss of cystic fibrosis 'miracle drug' BBC News 16th November 2023 (online) Available at https://www.bbc.co.uk/news/uk-england-leicestershire-67427900 [accessed 16 November 2023] [5]*Almulhem et al. Exploring the impact of elexacaftor-tezacaftor-ivacaftor treatment on opinions regarding airway clearance techniques and nebulisers: TEMPO a qualitative study in children with cystic fibrosis, their families and healthcare professionals. BMJ Open Respir Res. 2022 PMID: 36207030).*

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK CF Medical Association

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Example 1	We are concerned that this recommendation may imply that ……..
1	Firstly we would like to comment on the process and the distress this has caused people with CF and their families. The timing (midnight on a Friday) and the blunt wording were insensitive to a community, many of whom have experienced the impact of triple modulator therapy since 2020.

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	Parents of young infants, newly diagnosed and not yet eligible, have been particularly disappointed and concerned that when their child becomes eligible they will have no access. In addition, we have anecdotal evidence of patients potentially withdrawing from involvement in clinical trials, and not reporting significant adverse events, for fear of not being able to restart E-T-I, in light of the NICE guidance. We appreciate and support the transparent nature of NICE processes, but in this case the process has been harmful. NICE and the department of health should reflect carefully on how the process has been conducted and how beneficial this has been to NHSE in renegotiating a new contract.
2	As discussed in our initial comments we continue to be concerned about the conflation between dual therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) and triple therapy (E-T-I). The trial data support our clinical experience that dual therapies are minimally efficacious and clearly not cost effective. In contrast, the impact of E-T-I on our clinic population has been transformational related to both the larger number of eligible patients and the impact on outcomes, which mirrors the clinical trial data. Whilst we do not consider that E-T-I will be judged cost effective at list price with current NICE thresholds, we do feel that the modelling presented has not fairly represented the impact of this therapy on people with CF. In part this relates to the fact that many of our patient population enjoy good health (at the expense of a large daily treatment burden) and the modelling does not reflect the life changing impact of E-T-I and the new journey they are on. In addition to the responses to our comments, we have examined the responses to other stakeholder representations (which were on the whole measured and proportionate, and mirror ours) and we feel the committee has failed to appreciate these, for example when considering applying disease severity modifiers. Without standard therapy, most patients would die in childhood, and with standard therapy many die in their early adult life. That many can maintain health is a testament to the standard daily therapy that people with CF and their families maintain.
3	With respect to long term outlook, we do not understand or agree with the committee's judgement for a 3.5% year on year reduction in costs and QALY. In our opinion, there is clear evidence, that 1) Survival will be substantially improved (close relationship between survival and FEV1) 2) Many patients, especially younger ones without established lung disease, will be able to enjoy "normal health", they are on a different life journey 3) These benefits will be sustained, again especially for younger patients without established lung disease
4	Similarly, we feel that, consistent with NICE guidance there is a cogent argument for a higher ICER than £30,000, in light of the limited number of eligible patients and the impact.
5	With respect to treatment burden, we have objective measures from two NIHR funded trials (CF STORM and NEEMO) that patients are rationalising their nebulised treatment regimens. Whilst more evidence is required to ensure the safety of this approach, it reflects choices made by many patients, the benefit they perceive from E-T-I and their desire to reduce their substantial treatment burden. The reduction in treatment burden is key, but this also has an impact on NHS costs (approximate £1.5 million saving outlined in STORM protocol for the patients randomised to STOP nebulised therapies)
6	We acknowledge that E-T-I is a high cost drug and we appreciate the importance of a rigorous appraisal of cost effectiveness, especially as NHSE commissioners begin renegotiating the E-T-I contract, but at present we do not feel that decisions taken by the committee adequately reflect both clinical data and the lived experience of our patients. This will deliver societal changes that are difficult to map but will be likely extensive. It is our opinion that the profound impact on the quality of life of eligible patients has not been adequately appraised and principle 4 of the NICE process has been undermined.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 24 November 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Psychosocial Professionals in Cystic Fibrosis (UKPPCF) Committee

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As highlighted in the “uncaptured benefits of CFTR modulators” (slide 71 of ID3834 CF MTA committee slides) and raised in previous submissions, we are concerned that the psychological and social benefits of modulators are not adequately captured in the

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	current analysis. We thank the committee for acknowledging our previous comments on this topic and appreciate the challenges of including these factors in health economic modelling. However we feel it is important that the committee finds a way to take these factors in to account within the decision making process.
2	Without longer term data about the improvements in quality or life, school attendance, contributions to the workforce etc it does not feel possible to accurately assess some of the longer term benefits of modulators both in terms of outcomes and cost savings. Might this be better captured with lowering the discounted rate from 3.5 to 1.5%?
3	A healthier CF population will have financial savings (including outside of the NHS) e.g. • reduced sickness and carers related benefits • reduced housing adaptions and moves due to ill health within local authority housing depts • reduced social services costs for children (under disability team primarily) and adults in terms of personalisation/care budgets in the community • reduced need for community support services across local authority and voluntary sectors • reduced need for mental health support services • reduced prescription costs to NHS if people are working and able to pay for these There would also be potential financial benefits from: • increased employment levels and therefore household income levels (and taxes paid) • increased carer's potential income/employability • use of primary care services instead of higher tier specialist services like CF teams.
4	We are concerned that the current analysis does not take in to account the impact of CF on carers of adults. The initial analysis only took into account carers of children up to age 11 and the discussion to extend this to 18 still excludes the significant carer burden for adult patients..
5	This decision would lead to a two tier system within the CF community and in some cases within families. We are concerned that this would have a significant impact on the mental health of patients and their carers. Clinically we are already seeing high levels of distress for some families who are concerned their infants will not be able to access modulator treatment following the announcement of their interim findings.
6	We are concerned that this decision would be discriminatory based on age as children currently under 2 years of age would not be able to access Kaftrio once they reach the age of current eligibility (compared to those over 2 currently who would continue on the medication).

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS Lothian Dr Don Urquhart Consultant in Paediatric Respiratory and Sleep Medicine CF Centre Director Royal Hospital for Children and Young People Edinburgh

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Don Urquhart Consultant in Paediatric Respiratory and Sleep Medicine CF Centre Director Royal Hospital for Children and Young People Edinburgh

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I am concerned that the outcome of the NICE-MTA appraisal may result in a two-tier system of care for people with cystic fibrosis (CF). The process has, I think, proven beyond any reasonable doubt the clinical effectiveness for Elexacaftor/Tezacaftor/Ivacaftor (ETI) in people with CF. This is demonstrable in both clinical trials and real-world settings. The process has (thus far) however failed to demonstrate cost-effectiveness within the chosen health-economic models, leading to an inability for NICE to recommend ETI. Reassurances are given that existing NHS patients already on ETI will continue to receive this. Such a situation would leave: Tier A - existing patients on ETI aged >6 years continue to access ETI Tier B – a child who turns 6 could not be started on ETI e.g. child aged 6 with excellent lung health could be on ETI with an unwell 5-year old who is a cause for clinical concern being left without access. Such a 'date of birth lottery' is unacceptable in a publicly-funded health service.
2	I am concerned that the very young are those who will be disadvantaged most by being denied access to ETI. Work by Lopez and colleagues (J of CF)[1] reported a median projected life expectancy of 71.6 years for people with CF treated with ETI compared with just 38 years for those receiving standard care. These authors also demonstrated that projected gains in life expectancy are greater if ETI is started earlier with projected survival up to 82.5 years if ETI is started between the ages of 12 and 17. Thus, a child aged 15 who started ETI in 2020 might be expected to live to 82 years, whilst a 5 year old in 2023 who is denied access could only expect to live to 38 years. Again such a treatment lottery is unacceptable in a publicly-funded health service in my view. **REFERENCES:** 1. Lopez A, Daly C, Vega-Hernandez G, *et al.* Elexacftor/tezacaftor/ivacfator projected survival and long-term health outcomes in people with cystic fibrosis homozygous for f508del. *J Cyst Fibros* 2023;**22:**607-614.
3	I am concerned that a medication that is so overwhelming clinically effective cannot be recommended due to being unable to be demonstrated as being cost-effective. I urge NICE to consider the health economic models and whether these are designed for the evaluation of a drug such as ETI e.g. a drug that is given from aged 6 years (or 2 years as per licensing update of 15/11/2023) and continued lifelong to a median of perhaps 80 years of age.

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	I also urge Vertex Pharmaceuticals to revisit the pricing of ETI and whether this can be adapted in order to allow a more favourable cost-effectiveness appraisal. As a clinician who has seen first-hand the benefits that ETI confers to young people with CF, it would now feel unthinkable to be able to prescribe this for future generations of people with CF.
4	I would encourage all health benefits to be considered in the model - increase in time in work and school for people with CF as a result of less exacerbations - increase time in work for caregivers of people with CF as a result of less exacerbations - decreased travelling to and from appointments - increased virtual delivery of care - the impact on 'health miles' e.g. the impact on the environment of less travel to and/from clinic and the impact on the environment of withdrawing/reducing need for other treatments
5	
6	

Insert extra rows as needed

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Multiple Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Over 500 web comments were received during consultation. The appraisal committee received these in full in their papers. The key themes have been summarised in this document to ensure no personal data is inadvertently released into the public domain. This summary was also included in the committee papers.

Multiple Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Dear Stakeholders,

NICE is grateful to the members of the public, including people with cystic fibrosis (CF) and their carers, who took time to consider the draft guidance and respond using our website. NICE would like to thank stakeholders for providing details of people's personal experience of CF and treatment with Cystic Fibrosis Transmembrane Conductance Regulator modulators (CFTRms). The consultation closed on 24 November 2023 and NICE received 524 separate responses as part of the web comments.

Due to the high number of responses and the inclusion of personal identifiable data, it is not possible to provide redacted versions of the web comments in full. However, the key themes outlined below aim to summarise the content of the web comments.

Please be assured, the committee has received, and will consider, all web comments in full within its committee papers.

Key themes from web comments

CF, clinical effectiveness of CFTRms and continued access

- Most comments highlight that CF is a severe life limiting, life threatening disease. They describe the life changing impact of CFTRms on people with CF and their carers, and how CFTRms can give people living with CF greatly improved prospects for their quality of life and life expectancy.

- A strong theme from all web comments is that CFTRms should remain available on the NHS for all people eligible regardless of the cost.
- Life-changing treatments for genetic conditions that people have from birth, where there are no alternative options, should be prioritised over other areas of government and NHS spending, where there has historically been wastage. Taxpayers would agree that funding this treatment is a valuable use of money.
- CFTR modulators are a scientific breakthrough and withdrawing funding would be taking a step backwards.
- The impact of removing future access for people who are not yet eligible for CFTRms due to age, has not been accounted for.
- "*IVA-TEZ-ELX clearly and evidently extends life for people with CF significantly and it allows them to live a more pain free normal life*".
- "*Since receiving CFTRm, progress has been amazing and can now look forward to a full and long life. The family can plan for the future without the high levels of anxiety and caution that were limiting under the old regime. Able to fully engage in all sports and activities in and out of school; unless you knew otherwise you would be surprised to learn that she has CF. Prognosis is bright with hospitalization hopefully a thing of the past and demands on NHS and care services all but eliminated*."

Uncaptured benefits

- Many comments state there does not seem to be adequate effort to account for the benefit for young people (under 6 years old) who may have no deterioration in health as they age following treatment with CFTRms. This would give a significant improvement in quality of life and significant saving in costs of other treatments provided by the NHS which would be incurred without CFTRms.
    - Special consideration should be given to children to ensure they are not disadvantaged by any averaging of benefits over the whole population of CF patients. By starting CFTRms early,

children can avoid almost completely the damage that CF inflicts and live virtually normal lives, achieving life expectancy approaching normal levels. Also, the savings to the NHS from not having to treat people in conventional ways will be realised over a longer timeframe.
    - If young children start on CFTRms early in life, then the progressive health problems previously experienced by people with cystic fibrosis will be substantially delayed or even prevented completely.
    - Prevention of severe lung damage in young CF children should be priority to reduce their reliance on other aspects of NHS services.
    - There was consensus from the web comments that given the difference in outcomes for children and adults, a separate sub-group analysis for children should be carried out.
- There are many more important outcomes that should have been included for clinical effectiveness including blood sugar control for CF related diabetes, pancreatic recovery, exercise tolerance, sputum cultures, abdominal symptoms, reversal of bronchiectasis, reduced long-term bacterial colonisation, increased fertility, patient and carer quality of life and psychological impact.
- The full range of benefits to patients and their caregivers should be taken into account, including the prevention of hospitalisations and transplantations, and the ability of patients and their families to participate more fully in everyday life, education and work.
- Improvement in sweat chloride test results have not been considered. Many people taking IVA-TEZ-ELX have a sweat chloride test result range that would be considered normal for people who do not have CF.
- Infection with pseudomonas is common in CF and results in antibiotic resistance from repeated infections and use of IV antibiotics. Impact of CFTRms on pseudomonas infection has not been accounted for.

- Data was provided from NHSBT for the reduction in lung transplant waiting lists following the introduction of CFTRms:
    - Between 1 April 2013 to 31 March 2020 on average 65.7 adults with CF were added to the lung transplant waiting list each year, this represented 22.2% of the total patients during that period.
    - Between 1 April 2020 to 31 March 2023, an average of 9 adult patients with CF were added to the lung transplant waiting list each year, this represented 5.2% of total patients added to the waiting list during that period.
    - Between 1 April 2013 to 31 March 2020 on average 2.86 children with CF were added to the lung transplant waiting list each year, this represented 38.5% of the total patients during that period.
    - Between 1 April 2020 to 31 March 2023, an average of 0.3 children with CF were added to the lung transplant waiting list each year, this represented 4.2% of total patients added to the waiting list during that period.
- Data was provided from NHSBT for the reduction in lung transplants in people with CF following the introduction of CFTRms
    - Between 1 April 2013 to 31 March 2020 on average 47 adults with CF underwent lung transplantation each year, this represented 26.1% of the total patients transplanted during that period.
    - Between 1 April 2020 to 31 March 2023, an average of 7.7 adult patients with CF underwent lung transplantation each year, this represented 7.8% of total patients transplanted during that period.
    - Between 1 April 2013 to 31 March 2020 on average 3.7 children with CF underwent lung transplant each year, this represented

51.0% of the total children transplanted during that period.

- Between 1 April 2020 to 31 March 2023, no children with CF have undergone lung transplantation.

- "*The uncaptured benefits appear to be acknowledged by the committee but not factored in*".
- "*CF is a degenerative disease the earlier an individual has access to these drugs the greater the benefit to them in terms of preventing further damage to organs and therefore the greater benefits in terms of increasing life expectancy*".

Costs

- No inclusion of how much the NHS pays to support someone with CF who is not on CFTRms throughout their lifetime, including medication, hospitalization and care given.
  - Managing CF has a huge lifetime cost to NHS and individuals. Cost-effectiveness calculations do not include these costs. Namely other expensive medications, physiotherapy, hospital appointments and admissions, treating liver damage, pancreatitis, colon cancer, incontinence, depression/mental health support, oxygen provision, IVF, osteoporosis, Distal intestinal obstruction syndrome (DIOS), hearing loss, pneumothorax, haemoptysis, lung transplants, CF related diabetes.
  - Without access to CFTRms, which have proven clinical benefits, these costs would increase and must be accurately reflected.
- CFTRms have meant people with CF are able to work, pay tax and contribute to the economy in addition to their reduced standard care costs.
- The cost savings to the NHS of reduced healthcare costs with CFTRms treatment will be significant. The current real-world evidence mostly represents adults who were already at a lower baseline of health when starting IVA–TEZ–ELX, meaning that they

still require occasional acute care. As future generations take IVA–TEZ–ELX from a young age, they will use much less NHS resources over their lifetimes than current generations, so the cost savings will become even greater.

- This ‘substantive treatment burden’ with standard care should be part of the cost effectiveness evaluation as treatment of CFTRms would mean a huge cost saving over the lifetime of thousands of CF patients and should be included as an ‘uncaptured benefit.’ – “*the cost saving to the NHS from reducing the burden of CF on the service is incredibly valuable to consider*”.
- Many comments highlighted that hospital admissions and the requirement of intravenous antibiotics have greatly reduced, and for some people completely stopped, since treatment with CFTRms
- Evidence suggests hospital admissions will decrease because of the effect these drugs have on reducing bacterial infections.
    - Reduced colonisation of infections will reduce the need for lengthy admissions into hospitals for patients on intravenous antibiotics. Research also suggests CFTRms reduce the probability of patients requiring lung transplants.
- Reduced demand on social care due to improved life chances, access to work and contribute to society, reduced costs in provision of psychological support.
- “*No consideration of uncaptured benefits affecting the taxpayer outside of the NHS. Even if it is outside of the scope of NICE to include savings to other Government bodies and departments outside of the NHS in their calculations, and we would contend it is not, the existence of these should still be acknowledged*”.
- “*Given the very high costs of managing cystic fibrosis, the reduction in these existing costs associated with the use of CFTRms simply cannot be ignored*”.
- “*The current cost analysis of CF care, as per studies by Granger (2022) and Tappenden (2023), is overly simplistic. It fails to fully capture not only the direct but also indirect, and non-medical costs*

associated with CF. A more comprehensive approach is required, one that includes the perspectives of patients, caregivers, and healthcare providers. This broader perspective is crucial to accurately assess the real cost burden of CF."

Annual discount rate

- People with CF who have started treatment with IVA-TEZ-ELX have reported the medication has restored them to "full or near-full health".
- Many comments request a review of the decision to calculate annual discount rate at 3.5% per year, and consider 1.5%, given that all three stipulated criteria are met.
- For adults, although lung function may not be fully restored, they are able to live a normal healthy life. The additional benefit in children restoring lung function and therefore applying the 1.5% discount rate should be considered separately to adults.
- "*As the access agreement has already provided everyone from the age of 4 months, 2 or 6 (depending on genetics) with access of modulator therapy, the impacts of this appraisal will only be felt on children <6, who have been scientifically proven to be restored to very near full health".*

Impact on carers

- Carer utility benefit applied from treatment initiation should be extended above the age of 11 to age 18 years. Scenario analysis should consider carer utility benefit for life.
    - Carer responsibility and financial burden does not go away at 18 years, it extends and often increases into adulthood. As health tends to decline with age, adults with CF eventually become too unwell to work and contribute to the household.
- Extreme emotional challenges of the diagnosis of CF to children, their parents and their wider families are not accounted for.
- Analysis should account for the toll on the mental and physical health of parents, grandparents and family members and the impact on working parents.

- "*If this recommendation is implemented, I do not believe that both parents will be able to remain in work. One of us will need to become a full-time carer; the level of care needed without Kaftrio, and in respect to exacerbations, just isn't feasible long term if we are both working*."
- "*Underestimate caregiver utility benefit. It extends well beyond primary caregivers to extended family and friends*".

Treatment specific utility benefit

- The 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.
- From 159 adults with CF prior to initiation of IVA-TEZ-ELX and one year post initiation. There is a statistically significant improvement in all of the domains of the CFQR except digestion.
- "*The many non-respiratory benefits of treatments must be applied to ensure an inclusive, holistic representation of the treatment specific utility benefit. The effect of treatment with CTFR modulators on quality of life must be captured and included in the discussion and consultation*".

Long-term lung function decline with CFTRms

- Prediction of lung function benefit with CFTRms should be based on preventing lung function decline. For young children (below 6), lung function is near-full-health at baseline, and will sustain near-full-health lung function over a long period with CFTRms.
- "*Benefits likely to be much greater for children who have yet to develop any lung deterioration and who will have normal or near-normal life expectancies."*
- *"a separate sub-group analysis for children should be carried out"*
- Patients and clinical experts and patient testimony agreed that the effects on lung function have been sustained with IVA-TEZ-ELX.

- Recent published data demonstrates improvements in Lung Clearance Index and reduction in sweat chloride for children aged 2-5 years taking IVA-TEZ-ELX.

Severity modifier

- Many comments consider a severity modifier of 1 to be inadequate.
- It is evident from patient, caregiver and clinician testimonies that CF is a severe disease associated with considerable morbidity and substantial shortening of life.

Unlawful discrimination

- Comments highlight the current recommendations may discriminate against people with protected characteristics, specifically age and disability.
- *“the recommendations are unlawfully discriminating against children on the basis of age, as per the Equality Act 2010.”*
- *“Children will have to grow up alongside other people who are given these drugs on the NHS and will have to compare how difficult their life is and their condition is to those who are fortunate enough to have been born at a different time.”*

Dear [redacted],

Thank you for providing Vertex's response to the draft guidance consultation for ID3834 and the accompanying economic model. The EAG has now reviewed the response and has 3 points for clarification:

1. Please confirm the model structure of the MMRM Analysis of CFQ-R-8D Utility Score for Subjects ≥ 14 Years Old at Enrolment at Baseline and Post-Baseline Interim Analysis Set (Table a1.3 DOF – HEOR – Trajectory CFQ-R 8D results from IA2-REF- 22775.)?

    a. Please confirm which levels of the ppFEV1 covariate were included in this model (i.e., <40, >= 40 and <70, and ≥70, or if ppFEV1 was included as a continuous covariate);

Company response:

MMRM Model:

CFQ-R-8D (baseline, post-baseline) = Intercept + Treatment (0 = baseline, 1 = post-baseline) + categorical ppFEV1 (<40, 40-70, >70) (baseline, post-baseline)

Explanation:

Each patient will have two data inputs for each variable, one for baseline (values before treatment initiation with IVA/TEZ/ELX), one for post-baseline (values after treatment initiation with IVA/TEZ/ELX).

- Baseline value: most recent value prior to treatment initiation
- Post-baseline value: average of all available data points after the 30th day of treatment initiation.

Disease severity is measured by categories of ppFEV1 levels at corresponding timepoint (i.e. baseline and post-baseline).

- Categories are defined as:
    - Mild: >70 ppFEV1
    - Moderate: 40-70 ppFEV1
    - Severe: <40 ppFEV1
- Post-baseline values of disease severity: within patient average of all available ppFEV1 values after 30 days of treatment initiation is calculated first, followed by cohort average to inform categorical estimates.

The regression coefficient of “treatment”, is the incremental benefit of treatment on utility, after accounting for the ppFEV1 severity – the CEM model input.

A mixed effect model has been considered the best methodological approach since the baseline and post-baseline come from the same subject.

b. If feasible, please provide an analysis where ppFEV1 is included as a continuous covariate.

Outcomes of this analysis show no difference in the estimated treatment-specific utility benefit (0.0897 [0.0512, 0.1281]) compared to original analysis based on categorical values of disease severity by ppFEV1 levels (0.0894 [0.0726, 031063])

Outcomes of this analysis are presented below:

Table a1.3
MMRM Analysis of CFQ-R-8D Utility Score for Subjects ≥ 14 Years Old at Enrolment at Baseline and Post-Baseline
Interim Analysis Set

Visit	ELX/TEZ/IVA N = 202
Study Baseline	
n	198
LS mean (SE)	0.7515 (0.0158)
95% CI of LS mean	(0.7202, 0.7829)
Post-Baseline	
n	201
LS mean (SE)	0.8412 (0.0108)
95% CI of LS mean	(0.8199, 0.8625)
LS mean Diff (Post-Baseline vs Study Baseline), 95% CI	0.0897 (0.0512, 0.1281)

Previous results:

Table a1.3
MMRM Analysis of CFQ-R-8D Utility Score for Subjects ≥ 14 Years Old at Enrolment at Baseline and Post-Baseline
Interim Analysis Set

Visit	ELX/TEZ/IVA N = 202
Study Baseline	
n	198
LS mean (SE)	0.7395 (0.0088)
95% CI of LS mean	(0.7223, 0.7567)
Post-Baseline	
n	201
LS mean (SE)	0.8289 (0.0095)
95% CI of LS mean	(0.8103, 0.8475)
LS mean Diff (Post-Baseline vs Study Baseline), 95% CI	0.0894 (0.0726, 0.1063)

2. The EAG welcomes the use of a contemporaneous cohort, but feels the presented analysis does not provide clear evidence of no effect of COVID-19 within the contemporaneous cohort, which the EAG considers to be a key piece of data that should be available from this dataset:

    a. Please provide a graph of the contemporaneous cohorts from the US CFFPR analysis. The EAG would like this graph to be capable of displaying whether there is a change in the rate of decline of ppFEV1 during the COVID-19 pandemic for each cohort, accounting for the repeated measurements from individuals:

    - Please use as the x-axis “Date of Measurement” and the y-axis “ppFEV1”, and plot the raw data;

- The raw data when displayed on the graph should look similar to that of 11.4 Figure D1 from the Final Analysis (FA) for Kaftrio from the DCA for the ELX/TEZ/IVA and contemporaneous cohorts;

- Please use a regression that is capable of detecting non-linearity in the rate of decline between periods during the COVID pandemic and outside of the pandemic – for example using a non-linear model or a piecewise linear approach. If available, please provide the output of these regression models, e.g. estimates of the slope before, during and after the dates used to represent the COVID-19 pandemic;

- Examples of how this could look are given in Figure 1 (assumed COVID-19 preserves lung-function), Figure 2 (assumed COVID-19 accelerates decline), and Figure 3 (assumes no effect of COVID-19).

Figure 1:

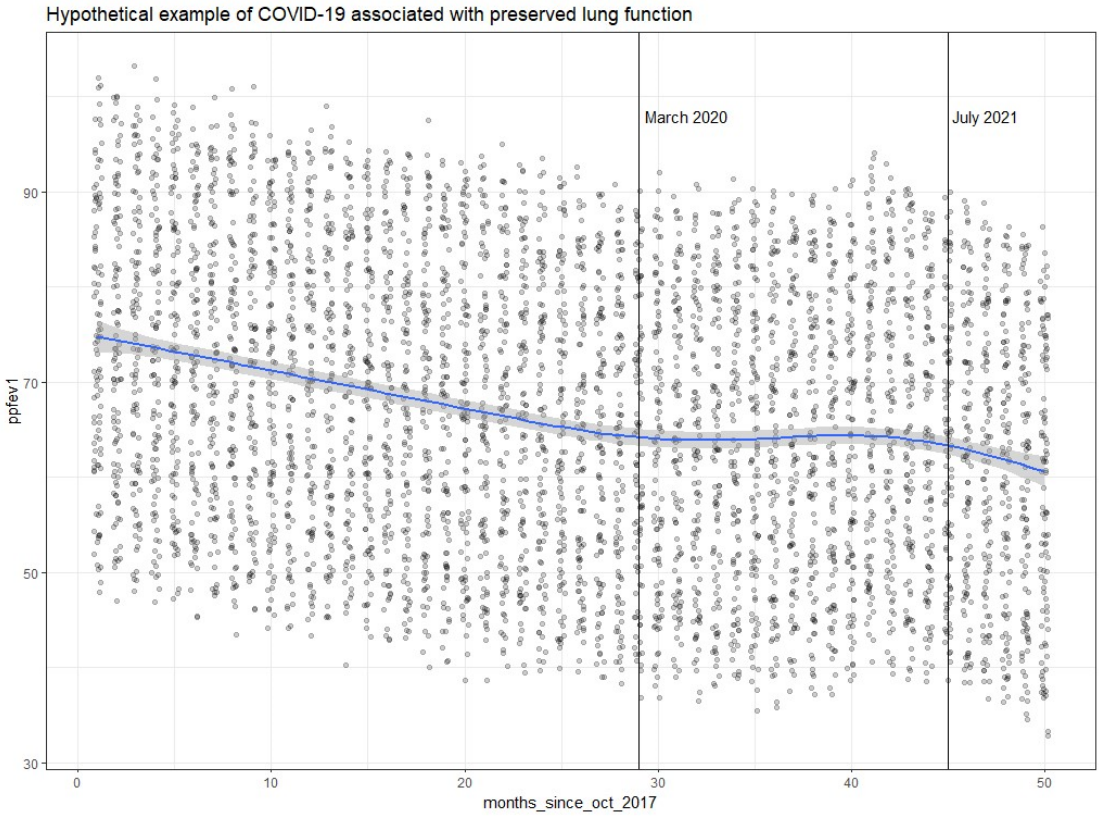


Figure 2:

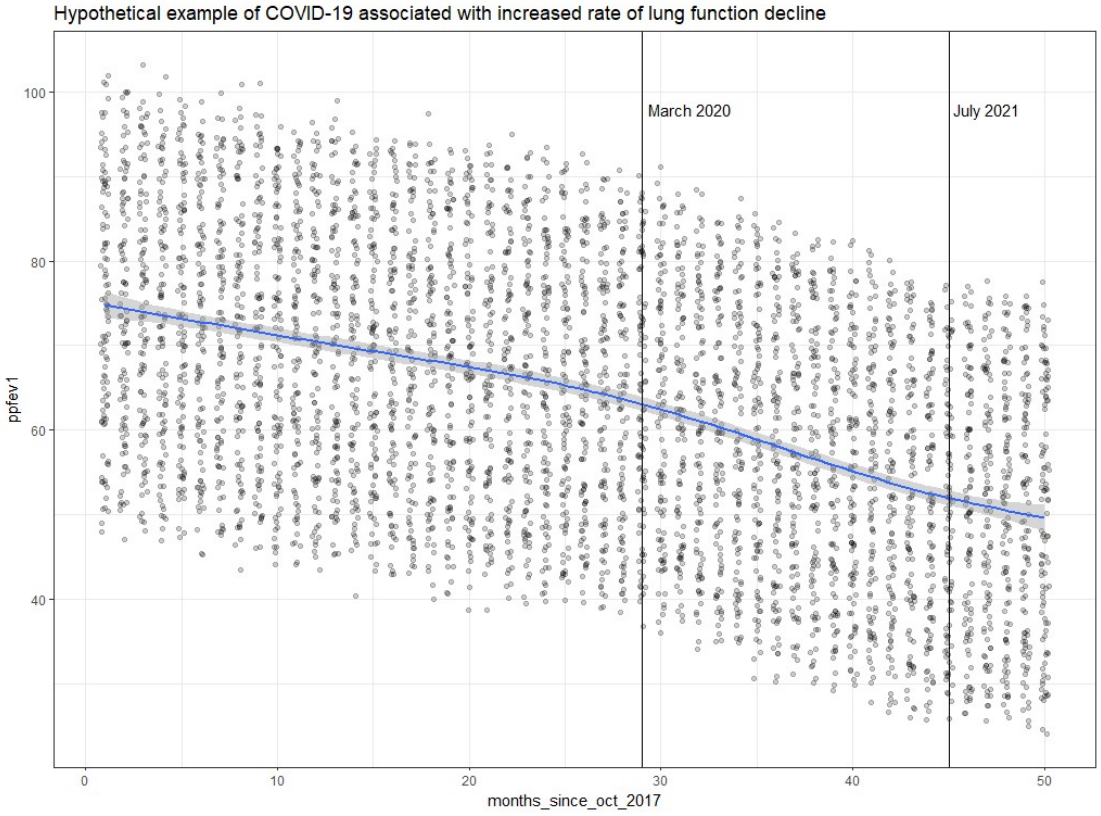
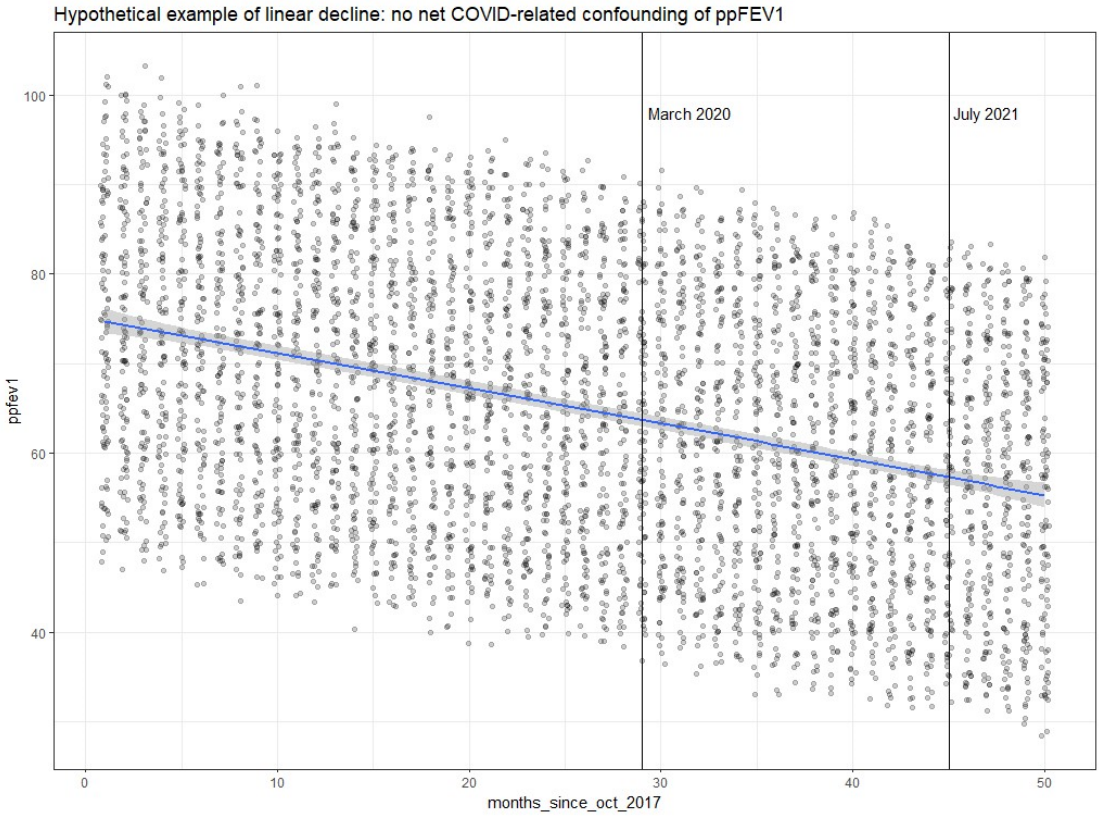


Figure 3



Company response

The US CFFPR study was not designed to determine the magnitude of effect that the COVID-19 pandemic had within the study cohorts, rather, the study was specifically designed to control for any potential confounding due to the effect of COVID-19, which was strongly suspected based on other research studies and data sources suggesting a complex interplay of risk factors and potential protective effects with CF/CFTRm and COVID-19.[1] For this reason, results of this study cannot provide "evidence of no effect of COVID-19 within the contemporaneous cohorts", but instead demonstrate that even though COVID-19 may have impacted within-group results, there is still a substantial

[1] Vitiello, A., Sabbatucci, M., Silenzi, A. et al. The impact of SARS-CoV-2 infection in patients with cystic fibrosis undergoing CFTR channel modulators treatment: a literature review. Respir Res 24, 278 (2023). https://doi.org/10.1186/s12931-023-02593-1

2 Average of the best available ppFEV1 in each quarter of the second year in the baseline period minus the average of the best available ppFEV1 in each quarter of the first year in the baseline period; ELX/TEZ/IVA-treated mean ± SD -0.9 ± 6.4; SMR-weighted comparator mean ± SD -0.7 ± 19.0; standardized difference -0.7%

treatment effect of IVA/TEZ/ELX when comparing to a contemporaneous group of IVA/TEZ/ELX-ineligible controls.

This analysis controlled for multiple factors such that any differences seen between the contemporaneous groups could be attributed solely to IVA/TEZ/ELX treatment:

- SMR weighting ensured cohorts were well-balanced on numerous characteristics and specifically included change in ppFEV1 prior to index date so that the pre-index ppFEV1 trajectory did not differ in the treated and ineligible cohorts, as well as year/quarter of index date so that the temporal distribution of index dates was similar between cohorts. By balancing on these factors and others (e.g., additional demographic characteristics: age at index, gender, race, ethnicity, type of health insurance; additional baseline clinical characteristics: ppFEV1, BMI, # of PEx, medication use, prevalence of respiratory microorganisms) and with no reason to believe that the pandemic differentially impacted IVA/TEZ/ELX-treated and IVA/TEZ/ELX-ineligible cohorts, the difference seen between groups can be attributed to the treatment effect.

The specific figure requested by NICE is unlikely to be informative:

- The study was designed such that each patient was assigned an index date based on IVA/TEZ/ELX initiation (treated cohort) or selected index date encounter (comparator cohort) and consequently individuals within each cohort are not followed over the same calendar time, even though the calendar times of index dates are balanced between the cohorts.

- Treated cohort individuals in this rate of change analysis had on average 3.0 ppFEV1 measurements per year:

    - More than 80% of individuals in both cohorts have their index date in Q4 2019 or Q1 2020 leaving insufficient time to capture

enough ppFEV1 values prior to March 2020 to model a post-index pre-COVID slope

- The period from July 2021 to December 2021 (end of data availability) would be insufficient time to capture enough ppFEV1 values to model a post-COVID slope

Because we are not asserting that there is no effect of COVID-19 within the contemporaneous cohort, and indeed, our study was expressly and carefully designed to control for any effects of COVID-19 within both cohorts, we do not believe that the requested analyses and scatterplots are necessary for interpreting the magnitude of IVA/TEZ/ELX treatment benefit in this population.

3. Please provide a list of changes that have been made to the economic model along with sheet and cell references.

Company response

Please see attached file outlining the changes.

Please could you provide responses to questions 1a and 3 by 5pm on 30 November 2023. The EAG recognises that questions 1b and 2 may take longer to address, so please send over answers when available.

[redacted]

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

Response to stakeholder comments on Draft Guidance

December 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135829.

1 Response to DG comments from the Company

Vertex Pharmaceuticals Ltd. (Boston, MA, USA) provided comments on the draft guidance document for ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]. In this document, the EAG responds to each of the Company's comments. The EAG also provides a brief commentary on the draft guidance comments submitted by other stakeholders in Section 2.

Table 1. EAG comment on Vertex response to Draft Guidance.

Comment Number	Title/summary of Vertex response	EAG comment
1	Executive summary	NA
2	Economic model	The EAG thanks the company for the identification of the model error relating to the calculation of PE. While a correction was previously made related to this calculation, the number of PE events for patients who had discontinued CFTR modulators was still linking to the ECM patient trace. Any further scenarios ran by the EAG have been implemented in the version provided by the company.
3 and 4	Impact of COVID-19 on lung function and rate of change in lung function: *Vertex maintains that the reduction in Rate of Change in lung function for IVA/TEZ/ELX is higher than the committee's preferred assumption and should be 100%.*	The Company has provided two new analyses to support the claim that the reduction in the rate of change in lung function for ELX/TEZ/IVA relative to established clinical management should be 100%: • An analysis of Study 445-105 which excluded measurements taken between March 2020 and July 2021; • A new, large-scale analysis of the US CFFPR with an ELX/TEZ/IVA treated cohort and a contemporaneous cohort. The EAG considers the US CFFPR analysis to be at risk of bias. However, it is re-assuring that the magnitude of COVID-19 related

		confounding may be small. The EAG considers the results are 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 UK CF Register. The EAG agrees with the Committee preference that the rate of decline data from the UK CF Registry represent the most robust and relevant data source for the current appraisal that directly measures ppFEV$_1$ decline from individuals treated with ELX/TEZ/IVA, although the EAG still notes the potential confounding of the data from the COVID-19 pandemic. The EAG considers that the data from the US CFFPR analysis would likely be able to resolve the issue of the impact of COVID-19 on lung function, but that these data have not yet been presented. The EAG has requested these data from the Company. The EAG does not consider the updated analysis of Study 445-105 analysis to be highly informative. The EAG's full critique of these two analyses is presented in Section 1.1.
5	Disease management costs *The EAG's approach to costs is flawed and lacks face validity. Vertex proposes an alternative approach which recognises reductions in drug and disease management costs for patients treated with CFTRms compared to ECM, as well as reflecting the fact that health state costs should vary by severity (in the EAG's approach costs*	The Company has provided alternative costs for disease management, ECM drug costs and pulmonary exacerbations (PEs). The Company has provided a range of references to the literature in support of their proposed costs. The EAG considers the proposed changes made by the Company to overestimate the reduction in costs based on the evidence available.

	across mild, moderate and severe disease are very similar).	The EAG has provided additional scenario analyses on costs, implemented on the committee preferences base case. The EAG's full critique is presented in Section 1.2.
6	Treatment specific utility increment *Vertex accepts the use of Acaster utilities but maintains that the treatment specific utility for patients on IVA/TEZ/ELX should be included.*	The Company has provided an updated analysis of the TRAJECTORY study providing an estimate of the change from baseline in CFQ-R-8D following treatment with ELX/TEZ/IVA, conditional on a patients $ppFEV_1$ category.[1] The EAG does not consider the analysis an appropriate method of calculating a treatment specific utility benefit independent of a patients' $ppFEV_1$, and instead considers it likely that the treatment specific utility benefit captures variability due to $ppFEV_1$ in addition to any treatment specific utility benefit. However, the EAG does not consider it unreasonable to include this utility benefit in the economic model, as it will likely capture benefits to HRQoL that occur for patients within $ppFEV_1$ categories, e.g., a benefit for increasing $ppFEV_1$ from 75% to 90% — which is not currently captured in the economic model. The EAG expands on this in Section 1.3.
7	Impact of CFTRm on caregiver burden *It is appropriate to apply a caregiver utility benefit for caregivers without an upper age limit, as was reflected by the caregivers providing evidence to the committee on 12th October.*	The EAG notes that the available evidence for carer HRQoL was based on carers of patients aged 6–11 for patients treated with ELX/TEZ/IVA. However, the EAG acknowledges the discussions held during the committee meeting and hearing from carers on the impact on caregivers health related quality of life (HRQoL). The EAG has implemented additional flexibility in the economic model in order to explore a scenario applying a caregiver

		utility up to age 18 (model changes described in Appendix 2).
8	Severity *The highest severity weighting should apply to cystic fibrosis. NICE's clarification that the 3.5% discount rate should apply in the QALY shortfall calculation used to derive the severity weight, even when the non-reference case discount rate applies is biased against chronic diseases. It is evident from patient, caregiver and clinical opinion that the 1.7 maximum weighting should apply.*	The EAG notes that 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.
9	Discount rate *Vertex maintains that a differential discount rate of 3.5% for costs and 1.5% for outcomes would be most appropriate but following discussion with NICE we provide evidence that the criteria for the non-reference case discount rate (1.5% for costs and outcomes) are met.*	The NICE Reference Case is 3.5% for both costs and outcomes. The EAG has provided a scenario analysis with the non-reference case discount rate (1.5% for costs and outcomes).
10	Comparators *Ivacaftor monotherapy should be included as a comparator for some F/gating patients in comparison with IVA/TEZ/ELX.*	Ivacaftor monotherapy was not included in the Final Scope as issued by NICE and has not been identified as an additional comparator required in the Draft Guidance. The EAG notes that ivacaftor monotherapy has a marketing authorisation for people with CF aged ≥4 months who have at least one copy of a gating mutation or at least one of the *R117H* mutation.[2, 3] In December 2022, 413 individuals with CF were receiving ivacaftor monotherapy in the UK.[4]

11	Summary and Company ICERs	The EAG notes that the ICERs presented in the Company base case are above those usually considered cost-effective by NICE.

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; CFQ-R, cystic fibrosis questionnaire revised; EAG, external assessment group; ECM, established clinical management; ELX, elexacaftor;; DCA, data collection agreement; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NA, not applicable; NICE, National Institute for Health and Care Excellence; MTA, multiple technology appraisal; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in one second; QALY, quality-adjusted life year; US CFFPR, United States Cystic Fibrosis Foundation Patient Registry, UK, United Kingdom

1.1 Impact of COVID-19 on lung function and rate of change in lung function

"Vertex maintains that the reduction in Rate of Change in lung function for IVA/TEZ/ELX is higher than the committee's preferred assumption and should be 100%."

The Company presented two new analyses of the rate of change in lung function for people treated with ELX/TEZ/IVA. These analyses explore the impact of COVID-19 on lung function decline within Study 445-105 and the US CFFPR.

The EAG welcomes the Company's attempts to quantitatively explore the potential confounding impact of COVID-19 on the rate of change of $ppFEV_1$, which the EAG considered to be key source of uncertainty in the long-term effectiveness data used in the economic model.

1. **Analysis of the 445-105 study excluding data during the pandemic[5]**

Vertex DG response: *The majority of data* [redacted] *from the 445-105 study was collected outside the period associated with the COVID-19 pandemic restrictions, i.e. outside the timeframe of March 2020 to July 2021 (3). A* post-hoc *rate of change analysis was conducted on the final dataset of study 445-105, excluding data collected between March 2020 and July 2021, as a means to reflect the timing of the most severe restrictions associated with the pandemic. The estimated annualised rate of change in ppFEV1 among the overall IVA/TEZ/ELX cohort was* [redacted] *(**Figure 1, Table 1**). This additional analysis supports the conclusion from the primary analysis of no decline in lung function (as measured in ppFEV1).*

The EAG is concerned that excluding measurements between March 2020 and July 2021 does not adequately remove the potential confounding effects of the COVID-19 pandemic on the rate of change of $ppFEV_1$. This is because, if factors associated with the COVID-19 pandemic – such as

reduced viral transmission – led to a reduction in the rate of ppFEV$_1$decline, patients' ppFEV$_1$ measurements after July 2021 would still be expected to be higher than they would have in the counterfactual scenario that the COVID-19 pandemic did not occur. Excluding measurements during the COVID-19 pandemic does not adequately account for COVID-19 confounding because the effects of this confounding would still be present in data collected after the COVID-19 pandemic, and therefore still affect rate-of-change measurements that include both pre- and post-pandemic data.

More robust assessments of the 445-105 study data would be:

- An analysis of the rate of change in measurements taken before March 2020 only;
- An analysis of the rate of change in measurements taken after July 2021 only;
- An analysis of all available data, including a dummy variable of COVID-19 in the model (EAG's preferred approach).

2. **US CFFPR analysis during the pandemic comparing patients treated with IVA/TEZ/ELX compared to a contemporaneous cohort.[6]**

Vertex DG response: *A non-interventional, retrospective, longitudinal study was conducted using data from the US CFFPR from October 21, 2019 through December 31, 2021, to assess the impact of COVID-19 on clinical outcomes. A cohort of people with CF (aged 12 years and older) who were treated with IVA/TEZ/ELX was compared with a contemporaneous cohort who were ineligible for and untreated with IVA/TEZ/ELX. A standardised mortality ratio (SMR) weighting based on propensity scoring methods was used to ensure the comparability between the treated cohort and comparator cohort, and that any impact of COVID-19 on the two cohorts is non-differential. The mean number of ppFEV1 measurements per patient for the IVA/TEZ/ELX-treated and comparator cohorts were* [redacted]*, respectively. The annualised rate of change in ppFEV1 among the IVA/TEZ/ELX-treated cohort* [redacted] *compared with* [redacted] *observed in the comparator cohort* [redacted]*, amounting to a* [redacted] *in the rate of lung function decline (**Figure 1, Table 1**, **Appendix 1**). The rate of decline in the untreated cohort of greater than* [redacted] *percentage points during this period is counter to any protective effect of COVID lockdowns on lung function decline in CF patients*.

The EAG welcomes the use of a contemporaneous control cohort to investigate the impact of the COVID-19 pandemic on clinical outcomes, and notes this is a large dataset that was not available at the time of the first Appraisal Committee Meeting. Data were available from [redacted] ELX/TEZ/IVA treated patients and [redacted] contemporaneous control patients, but the rate of change analysis was performed in

only people having at least 3 non-missing ppFEV$_1$ measures from at least 3 different quarters in the follow-up period ([redacted] for ELX/TEZ/IVA, and [redacted] for the contemporaneous control cohort as only an SMR weighted sample size was reported[redacted]).

The EAG notes that:

- The overall estimate of annualised rate of change in the ELX/TEZ/IVA treated cohort [redacted] i.e., an overall reduction close to [redacted] throughout the follow-up period. The EAG notes, however, that:
    - The analysis was not prespecified, and details on the conduct of the analyses were limited. For example:
        - It is unclear why Month 2 and Month 24 were chosen as the two timepoints for the rate of change analysis, rather than, e.g. Month 4 (to provide an increased certainty of excluding acute treatment effects) and until last available data point (to use all available data);
        - It is unclear why patients with only two ppFEV$_1$ measurements were excluded, as they could have provided data from the whole cohort that could have informed the analysis.

The EAG would have liked to have seen a pre-specified analysis plan and sensitivity analyses to assess the robustness of the results around the key analytical decisions, but these were not provided (or are unavailable).

The Company also provided a comparison of the rate of decline of ELX/TEZ/IVA treated patients with at least one *F508del* mutation with the rate of decline of untreated patients without an *F508del* mutation. From this, the Company claims that ELX/TEZ/IVA treatment leads to [redacted] reduction in the rate of lung function decline. The EAG does not consider this to be an appropriate interpretation of the analysis as the two cohorts, despite SMR weighting, are expected to have different underlying rates of ppFEV$_1$ decline. Moreover, the EAG does not consider the analysis to have adequately excluded any potential effects of COVID-19 related confounding. The EAG notes that while the absolute difference between each cohort is a valid statistic comparing the two cohorts and would exclude impacts of COVID-19 confounding, the relative difference would still be subject to COVID-19 related confounding.

As an example of this issue, consider the hypothetical scenario that COVID-19 was associated with a preservation of +0.5% ppFEV$_1$ per year:

Company original analysis:

- Absolute difference in ppFEV$_1$: [redacted]
- Relative difference in ppFEV$_1$: [redacted]

Scenario correcting for a hypothetical annual 0.5% preservation of ppFEV$_1$ associated with COVID–19:

- Absolute difference in ppFEV$_1$: [redacted]
- Relative difference in ppFEV$_1$: [redacted]

While the absolute difference in annualised changes in ppFEV$_1$ between cohorts is robust to the same level of confounding applied to each cohort, the relative difference is not.

The EAG notes that the overall annualised rate of decline in the contemporaneous cohort of [redacted] is consistent with no, or a small, confounding effect of COVID-19 measurements, and this is compatible with both a near 100% relative reduction in ppFEV$_1$ decline (if there is no confounding), or a relative reduction in ppFEV$_1$ decline closer to [redacted] (if there is a small confounding effect).

The EAG considers that the US CFFPR data from the contemporaneous cohort should contain the necessary data to estimate whether there was a confounding effect of COVID-19 through either of the following analyses:

- An analysis *within* the contemporaneous control cohort showing no appreciable change in the rate of ppFEV$_1$ decline during the COVID-19 pandemic and;
- An analysis of the ELX/TEZ/IVA treated cohort including a dummy variable of COVID-19 in the model analysing all available data.

The EAG has requested the Company provide the first of these analyses.

Overall, the EAG notes that:

- The new 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;
    - If the Company were able to provide these data, the EAG may consider a 100% relative reduction in the rate of ppFEV$_1$ decline to be an appropriate interpretation

of the US CFFPR dataset, within the length of follow-up period of the study. However, the EAG notes this would be inconsistent with the data observed in the UK CF Register, and there would be large outstanding uncertainty as to whether this 100% reduction would be applicable across a patient's lifetime.

- As a non-pre-specified analysis with no sensitivity analyses, the Company's analysis of the US CFFPR data is at high risk of bias;
- The Company has not presented any further data from the UK CF Registry, i.e., the most relevant data source which did show a long-term decline in $ppFEV_1$ for treated patients;
- The Company has not attempted to address uncertainty around the acute period for TEZ/IVA and LUM/IVA, which was highlighted in the Draft Guidance ("*The committee added that it would like to see a scenario analysis that extended the acute treatment effect window up to week 24*."). The EAG considers a scenario extending the length of the acute period would also be informative for all ELX/TEZ/IVA analysis;
- There is outstanding unresolvable uncertainty concerning whether the "long-term" rate of decline observed in the current data sources will generalise throughout the length it is applied in the economic model – i.e., a patient's lifetime.

The EAG further notes the similarities between the predictions of a 100% decline and a [redacted] decline over the relatively short periods of follow-up that are currently available. For example, in the model, a 20-year-old F/F patient with a $ppFEV_1$ of 80% would have expected to decline to a $ppFEV_1$ after 4 years – including an acute treatment effect of 14.2% when initiating ELX/TEZ/IVA – of:

- 94.2%, if treated by ELX/TEZ/IVA with a 100% reduction in the rate of decline;
- [redacted], if treated by ELX/TEZ/IVA with a [redacted] reduction in the rate of decline;
- 70.44% on ECM.

At 60 years of age, the individual's predicted $ppFEV_1$ would be:

- 94.2%, if treated by ELX/TEZ/IVA with a 100% reduction in the rate of decline;
- [redacted], if treated by ELX/TEZ/IVA with a [redacted] reduction in the rate of decline;
- 42.6% on ECM.

1.1.1 Further data from the German CF Register

An observational study from the German CF Register was published in September 2023 containing data on the change from baseline in $ppFEV_1$ of 2,645 people with CF treated with ELX/TEZ/IVA in Germany over a 12 month follow up period.[7] The change from baseline in $ppFEV_1$ over 3-month

windows is presented in Table 2. The majority of the data collection in this study also happened during the COVID-19 pandemic. The EAG does not consider these data able to discriminate between a long-term 100% relative reduction in $ppFEV_1$ decline or a [redacted] reduction, but the EAG also notes the potential that the acute increase in $ppFEV_1$ may continue after the 28-day window used by the Company in its analyses. The EAG notes that a greater quantity of data from a longer follow-up window are available as part of the UK Data Collection Agreement.

Table 2. Change from baseline in $ppFEV_1$ over one year of follow-up from the Germany CF Registry, Sutharsan *et al.* 2023 analysis.[7]

Time	Change from baseline in $ppFEV_1$ (95% Confidence Interval)
1 to 3 months post ELX/TEZ/IVA	11.3 (10.8 to 11.7)
4 to 6 months post ELX/TEZ/IVA	11.6 (11.1 to 12.1)
7 to 9 months post ELX/TEZ/IVA	11.7 (11.2 to 12.3)
10 to 12 months post ELX/TEZ/IVA	11.3 (10.8 to 11.8)

Abbreviations: ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

1.2 Disease management costs

The Company has provided alternative costs for disease management, ECM drug costs and pulmonary exacerbations (PEs), stating that the EAG's proposed costs are flawed and lack face validity. The Company has provided a range of links to the literature in support of their proposed costs. The EAG discusses each of the Company's proposed changes to costs in turn below.

a. Reductions applied to ECM drug and disease management costs on CFTRM initiation

The Company proposed a reduction in both ECM drug costs and disease management costs of 70% based on studies of ivacaftor monotherapy showing ~50% reduction in costs compared to ECM, and ELX/TEZ/IVA being shown/predicted to have a greater impact than IVA monotherapy.

The EAG notes that the majority of the referenced studies show a reduction in healthcare resource use classed as hospitalisations and IV antibiotic use. In two of the studies referenced (Simmonds *et*

al. 2022[8] and Volkova *et al.* 2020[9]), which show a reduction in hospitalisation and IV antibiotics post ivacaftor, IV antibiotic use and hospitalisation was due to PEs. Both the retrospective study from the Manchester CF Centre (Mitchell *et al.* 2021)[10] and Vega-Hernandez *et al.* 2023[11] showed reductions in inpatient stay following use of CFTR modulators; however, it is unclear from the studies if this is also due to reduced PEs or for other reasons. The EAG notes that PEs are separately costed in the model and the impact of fewer PEs due to CFTRm are already accounted for in this way. In addition, while Vega-Hernandez *et al.*[11] observed reductions in hospitalisations and length of stay, there were no statistically significant differences in the rate of prescriptions, IV antibiotics and patient interactions with primary health care services compared to the previous year when patients were not on a CFTRm. As previously discussed, the EAG notes that [redacted]

In relation to ECM drug costs, the EAG notes that the UK CF Trust final analysis report showed [redacted].[12] However, in-line with stakeholder comments and ongoing clinical trials, the EAG acknowledges that use of ECM therapies may decline with the use of CFTR modulators. Nonetheless, the EAG does not consider that there is currently robust evidence to support reducing ECM drug costs by 70% for patients on CFTR modulator treatments, as suggested by the Company.

The EAG notes that previous scenarios were provided applying a reduction in ECM costs for CFTR modulator patients of 23% and 40%. The results of these scenarios when applied to the committee preferences have been provided in Appendix 1.

The EAG is aware of comments made during the committee meeting, and from stakeholder engagement on the draft guidance, that disease management costs may be lower in clinical practice for patients on CFTR modulators, particularly for younger patients initiating treatment. In light of a lack of robust evidence on the magnitude of reduction, the EAG has also explored two illustrative scenarios in which costs in the CFTR modulator arms of the model for ECM drug costs and health state costs are reduced by the same proportions applied in the ECM drug costs only scenario (23% and 40%, respectively).

b. Cost differentiation between health states based on disease severity (ppFEV1)

The EAG thanks the Company for highlighting previous studies showing a differentiation in health states costs across disease severity. The EAG notes, however, that it is difficult to compare many of these costs to those used in the model (Tappenden *et al.* 2023)[13] as the majority of studies include the costs of PE and/or drug costs (which have been costed separately in the model). The Company adjusts health state costs using ratios reported to be from Ramoagopalan *et al.* 2014.[14] The EAG notes that the ratios applied by the Company are not sourced directly from the study but are based on the Company's original estimation of costs for each health state after attempting to remove the costs of PEs from hospitalisation and pharmacotherapy costs. The EAG considers that this may not have fully removed the costs of PEs from the estimates and, from the information available to the EAG, the methods used to remove the costs of PE appear to be based on arbitrary assumptions. The EAG also notes that the mean health care costs due to health care professional visits in Ramagopalan *et al.* were extremely similar across severity groups. Health care professional visit resource use makes up the vast majority of the health state costs sourced from Tappenden 2023[13] and therefore Ramagopalan *et al.*[14] shows a similar situation to that observed in Tappenden 2023.[13]

c. PE cost reduction post CFTRM initiation driven by reduced severity

The EAG's cost applied for PE was based on Tappenden 2023 and following feedback from clinical experts that a standard course of treatment is used to treat PEs. The Company applied a 50% reduction in the EAG's cost of PEs for patients on CFTR modulators. The Company highlight that in the [redacted] However, the EAG acknowledges the points highlighted by clinical experts during the committee meeting that there may be a reduced requirement for IV antibiotics for patients experiencing a PE when treated with CFTR modulators. Therefore, the EAG has provided an illustrative scenario using the Company's proposed 50% reduction in PE costs to reflect reduced usage of IV antibiotics or days in hospital.

d. Reduction to the mild health status ($ppFEV_1 \geq 70$) medicines costs

The Company has proposed an 81% reduction in the ECM drug costs for the $ppFEV_1$ severity group ≥70. The Company states that this is due to pharmacotherapy costs in Ramoagopalan *et al.*[14] for the mild health state being 81% lower than that of the costs used for moderate and severe health states. The EAG notes that the 81% difference between pharmacotherapy costs for $ppFEV_1$ <40 versus ≥70 is not sourced directly from Ramoagopalan *et al.* 2014[14] but is instead based on the Company's

estimates of costs after attempting to remove the costs of PE. The EAG notes that the cost of pharmacotherapy in Ramoagopalan *et al.*[14] includes IV antibiotics, which the majority of patients initiated due to a PE. As previously noted, the EAG believes the Company's estimates of costs from Ramoagopalan *et al.*[14] may not have fully removed the costs of PE. Therefore, based on the available evidence, the EAG does not agree that this reduction is applied in the base case.

1.3 Treatment specific utility

"Vertex accepts the use of Acaster utilities but maintains that the treatment specific utility for patients on IVA/TEZ/ELX should be included."

The Company has accepted the Committee's preferences of using the utility values from Acaster 2015,[15] but has stated that a treatment specific utility benefit should be included for patients treated with ELX/TEZ/IVA.

The Company presented an updated analysis from TRAJECTORY (interim analysis [IA] 2, with interim analysis 1 being presented at the first meeting). TRAJECTORY is a real-world observational study performed in the UK, Germany, and Spain with patients with at least 1 CFQ-R measurement in both the 12 months prior to the index date and the 12 months following the index date.[16]

The Company performed a mixed model repeated measures (MMRM) analysis predicting patients' CFQ-R-8D utility scores with $ppFEV_1$ category (<40%, ≥40 to <70%, ≥70%) as a covariate. The results of the original and IA2 analyses are presented in Table 3.

Table 3. Company MMRM analyses of TRAJECTOR (IA1 and IA2)

Parameter	Estimate (95% confidence interval) – TRAJECTORY	
Analysis	IA1[17]	IA2[1]
Baseline	[redacted]	[redacted]
LS mean change from baseline (attributed to ELX/TEZ/IVA)	[redacted]	[redacted]
$ppFEV_1$ category	NR	NR

Abbreviations: ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; IA, interim analysis; NR, not reported

The EAG notes that the structure of the MMRM model used to estimate changes in CFQ-R-8D utility will be insensitive to changes in patients' quality of life due to changing $ppFEV_1$, as $ppFEV_1$ is treated as ordered categories (<40%, ≥40 to <70%, ≥70%) rather than a continuous variable in the model. As an example, the model treats a patient with a $ppFEV_1$ of 71% and a patient with a $ppFEV_1$ of 100%

equally in terms of ppFEV$_1$. In this model, the increase in quality of life for a patient who's ppFEV$_1$ increases, but their ppFEV$_1$ category does not change, would be attributed to the ELX/TEZ/IVA "treatment specific utility". Therefore, the estimate of the treatment specific utility of ELX/TEZ/IVA reported in this model is not a treatment specific utility gain associated with ELX/TEZ/IVA independent of ppFEV$_1$ but is an estimate of change from baseline in CFQ-R-8D attributed to ELX/TEZ/IVA, *conditional* on a patient's ppFEV$_1$ category.

The EAG notes, however, that the ppFEV$_1$ categories included in the economic model match those used for the analysis of TRAJECTORY. As such, the utility values used in the economic model are equally insensitive to changes in quality of life attributed to, for example, a 10% increase in ppFEV$_1$ from 75% to 85%. The EAG notes that treatment with ELX/TEZ/IVA is associated with such changes, ECM is not. Therefore, the EAG does not consider it unreasonable to include the additional utility benefit associated with ELX/TEZ/IVA calculated from the TRAJECTORY IA2, on the understanding that this does not represent a treatment specific utility benefit of ELX/TEZ/IVA independent of ppFEV$_1$ category, but instead likely captures both:

- A QoL benefit associated with increased ppFEV$_1$ due to treatment with ELX/TEZ/IVA within a ppFEV$_1$ category;
- Any other treatment specific utility benefit not captured by ppFEV$_1$.

The EAG consider this an unsatisfactory – but potentially justified – method of identifying the QoL benefit of patients on ELX/TEZ/IVA. A more robust analysis of HRQoL could have been performed using ppFEV$_1$ as a continuous variable, with various linear and non-linear model structures explored, in order to appropriately characterise the relationship between ppFEV$_1$ and HRQoL, and to isolate any treatment specific utility associated with ELX/TEZ/IVA, conditional on ppFEV$_1$. The EAG notes that the Company had also employed a similar approach to estimate the utility benefit for TEZ/IVA to that used for ELX/TEZ/IVA, albeit limited details were available for the EAG to review. [redacted], which is applied in the Company's updated base-case analysis. The EAG provide a scenario analysis (see Appendix 1), which includes a treatment-related utility benefit for both TEZ/IVA (F/RF population only) and ELX/TEZ/IVA.

The EAG also notes that the treatment specific utility is based HRQoL data scored using the CFQ-R-8D. This differs to the measurement of utility used for model health states, which uses EQ-5D-3L values from Acaster *et al.*,[15] in line with the NICE reference case.

The EAG notes that in the version if the economic model provided to the EAG from the Company including their preferred base-case, the treatment utility benefit applied was incorrectly applied as the value from IA1 rather than the updated IA2, presented here. The EAG has updated this analysis and presents the results of the company's preferred base-case in Appendix 1.

2 Other stakeholder responses

The EAG notes that ten further stakeholder comments on the Draft Guidance (DG) were received, not including the Company response to DG. The EAG notes agreement with many of the issues raised and wishes to highlight the common themes of these stakeholder responses that are most relevant to the economic modelling and/or are uncaptured benefits within the economic model.

- **Incident population of children aged 2 years:** As outlined in the Assessment Report, the EAG agrees that the incident population of children aged 2 years eligible for ELX/TEZ/IVA will likely receive the greatest clinical benefits from ELX/TEZ/IVA by initiating treatment before most irreversible lung damage has occurred. The EAG also notes the plausible potential for ELX/TEZ/IVA to prevent the development of CF related diabetes, and potentially preserve pancreatic function, if initiated early. However, as pancreatic damage can occur before the age of 2 years, it is unclear the magnitude to which initiating ELX/TEZ/IVA at 2 years will lead to an increased rate of pancreatic sufficiency in this population;
- **Reduced treatment need for ECM therapies and the effects of co-adherence to non-CFTR modulators:** The EAG agrees with various stakeholders that the need for, and cost of non-CFTR modulator therapies may be reduced for patients treated with ELX/TEZ/IVA. The EAG notes this is an active area of research, with some stakeholders and early data highlighting that co-adherence and continued use of non-CFTR modulator therapies may be important in realising the full clinical benefit of ELX/TEZ/IVA;
- **Uncaptured benefits in the economic model.** Stakeholders raised a range of symptoms and diseases that are not explicitly tracked in the economic model, including but not limited to: gastrointestinal symptoms; changes in cystic fibrosis related liver disease; sinus disease; bronchiectasis; bowl and bladder control; changes in chronic infection status; coughing and sneezing; and depression and mental health. The EAG agrees that treatment with ELX/TEZ/IVA will have large and clinically meaningful effects for most of these features of CF, and for others not included in this list. The EAG notes that although these features are not individually tracked in the economic model, which is a necessary simplification of CF, the effects on a patients quality of life and costs of therapies are partially tracked through the direct measurement of EQ-5D and CFQ-R-8D in CF patients, and through the use of overall, pooled, statistics of disease management costs. The EAG notes that should a treatment specific utility increment be included for ELX/TEZ/IVA, this may also capture further

increases in quality of life a patient on ELX/TEZ/IVA would experience, if these benefits do not already correlate with $ppFEV_1$;

- **Other uncaptured benefits:** Stakeholders raised further benefits that are not captured in the economic modelling, which the EAG had highlighted in its earlier response to stakeholder comments on the Assessment Report. These included:
    - Effect on employment, education and finance;
    - Effects on fertility;
    - Effects on rates of specific bacterial infections.

  The EAG agrees that treatment with ELX/TEZ/IVA will have large positive effects on employment, education, finance and fertility in people with CF. However, these benefits are not routinely captured in the NICE reference case. The EAG agrees that these represent large uncaptured benefits of ELX/TEZ/IVA treatment. The EAG also recognises that both the EAG's and Company's economic model is likely conservative in assuming no changes in the rates of specific bacterial infections for people with CF;
- **Distinction between dual therapies and triple therapy:**
    - The UK CF Medical Association highlighted that they "continue to be concerned about the conflation between dual therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) and triple therapy (E-T-I). The trial data support our clinical experience that dual therapies are minimally efficacious". The EAG agrees that the evidence of the acute and long-term clinical efficacy of LUM/IVA and TEZ/IVA is consistent with much smaller effects than those observed for ELX/TEZ/IVA. The EAG has therefore re-presented a scenario analysis with its original preferences of the reduction in the long-term rate of $ppFEV_1$ decline for LUM/IVA (0%) and TEZ/IVA (17.2%).
- **CF Voices Survey:** The EAG would like to highlight the substantial amount of work performed by CF Voices in performing an online survey in November 2023, which received 175 responses from patients and carers. The EAG notes the transparency of CF Voices in providing the raw survey data. The responses of the CF Voices survey presented in the CF Voices Survey Analysis provide strong qualitative evidence on the effectiveness of ELX/TEZ/IVA and the large positive impact it has on the lives of individuals with CF and their carers.

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4 Appendices

4.1 Appendix 1: scenario analysis

4.1.1 Severity modifier

Severity modifier calculations based on committee preferences applied in the economic model.

Table 4. Severity modifier calculations with shortfall calculations estimated from Schnieder *et al.*2021[18]

	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**

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

4.1.2 Fully incremental scenario analyses results

Table 5. Fully incremental scenario analysis results applied to committee preferences base-case

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – No LT decline in ppFEV$_1$ for patients on ELX/TEZ/IVA							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – LUM/IVA ppFEV$_1$ LT decline 0%, TEZ/IVA ppFEV$_1$ decline 17.2%							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 3- ELX/TEZ/IVA and TEZ/IVA (F/RF population) treatment specific utility benefit applied							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 4 – Carer utility applied for ELX/TEZ/IVA patients up to age 18							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 5 – 23% reduction in ECM drug costs on CFTR modulators							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							

ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 6 – 40% reduction in ECM drug costs on CFTR modulators							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 7 –23% reduction in ECM drug costs and health state costs on CFTR modulators							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						

TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 –40% reduction in ECM drug costs and health state costs on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 - Reduction in PE costs of 50% for patients on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10- 1.5% discount rate for costs and outcomes							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population**

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; PE, pulmonary exacerbation; CFTR, cystic fibrosis transmembrane conductance regulator; LT, long-term

4.1.3 Pairwise (versus ECM) scenario analysis results

Population	Absolute			Incremental			ICER (versus ECM)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – No LT decline in ppFEV$_1$ for patients on ELX/TEZ/IVA							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – LUM/IVA ppFEV$_1$ LT decline 0%, TEZ/IVA ppFEV$_1$ decline 17.2%							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3- ELX/TEZ/IVA and TEZ/IVA (F/RF population) treatment specific utility benefit applied							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Carer utility applied for ELX/TEZ/IVA patients up to age 18							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 – 23% reduction in ECM drug costs on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 – 40% reduction in ECM drug costs on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 –23% reduction in ECM drug costs and health state costs on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8 –40% reduction in ECM drug costs and health state costs on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 - Reduction in PE costs of 50% for patients on CFTR modulators							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10- 1.5% discount rate for costs and outcomes							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population**

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; PE, pulmonary exacerbation; CFTR, cystic fibrosis transmembrane conductance regulator; LT, long-term

4.2 Appendix 2:

4.2.1 Model changes

In order to apply a scenario in which a carer utility benefit is applied up to age 18 only, changes were made to the model to incorporate this change, detailed below:

On the "Dashboard" worksheet, the cell "dblCareUtil" has changed from determining whether caregiver utility will be included or excluded to a cell determining whether caregiver utility will be restricted to those <18; the text on the dashboard reflects this. Within the patient trace worksheets for the CFTRm treatments ("patient trace Sym", "patient trace Ork" and "patient trace Kaf") the formula in the CC column, containing caregiver utility calculations has been edited. Previously this formula contained a "Switch" calculation which would set the value to 0 if "dblCareUtil" was set to "No". This is replaced with a "Switch" calculation that will force the value of caregiver utility to be 0 if a patient is over 18 only if "dblCareUtil" is set to "Yes". An additional drop-down treatment profile has been added to the dashboard for Kaftrio ("committee preference + carerQoL <18") which includes the carer utility value in all age groups.

4.2.2 Updated Company base-case results

The Company provided a version of the EAG model with Company preferences applied. As previously noted the treatment utility benefit applied for ELX/TEZ/IVA used the value from IA1 rather than the submitted IA2. The EAG has amended this value for the Company's base case and re-ran the results, presented below:

Table 6. Company preferred base-case fully incremental analysis results

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
F/F							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management

Table 7. Company preferred base-case pairwise versus ECM results

Population	Absolute			Incremental			ICER (pairwise versus ECM)
	Costs	QALY	LY	Costs	QALY	LY	
F/F							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management

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

Addendum: additional cost-effectiveness scenario analyses results

December 2023

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135829.

1 Severity modifier

Severity modifier calculations based on committee preferences applied in the economic model are shown in Table 1. Results in this document provide the results of the F/RF population with both a severity modifier of 1.2 applied and no severity modifier, as requested by NICE.

Table 1. Severity modifier calculations with shortfall calculations estimated from Schnieder *et al.* 2021[18]

	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**

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

2 Company base case, cumulative ICERs

2.1 Fully incremental results

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – Company preferred costs							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – Scenario 1 + treatment utility benefit (ELX/TEZ/IVA and TEZ/IVA [RF only])							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							

ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 – Scenario 2 + no LT ELX/TEZ/IVA decline							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Scenario 3 + lifetime carer utility benefit							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 – Scenario 4 + 1.5% discount rate							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 – Scenario 5 + 1.7 severity modifier (Company base case)							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population as per the calculated severity modifier**

Abbreviations: ECM, established clinical management; ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LT, long-term; LUM/IVA, lumacaftor/ivacaftor; LY, life year; QALY, quality adjusted life year; TEZ/IVA, tezacaftor/ivacaftor

2.2 Pairwise (versus ECM) results

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – Company preferred costs							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – Scenario 1 + treatment utility benefit (ELX/TEZ/IVA and TEZ/IVA [RF only])							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							

ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 – Scenario 2 + no LT ELX/TEZ/IVA decline							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Scenario 3 + lifetime carer utility benefit							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 5 – Scenario 4 + 1.5% discount rate							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						
IVA/TEZ/ELX	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 6 – Scenario 5 + 1.7 severity modifier							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population as per the calculated severity modifier**

3 Additional combination scenario analyses

The tables below present the results of numerous combination scenario analyses. All results are provided with a 1.2 severity modifier applied, with results for the F/RF population also shown with no severity modifier applied.

3.1 Fully incremental results

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – Committee preferences + all EAG costs combined (40% reduction in health state and drug costs and 50% reduction PE costs), 100% ppFEV$_1$ decline, treatment utility benefit, carer utility benefit to 18 and 1.5% discount rate							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – Scenario 1 except with ELX/TEZ/IVA ppFEV$_1$ decline 77%							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 – Committee preferences + company drug costs, 100% ppFEV$_1$ decline, treatment utility benefit, carer utility benefit to 18 and 1.5% discount rate)							

F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Scenario 3 except with ELX/TEZ/IVA ppFEV$_1$ decline 77%							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 5 – Committee preferences + all EAG costs combined (40% reduction in health state and drug costs and 50% reduction PE costs)							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 6 – Scenario 5 + treatment utility benefit							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						

TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 – Company base-case except with a carer utility benefit applied up to 18 years old							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population**

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, established clinical management; ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LT, long-term; LUM/IVA, lumacaftor/ivacaftor; LY, life year; PE, pulmonary exacerbation; QALY, quality adjusted life year; TEZ/IVA, tezacaftor/ivacaftor

3.2 Pairwise (versus ECM) results

Population	Absolute			Incremental			ICER (versus ECM)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
IVA/TEZ/ELX	[redacted]						
Scenario 1 – Committee preferences + all EAG costs combined (40% reduction in health state and drug costs and 50% reduction PE costs), 100% ppFEV$_1$ decline, treatment utility benefit, carer utility benefit to 18 and 1.5% discount rate							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/Gating							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/RF*							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 2 – Scenario 1 except with ELX/TEZ/IVA ppFEV$_1$ decline 77%							
F/F genotype							
ECM	[redacted]						
LUM/IVA	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
F/MF							
ECM	[redacted]						
ELX/TEZ/IVA	[redacted]						

F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3- Committee preferences + company drug costs, 100% ppFEV$_1$ decline, treatment utility benefit, carer utility benefit to 18 and 1.5% discount rate							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Scenario 3 except with ELX/TEZ/IVA ppFEV$_1$ decline 77%							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							

ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 – Committee preferences + all EAG costs combined (40% reduction in health state and drug costs and 50% reduction PE costs)							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 – Scenario 5 + treatment utility benefit							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF*							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 – Company base-case except with a carer utility benefit applied up to 18 years old							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** No severity modifier applied in the F/RF population**

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; PE, pulmonary exacerbation; CFTR, cystic fibrosis transmembrane conductance regulator; LT, long-term

4 Results of EAG scenario analysis for F/RF population with 1.2 severity modifier

4.1 Fully incremental scenario analysis results (F/RF only)

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – No LT decline in ppFEV$_1$ for patients on ELX/TEZ/IVA							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – LUM/IVA ppFEV$_1$ LT decline 0%, TEZ/IVA ppFEV$_1$ decline 17.2%							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3- ELX/TEZ/IVA and TEZ/IVA (F/RF population) treatment specific utility benefit applied							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Carer utility benefit applied for ELX/TEZ/IVA patients up to age 18							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5 – 23% reduction in ECM drug costs on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6 – 40% reduction in ECM drug costs on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7 – 23% reduction in ECM drug costs and health state costs on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 8 – 40% reduction in ECM drug costs and health state costs on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9 – Reduction in PE costs of 50% for patients on CFTR modulators							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10 – 1.5% discount rate for costs and outcomes							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; PE, pulmonary exacerbation; CFTR, cystic fibrosis transmembrane conductance regulator; LT, long-term

4.2 Pairwise (versus ECM) scenario analysis results (F/RF only)

Population	Absolute			Incremental			ICER (fully incremental)
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 – No LT decline in $ppFEV_1$ for patients on ELX/TEZ/IVA							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 – LUM/IVA $ppFEV_1$ LT decline 0%, TEZ/IVA $ppFEV_1$ decline 17.2%							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 – ELX/TEZ/IVA and TEZ/IVA (F/RF population) treatment specific utility benefit applied							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 – Carer utility benefit applied for ELX/TEZ/IVA patients up to age 18							

ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 5 – 23% reduction in ECM drug costs on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 6 – 40% reduction in ECM drug costs on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 7 – 23% reduction in ECM drug costs and health state costs on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 8 – 40% reduction in ECM drug costs and health state costs on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 9 – Reduction in PE costs of 50% for patients on CFTR modulators							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						
Scenario 10 – 1.5% discount rate for costs and outcomes							
ECM	[redacted]						
TEZ/IVA	[redacted]						
ELX/TEZ/IVA	[redacted]						

Abbreviations: ED, extendedly dominated; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; LUM/IVA, lumacaftor/ivacaftor; TEZ/IVA, tezacaftor/ivacaftor; QALY, quality adjusted life year; LY, life year; ICER, incremental cost effectiveness ratio; ECM, established clinical management; PE, pulmonary exacerbation; CFTR, cystic fibrosis transmembrane conductance regulator; LT, long-term

ID3834 - Summary and explanation of final model & results based on Committee's preferred assumptions

This note does not represent acceptance of the committee's assumptions, rather an overview and explanation of the final model used as a basis for decision-making.

Following the second Appraisal Committee Meeting, NICE confirmed the Committee's preferred assumptions in communications with Vertex. While the majority of the assumptions could be directly implemented into the EAG cost effectiveness model (v6), some required a number of additional changes.

These were as follows:

- Caregiver utility: to be applied from birth to age 18. This required some reprogramming to the EAG CE model (v6)
- Inclusion of Ivacaftor monotherapy as a comparator

A summary of the deterministic cost-effectiveness results is shown in the table below. All ICERs shown include confidential PAS prices for LUM/IVA, TEZ/IVA and IVA/TEZ/ELX.

Table 1: PAS price used to generate ICERs

Product	Monthly (28-day) cost (list)	Annual cost (list)	Monthly (28-day) cost (PAS)	Annual cost (PAS)
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]
IVA/TEZ/ELX	£[redacted]	[redacted]	[redacted]	[redacted]
IVA (monotherapy)	£[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Fully incremental analysis with confidential PAS prices

F/F Cost-Effectiveness Results							
Treatment	**Absolute**			**Incremental**			**Incremental ICER**
	Costs	QALY	LY	Costs	QALY	LY	
ECM	[redacted]						
LUM/IVA							
TEZ/IVA							
IVA/TEZ/ELX							
F/Gating Cost-Effectiveness Results							
Treatment	**Absolute**			**Incremental**			**Incremental ICER**
	Costs	QALY	LY	Costs	QALY	LY	
ECM	[redacted]						
IVA							
IVA/TEZ/ELX							
F/MF Cost-Effectiveness Results							
Treatment	**Absolute**			**Incremental**			**Incremental ICER**

	Costs	QALY	LY	Costs	QALY	LY	
ECM	[redacted]						
IVA/TEZ/ELX							
F/RF Cost-Effectiveness Results							
Treatment	**Absolute**			**Incremental**			**Incremental ICER**
	Costs	QALY	LY	Costs	QALY	LY	
ECM	[redacted]						
TEZ/IVA							
IVA/TEZ/ELX							

1 APPRAISAL COMMITTEE PREFERRED ASSUMPTIONS (REQUIRING MODIFICATIONS TO THE MODEL)

1.1 Caregiver utility challenge

Following the second Appraisal Committee Meeting, NICE confirmed that a caregiver utility increment should be applied in the model ***up until the age of 18 (or under)***. However, the NICE EAG cost effectiveness model (v6) does not have the functionality to include a caregiver utility benefit up until the age of 18. The model can only apply caregiver utility benefits up until the age of 12 (or under), or for the lifetime. Vertex took the initiative to reprogram the NICE EAG model (v6) to allow for the inclusion of a caregiver utility benefit up until the age of 18 and accommodate the Committee's preferred base case.

A detail overview of the changes implemented in the model is provided in Appendix 2.

1.2 Data inputs for KLD and sources

The NICE committee agreed to include Ivacaftor monotherapy as a comparator in the NICE EAG model after the second Appraisal Committee Meeting.

The table below describes the IVA-specific efficacy inputs as used in the updated model. The data tables in the original submission where this information can be found are also listed in the source column for ease of reference. For data pertaining to patients aged 2-5, references to the original submission are not provided as this population was not included in the initial scope of this MTA.

Table 3: Data inputs for Ivacaftor (monotherapy)

Variable	Model Inputs		Source
	PBO-adjusted $ppFEV_1$ increment (95% CI)	Acute period duration (weeks)	
Acute increase in ppFEV1 by genotype and CFTRm for patients initiating treatment at age ≥12	[redacted]	8	(1) Table 87 in original submission
Acute increase in ppFEV1 by genotype and CFTRm for patients initiating treatment at age 6-11	10.0 (4.5 to 15.5)	48	(2) Table 88 in original submission
Acute increase in ppFEV1 by genotype and CFTRm for patients initiating treatment at age 2-5	10.0 (4.5 to 15.5)	48	Assumption

	Reduction in rate of ppFEV$_1$ decline relative to ECM alone		Source
Long-term reduction in rate of ppFEV1 decline for patients treated with CFTRm (aged ≥2 years)	47.1%		(3) Table 91 in original submission
	Calibrated PEx rate ratio		Source
PEx rate ratio in patients treated with CFTRm aged ≥12 years (uncalibrated and calibrated)	[redacted]		(4) Table 93 in original submission
	PBO-adjusted WFAZ increment (95% CI)	Acute period duration (weeks)	Source
Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age ≥12	[redacted]	8	[redacted] submission
Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age 6-11	[redacted]	48	[redacted] submission
Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age 2-5	[redacted]	24	(8)
	Acute period (weeks)	Annual rate (per pt-year)	Source
Annual treatment discontinuation rate in patients initiating CFTRm at age ≥12	48	0.081	(4) Table 104 in original submission
Annual treatment discontinuation rate in patients initiating CFTRm at age 6-11	48	0.000	(2) Table 105 in original submission
Annual treatment discontinuation rate in patients initiating CFTRm at age 2-5	24	0.065	(8)
	Post-acute period (weeks)	Annual rate (per pt-year)	Source
Annual treatment discontinuation rate in patients initiating CFTRm at age ≥12	96	0.036	(6) Table 104 in original submission
Annual treatment discontinuation rate in patients initiating CFTRm at age 6-11	96	0.043	(6) Table 105 in original submission
Annual treatment discontinuation rate in patients initiating CFTRm at age 2-5	84	0.019	(9)
	Compliance	Duration (weeks)	Source
Compliance during acute period for patients initiating CFTRm treatment at age ≥12	[redacted]	48	(7) Table 108 in original submission
Compliance during acute period for patients initiating CFTRm treatment at age 6-11	[redacted]	48	(5) Table 109 in original submission
Compliance during acute period for patients initiating CFTRm treatment at age 2-5	[redacted]	24	(8)

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, Established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; PBO, Placebo; PEx, Pulmonary Exacerbations; ppFEV1, Percentage of predicted FEV1; WFAZ, weight-for-age z-score

2 APPENDIX – MODEL CHANGE LOG

This section describes updates made by Vertex on the NICE EAG model (v6) which includes the following update:

1. Functionality to add caregiver utility up to age 18 year: NICE committee agreed to use caregiver treatment-specific utility increment for patients who are on IVA/TEZ/ELX treatment up until the age of 18 years.
2. Inclusion of Kalydeco as a comparator: Ivacaftor monotherapy was included as a comparator for F/gating patients based on the preferred inputs decided in the ACM 2.
3. PEx costs for CFTRm arm: Vertex identified that the calculation of PEx costs in the CFTRm arm are still estimated based on the total number of PEx events of the ECM arm leading to an overestimation of the disease management costs in the CFTRm arm.
4. Correction of the EAG fully incremental analysis calculator: misleading ICER formula for when treatments are dominant or dominated. When ICER is negative, the treatment can either be dominant over the comparator if the incremental costs are negative (savings on costs) or dominated if the incremental QALY is negative.

2.1 Caregiver utility up to age 18 years

Following the Second Appraisal Committee Meeting, NICE confirmed that a caregiver utility increment should be applied in the model up until the age of 18. See below for model changes.

Table 4: Change log of caregiver utility

Worksheet	Updates (Cell references refer to new column/rows added)	
Dashboard	"Caregiver utility applied to patients under age (years)*" (user to include age limit)	C27 label G27 user to include age limit, **currently set as 18 years of age** ***Note:*** *User must select "Yes" for "Caregiver utility" in cell G22*
"Patient trace Okb", cells CC6:CC130	EAG version	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, SWITCH(H6:H130,1,dblOrkFfgenAge1CareUtilUsed,2,dblOrkFfgenAge2CareUtilUsed,dblOrkFfgenAge3CareUtilUsed),0),0)))
	Vertex adaptation	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, **IF(F6:F130<Dashboard!$G$27,** SWITCH(H6:H130,1,dblOrkFfgenAge1CareUtilUsed,2,dblOrkFfgenAge2CareUtilUsed, dblOrkFfgenAge3CareUtilUsed),**0)**,0),0)))
"Patient trace Sym", cells CC6:CC130	EAG version	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, SWITCH(H6:H130,1,dblSymFfgenAge1CareUtilUsed,2,dblSymFfgenAge2CareUtilUsed,dblSymFfgenAge3CareUtilUsed),0),0))

Worksheet	Updates (Cell references refer to new column/rows added)	
	Vertex adaptation	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, **IF(F6:F130<Dashboard!$G$27,** SWITCH(H6:H130,1,dblSymFfgenAge1CareUtilUsed,2,dblSymFfgenAge2CareUtilUsed, dblSymFfgenAge3CareUtilUsed)**,0)**,0),0))
"Patient trace Sym", cells CC133:CC257	EAG version	=(C133:C257/365.25)*(A133:A257<=dblTimeHorizon-BY132)*SWITCH(BY133:BY257,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L133:L257,1, SWITCH(H133:H257,1,dblSymFrfgenAge1CareUtilUsed,2,dblSymFrfgenAge2CareUtilUsed,dblSymFrfgenAge3CareUtilUsed),0),0))
	Vertex adaptation	=(C133:C257/365.25)*(A133:A257<=dblTimeHorizon-BY132)*SWITCH(BY133:BY257,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L133:L257,1, **IF(F6:F130<Dashboard!$G$27,** SWITCH(H133:H257,1,dblSymFrfgenAge1CareUtilUsed,2,dblSymFrfgenAge2CareUtilUsed,dblSymFrfgenAge3CareUtilUsed)**,0)**,0),0))
"Patient trace KLD", cells CC6:CC130	EAG version	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, SWITCH(H6:H130,1,dblKLDFgatAge1CareUtilUsed,2,dblKLDFgatAge2CareUtilUsed,dblKLDFgatAge3CareUtilUsed),0),0))
	Vertex adaptation	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, **IF(F6:F130<Dashboard!$G$27,** SWITCH(H6:H130,1,dblKLDFgatAge1CareUtilUsed,2,dblKLDFgatAge2CareUtilUsed, dblKLDFgatAge3CareUtilUsed)**,0)**,0),0))
"Patient trace Kaf", cells CC6:CC130	EAG version	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, SWITCH(H6:H130,1,dblKafFfgenAge1CareUtilUsed,2,dblKafFfgenAge2CareUtilUsed,dblKafFfgenAge3CareUtilUsed),0),0)))
	Vertex adaptation	=(C6:C130/365.25)*(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(BY6:BY130,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L6:L130,1, **IF(F6:F130<Dashboard!$G$27,** SWITCH(H6:H130,1,dblKafFfgenAge1CareUtilUsed,2,dblKafFfgenAge2CareUtilUsed, dblKafFfgenAge3CareUtilUsed)**,0)**,0),0)))
"Patient trace Kaf", cells CC133:CC257	EAG version	=(C133:C257/365.25)*(A133:A257<=dblTimeHorizon-BY132)*SWITCH(BY133:BY257,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L133:L257,1, SWITCH(H133:H257,1,dblKafFrfgenAge1CareUtilUsed,2,dblKafFrfgenAge2CareUtilUsed,dblKafFrfgenAge3CareUtilUsed),0),0))
	Vertex adaptation	=(C133:C257/365.25)*(A133:A257<=dblTimeHorizon-BY132)*SWITCH(BY133:BY257,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L133:L257,1,**IF(F133:F257<Dashboard!$G$27,**

Worksheet	Updates (Cell references refer to new column/rows added)	
		SWITCH(H133:H257,1,dblKafFrfgenAge1CareUtilUsed,2,dblKafFrfgenAge2CareUtilUsed, dblKafFrfgenAge3CareUtilUsed),0),0),0))
"Patient trace Kaf", cells CC260:CC384	EAG version	=(C260:C384/365.25)*(A260:A384<=dblTimeHorizon-BY259)*SWITCH(BY260:BY384,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L260:L384,1, SWITCH(H260:H384,1,dblKafFmfgenAge1CareUtilUsed,2,dblKafFmfgenAge2CareUtilUsed,dblKafFmfgenAge3CareUtilUsed),0),0))
	Vertex adaptation	=(C260:C384/365.25)*(A260:A384<=dblTimeHorizon-BY259)*SWITCH(BY260:BY384,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L260:L384,1, **IF(F260:F384<Dashboard!$G$27,** SWITCH(H260:H384,1,dblKafFmfgenAge1CareUtilUsed,2,dblKafFmfgenAge2CareUtilUsed,dblKafFmfgenAge3CareUtilUsed),**0)**,0),0))
"Patient trace Kaf", cells CC387:CC511	EAG version	=(C387:C511/365.25)*(A387:A511<=dblTimeHorizon-BY386)*SWITCH(BY387:BY511,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L387:L511,1, SWITCH(H387:H511,1,dblKafFgatgenAge1CareUtilUsed,2,dblKafFgatgenAge2CareUtilUsed,dblKafFgatgenAge3CareUtilUsed),0),0))
	Vertex adaptation	=(C387:C511/365.25)*(A387:A511<=dblTimeHorizon-BY386)*SWITCH(BY387:BY511,0,0,SWITCH(dblCareUtil,"Yes",SWITCH(L387:L511,1,**IF(F387:F511<Dashboard!$G$27,** SWITCH(H387:H511,1,dblKafFgatgenAge1CareUtilUsed,2,dblKafFgatgenAge2CareUtilUsed,dblKafFgatgenAge3CareUtilUsed),**0)**,0),0))

2.2 KLD (IVA) update to NICE EAG model v6 with above corrections

The NICE committee agreed to include Ivacaftor monotherapy as a comparator in the NICE EAG model after the second Appraisal Committee Meeting. See below description of changes:

Table 5: Change log of including IVA in the EAG model

Worksheet	Updates (Cell references refer to new column/rows added)	
Cover page	KLD noted in comparators	C5
Dashboard	IVA costs (variable for IVA use in combinations e.g. LUM/IVA,. And a variable for use in monotherapy i.e. KLD)	L16:R17 for IVA price in combo. L18:R19 for IVA price in monotherapy
	KLD (IVA) selected comparator in F/Gating	E51:G51

Worksheet	Updates (Cell references refer to new column/rows added)	
	Treatment profile option for KLD	N74
Data Library	KLD specific inputs	Rows 15 for loaded profile. Rows 1180 to 1328 for inputs
Deterministic results	KLD results in F/Gating	Column C to H rows 20; 37; 54; 71 for results. W15:AE15; AH13:AO15 for fully incremental results. Column W to AC for graphs
DSA results	KLD results in F/Gating	Column H to K for IVA. All other result formulas in sheet updated for new offsets in lookup ranges in results sheet
Probabilistic results	KLD results in F/Gating	C20:K20
results	KLD deterministic results in F/Gating	C32:J32 for summary. C63:I63; C93:L93; M97:M203 for summary breakdown
	KLD probabilistic results in F/Gating	Q32:X32
	KLD DSA results in F/Gating	Z35:AC37. Column AE to AK updated to include KLD input variables. Column BS to BU; DC to DE for upper lower results. Column GY to ID for incremental results with KLD
Probabilistic output	KLD probabilistic iterations result in F/Gating	Row 35 to 37
Deterministic output	KLD per patient results in F/Gating	Row 189 to 205; 223; 232; 238; 244
Patient trace ECM	KLD on treatment calculations	Column CR
Patient trace KLD	KLD engine	Entire sheet. Based on formulas for Kaftrio F/Gating engine but adjusted to KLD inputs e.g. “dblKLDFgat” used in formula named ranges instead of “dblKafFgat”
Lists	KLD assignment to F/Gating	E3:E8
	KLD min age	E9
	Dropdown for F/Gating comparators	K3:K6
	Profile names for KLD scenarios	Column W
VBA	Run_Analysis module	Updated L variable to max at 36 to include KLD in DSA
	RunModel module	Added range for KLD output and code to update KLD engine in calculation, signified by “KLD update” in code comments

2.3 PEx costs for CFTRm arm

In the NICE EAG model version 6.0, Vertex identified that the calculation of PEx costs in the CFTRm arm are estimated based on the total number of PEx events of the ECM arm. Therefore, cost calculations in the CFTRm arm were updated to link to each appropriate worksheet. See below description of each change.

Table 6: Change log of PEx costs for CFTRm arm

Worksheet	Corrections	
"Patient trace Okb", cells CG6:CG130	EAG version	=(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)), SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)*dblCostEcmFev40PexUsed*[redacted]IF(P6:P130<70,dblCostEcmFev70_40Used+(365.25/C6:C130)*dblCostEcmFev70[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*dblCostEcmFev70PexUsed*[redacted])*(C6:C130/365.25))))
	Vertex correction	=(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)), SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)*dblCostEcmFev40PexUsed*[redacted]F(P6:P130<70,dblCostEcmFev70_40Used+(365.25/C6:C130)*dblCostEcmFev70_40PexUsed*[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*dblCostEcmFev70PexUsed*[redacted])*(C6:C130/365.25))))
"Patient trace Sym", cells CG6:CG130	EAG version	=(A6:A130<=dblTimeHorizon-BY5)*SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)), SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)*[redacted],IF(P6:P130<70,dblCostEcmFev70_40Used+(365.25/C6:C130)*dblCostEcmFev70[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*[redacted]C6:C130/365.25)))
	Vertex correction	=(A6:A130<=dblTimeHorizon-BY5)*SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)),

Worksheet	Corrections	
		SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)*dblCostEcmFev40PexUsed*[redacted],IF(P6:P130<70,dblCostEcmFev70_40Used+(365.25/C6:C130)*dblCostEcmFev70_40PexUsed*[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*dblCostEcmFev70PexUsed[redacted])*(C6:C130/365.25)))
"Patient trace Sym", cells CG133:CG257	EAG version	=(A133:A257<=dblTimeHorizon-BY132)*(SWITCH(L133:L257, 1, SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostCftrmFev40Used+(365.25/C133:C257)*dblCostCftrmFev40PexUsed*AJ133:AJ257,IF(P133:P257<70,dblCostCftrmFev70_40Used+(365.25/C133:C257)*dblCostCftrmFev70_40PexUsed*AJ133:AJ257,dblCostCftrmFev70Used+(365.25/C133:C257)*dblCostCftrmFev70PexUsed*AJ133:AJ257))*(C133:C257/365.25)), SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostEcmFev40Used+(365.25/C133:C257)*dblCostEcmFev40PexUsed*[redacted]40Used+(365.25/C133:C257)*dblCostEcmFev70_40PexUsed*[redacted]dblCostEcmFev70Used+(365.25/C133:C257)*dblCostEcmFev70PexUsed*[redacted])*(C133:C257/365.25))))
	Vertex correction	=(A133:A257<=dblTimeHorizon-BY132)*(SWITCH(L133:L257, 1, SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostCftrmFev40Used+(365.25/C133:C257)*dblCostCftrmFev40PexUsed*AJ133:AJ257,IF(P133:P257<70,dblCostCftrmFev70_40Used+(365.25/C133:C257)*dblCostCftrmFev70_40PexUsed*AJ133:AJ257,dblCostCftrmFev70Used+(365.25/C133:C257)*dblCostCftrmFev70PexUsed*AJ133:AJ257))*(C133:C257/365.25)), SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostEcmFev40Used+(365.25/C133:C257)*dblCostEcmFev40PexUsed[redacted],IF(P133:P257<70,dblCostEcmFev70_40Used+(365.25/C133:C257)*dblCostEcmFev70_40PexUsed*[redacted],dblCostEcmFev70Used+(365.25/C133:C257)*dblCostEcmFev70PexUsed*[redacted]*(C133:C257/365.25))))
"Patient trace Kaf", cells CG6:CG130	EAG version	=(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)), SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)[redacted],IF(P6:P130<70,dblCostEcmFev70_40Used+(365.25/C6:C130)*dblCostEcmFev70[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*[redacted]))*(C6:C130/365.25))))
	Vertex correction	=(A6:A130<=dblTimeHorizon-BY5)*(SWITCH(L6:L130, 1, SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostCftrmFev40Used+(365.25/C6:C130)*dblCostCftrmFev40PexUsed*AJ6:AJ130,IF(P6:P130<70,dblCostCftrmFev70_40Used+(365.25/C6:C130)*dblCostCftrmFev70_40PexUsed*AJ6:AJ130,dblCostCftrmFev70Used+(365.25/C6:C130)*dblCostCftrmFev70PexUsed*AJ6:AJ130))*(C6:C130/365.25)), SWITCH(BY6:BY130,0,0,IF(P6:P130<40,dblCostEcmFev40Used+(365.25/C6:C130)*dblCostEcmFev40PexUsed[redacted],IF(P6:P130<70,dblCostEcmFev70_40Used+

Worksheet	Corrections	
		(365.25/C6:C130)*dblCostEcmFev70_40PexUsed[redacted],dblCostEcmFev70Used+(365.25/C6:C130)*dblCostEcmFev70PexUsed*[redacted])*(C6:C130/365.25))))
"Patient trace Kaf", cells CG133:CG257	EAG version	=(A133:A257<=dblTimeHorizon-BY132)*(SWITCH(L133:L257, 1, SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostCftrmFev40Used+(365.25/C133:C257)*dblCostCftrmFev40PexUsed*AJ133:AJ257,IF(P133:P257<70,dblCostCftrmFev70_40Used+(365.25/C133:C257)*dblCostCftrmFev70_40PexUsed*AJ133:AJ257,dblCostCftrmFev70Used+(365.25/C133:C257)*dblCostCftrmFev70PexUsed*AJ133:AJ257))*(C133:C257/365.25)), SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostEcmFev40Used+(365.25/C133:C257)[redacted] F(P133:P257<70,dblCostEcmFev70_40Used+(365.25/C133:C257)*dblCostEcmFev70_[redacted],dblCostEcmFev70Used+(365.25/C133:C257)*[redacted]))*(C133:C257/365.25))))
	Vertex correction	=(A133:A257<=dblTimeHorizon-BY132)*(SWITCH(L133:L257, 1, SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostCftrmFev40Used+(365.25/C133:C257)*dblCostCftrmFev40PexUsed*AJ133:AJ257,IF(P133:P257<70,dblCostCftrmFev70_40Used+(365.25/C133:C257)*dblCostCftrmFev70_40PexUsed*AJ133:AJ257,dblCostCftrmFev70Used+(365.25/C133:C257)*dblCostCftrmFev70PexUsed*AJ133:AJ257))*(C133:C257/365.25)), SWITCH(BY133:BY257,0,0,IF(P133:P257<40,dblCostEcmFev40Used+(365.25/C133:C257)*dblCostEcmFev40PexUsed*[redacted],IF(P133:P257<70,dblCostEcmFev70_40Used+(365.25/C133:C257)*dblCostEcmFev70_40PexUsed[redacted]dblCostEcmFev70Used+(365.25/C133:C257)*dblCostEcmFev70PexUsed*[redacted])*(C133:C257/365.25))))
"Patient trace Kaf", cells CG260:CG384	EAG version	=(A260:A384<=dblTimeHorizon-BY259)*SWITCH(L260:L384, 1, SWITCH(BY260:BY384,0,0,IF(P260:P384<40,dblCostCftrmFev40Used+(365.25/C260:C384)*dblCostCftrmFev40PexUsed*AJ260:AJ384,IF(P260:P384<70,dblCostCftrmFev70_40Used+(365.25/C260:C384)*dblCostCftrmFev70_40PexUsed*AJ260:AJ384,dblCostCftrmFev70Used+(365.25/C260:C384)*dblCostCftrmFev70PexUsed*AJ260:AJ384))*(C260:C384/365.25)), SWITCH(BY260:BY384,0,0,IF(P260:P384<40,dblCostEcmFev40Used+(365.25/C260:C384)[redacted] F(P260:P384<70,dblCostEcmFev70_40Used+(365.25/C260:C384)*dblCostEcmFev70_[redacted],dblCostEcmFev70Used+(365.25/C260:C384)*[redacted]))*(C260:C384/365.25)))
	Vertex correction	=(A260:A384<=dblTimeHorizon-BY259)*SWITCH(L260:L384, 1, SWITCH(BY260:BY384,0,0,IF(P260:P384<40,dblCostCftrmFev40Used+(365.25/C260:C384)*dblCostCftrmFev40PexUsed*AJ260:AJ384,IF(P260:P384<70,dblCostCftrmFev70_40Used+(365.25/C260:C384)*dblCostCftrmFev70_40PexUsed*AJ260:AJ384,dblCostCftrmFev70Used+(365.25/C260:C384)*dblCostCftrmFev70PexUsed*AJ260:AJ384))*(C260:C384/365.25)), SWITCH(BY260:BY384,0,0,IF(P260:P384<40,dblCostEcmFev40Used+(365.25/C260:C384)*dblCostEcmFev40PexUsed*[redacted],IF(P260:P384<70,dblCostEcmFev70_40Used+(365.25/C260:C384)*dblCostEcmFev70_40PexUsed[redacted],dblCostEcmFev70Used+(365.25/C260:C384)*dblCostEcmFev70PexUsed*[redacted]))*(C260:C384/365.25)))

Worksheet	Corrections	
"Patient trace Kaf", cells CG387:CG511	EAG version	=(A387:A511<=dblTimeHorizon-BY386)*SWITCH(L387:L511, 1, SWITCH(BY387:BY511,0,0,IF(P387:P511<40,dblCostCftrmFev40Used+(365.25/C387:C511)*dblCostCftrmFev40PexUsed*AJ387:AJ511,IF(P387:P511<70,dblCostCftrmFev70_40Used+(365.25/C387:C511)*dblCostCftrmFev70_40PexUsed*AJ387:AJ511,dblCostCftrmFev70Used+(365.25/C387:C511)*dblCostCftrmFev70PexUsed*AJ387:AJ511))*(C387:C511/365.25)), SWITCH(BY387:BY511,0,0,IF(P387:P511<40,dblCostEcmFev40Used+(365.25/C387:C511)*dblCostEcmFev40PexUsed*[redacted],IF(P387:P511<70,dblCostEcmFev70_40Used+(365.25/C387:C511)*dblCostEcmFev70_[redacted],dblCostEcmFev70Used+(365.25/C387:C511)*[redacted]))*(C387:C511/365.25)))
	Vertex correction	=(A387:A511<=dblTimeHorizon-BY386)*SWITCH(L387:L511, 1, SWITCH(BY387:BY511,0,0,IF(P387:P511<40,dblCostCftrmFev40Used+(365.25/C387:C511)*dblCostCftrmFev40PexUsed*AJ387:AJ511,IF(P387:P511<70,dblCostCftrmFev70_40Used+(365.25/C387:C511)*dblCostCftrmFev70_40PexUsed*AJ387:AJ511,dblCostCftrmFev70Used+(365.25/C387:C511)*dblCostCftrmFev70PexUsed*AJ387:AJ511))*(C387:C511/365.25)), SWITCH(BY387:BY511,0,0,IF(P387:P511<40,dblCostEcmFev40Used+(365.25/C387:C511)*dblCostEcmFev40PexUsed*[redacted],IF(P387:P511<70,dblCostEcmFev70_40Used+(365.25/C387:C511)*dblCostEcmFev70_40PexUsed[redacted],dblCostEcmFev70Used+(365.25/C387:C511)*dblCostEcmFev70PexUsed*[redacted]))*(C387:C511/365.25)))

2.4 Correction EAG fully incremental analysis calculation

Table 7: Correction EAG fully incremental analysis calculation

Worksheet	Updates (Cell references refer to new column/rows added)	
Deterministic results, cells AO6:AO19	Amended misleading formula to evaluate if treatment is dominant or dominated by the comparator	Changed cells AO6:AO8, AO11, AO14:AO15 and AO18:AO19. Below is an example of the change: Cells AO6: EAG version: =IF(AL6/AM6>0,AL6/AM6,"Dominated") Vertex correction =IF(AL6/AM6>0,AL6/AM6,IF(AL6<0,"Dominant","Dominated"))

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BMJ TAG

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID384]

EAG response to Company summary and explanation of final model & results based on Committee's preferred assumptions

January 2024

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135829.

1 Introduction

The evidence assessment group (EAG) received an updated EAG model in which the Company implemented the Committee's preferred assumptions following appraisal committee meeting 2 (ACM2), including the inclusion of ivacaftor monotherapy as a comparator in the F/Gating population. Here, the EAG provides a brief validation of the Company's additions to the model and a critique of the assumptions used for ivacaftor monotherapy in the model. Overall, the EAG is satisfied that the Company amendments are implemented correctly, and that the data and assumptions used for ivacaftor monotherapy are reasonable, and consistent with the approaches preferred by Committee for ELX/TEZ/IVA, TEZ/IVA and LUM/IVA.

1.1 Model amendments

The EAG notes that the implementation of ivacaftor as a comparator was conducted in an earlier version of the EAG model and not the version used for decision making at ACM2. Therefore, the corrections noted by the company (Issue 2.1 and 2.3 in the Company summary document) had already been addressed prior to ACM2. The EAG observed a number of discrepancies between the ICERs estimated in the Company's adjusted model implementing the Committee's preferences compared to the EAG's latest model. Therefore, the EAG made the following amendments to the model inputs in the Company's amended version of the model:

1. Applying the 40% reduction in health state costs for patients on CFTRms. This was only applied to the concomitant drug costs in the Company's amended model.
2. The EAG model had used a compliance rate of [redacted] for ELX/TEZ/IVA F/F population age 12+. The Company had used a value of [redacted] in their updated version of the model which the EAG notes is the correct value, in line with the inputs reported in the EAG report. Therefore, the EAG notes that this is the correct version to be used in the model.
3. Caregiver disutility value of [redacted] as per the value considered during ACM1/2 by Committee members. The Company has used a value of [redacted] for the caregiver disutility, however the EAG was not provided with any further details on the source of this alternative value. As such, the EAG has continued to use [redacted]

1.2 Model validation

Due to time constraints the EAG was not able to add ivacaftor monotherapy as an additional comparator into their latest version of the model. Therefore, as per the request of NICE, the EAG undertook validation of the addition of ivacaftor monotherapy as a comparator for the F/gating population undertaken by the Company. The EAG was satisfied that the implementation of the additional ivacaftor arm into the model had been done correctly for deterministic model results. A number of checks were conducted in order to validate the implementation, including but not limited to:

- Searching for references to other treatments in the trace;
- Attempting to run deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA), both do not appear to be functional;
- Running upper and lower bounds for all ivacaftor inputs and ensuring cost, quality adjusted life years (QALYs) and life years (LYs) results appear valid compared to the base case;
- Matching profiles to the EAG model and comparing results;
- Checking the implementation of caregiver utility age limit.

The EAG also reviewed the inputs used by the company to inform the ivacaftor monotherapy arm. The EAG's review is provided in Table 1.

Variable	Model Inputs		EAG comment
	PBO-adjusted ppFEV$_1$ increment (95% CI)	Acute period duration (weeks)	
Acute increase in ppFEV$_1$ by genotype and CFTRm for patients initiating treatment at age ≥12	[redacted]	8	Appropriate. In-line with Company pooled IVA vs PBO effect estimate (Table 68 of original CS) and EAG fixed effects NMA (Table 41 of the EAG report)
Acute increase in ppFEV$_1$ by genotype and CFTRm for patients initiating treatment at age 6-11	10.0 (4.5 to 15.5)	48	Appropriate, direct trial estimate from Davies 2013.[1] The EAG considers the estimate to be at a small risk of bias due to being observed in patients with at least one *G551D* mutation, but not specifically with an *F508del*/*G551D* genotype. However, the EAG notes that in Davies 2013, [redacted] of patients had an F508del mutation on the second allele, and so the magnitude of any bias is expected to be low. The EAG considers that the 10.0 treatment effect estimate is at risk of overestimating the treatment effect that would have been observed for eligible patients with an *R117H* mutation, which is associated with a milder CF phenotype than the *G551D* mutation. However, the EAG notes that most modelled patient profiles in the 6 to 11 years age group are from F/*G551D* individuals, and therefore the 10.0 treatment effect estimate is reasonable.
Acute increase in ppFEV1 by genotype and CFTRm for patients initiating treatment at age 2-5	10.0 (4.5 to 15.5)	48	Appropriate. The assumption is consistent with the Company and EAG approach of applying data from the 6 to 11 years age group when data were not available for the 2 to 5 years age group.
	Reduction in rate of ppFEV$_1$ decline relative to ECM alone		EAG comment

Long-term reduction in rate of ppFEV1 decline for patients treated with CFTRm (aged ≥2 years)	47.1%	Appropriate, propensity-score matched analysis of clinical trial data (ivacaftor-treated *G551D* patients) to US CFFPR F/F patients from Sawicki 2015.[2] The EAG notes the Company's approach in using clinical trial data matched to registry-based data is consistent with the approach preferred by the Committee at ACM1 and ACM2 for LUM/IVA and TEZ/IVA. The EAG has previously outlined how such analyses are at high risk of bias due to residual confounding and an inadequate removing the acute treatment effects, but the EAG does not consider the overall risk of bias to be substantially elevated in the IVA analysis relative to the committee preferred LUM/IVA or TEZ/IVA analyses. The methods of IVA analysis differed from the LUM/IVA and TEZ/IVA analyses in two important ways: • In the IVA analysis, $ppFEV_1$ measurements taken 30 days following treatment initiation were excluded to remove the acute treatment effect, whereas this was 23 days in the LUM/IVA analysis and 24 days in the TEZ/IVA analysis. The EAG considers the approach in the IVA analysis to be more appropriate than that in the LUM/IVA and TEZ/IVA analyses. • The IVA analysis matched patients with at least one *G551D* mutation treated with ivacaftor to a contemporaneous cohort of *F508del* homozygous patients, under the assumption that these patients have similar clinical phenotypes. The EAG accepts that, due to the rapid uptake of IVA monotherapy for eligible patients, matching to a larger cohort of non-*G551D* patients was necessary to construct an untreated contemporaneous cohort, although the EAG notes this elevates the risk of residual confounding in the analysis. As noted for the acute treatment effect applied for the 6 to 11 years population, the EAG notes that estimates from a cohort of patients with at least one *G551D* population may not be fully representative of the population relevant to current appraisal, i.e., all F/Gating or F/*R117H* patients who would also be eligible for ELX/TEZ/IVA. However, the EAG does not expect the magnitude of this bias to be large, and notes that most modelled patient profiles are from F/*G551D* individuals.

			The EAG notes that the 47.1% reduction in ppFEV$_1$ decline for IVA in the F/Gating is smaller than the 61.5% modelled for TEZ/IVA and similar to the 42.0% modelled for LUM/IVA. Based on the EAG's original preferred analyses for LUM/IVA and TEZ/IVA, the EAG considers it surprising that the IVA estimate within the F/Gating genotype is not larger than the estimates for LUM/IVA and TEZ/IVA in the F/F genotypes. The EAG considers this likely attributable to an overestimate of the long-term effects of LUM/IVA and TEZ/IVA, which the EAG has previously highlighted. The EAG notes an alternative, UK registry-based analysis of the long-term impact of IVA on the rate of ppFEV$_1$ decline is available from Newsome *et al.*,[3, 4] which was highlighted in the EAG report. However, the EAG considers the current analysis presented by the Company to be more consistent with the LUM/IVA, TEZ/IVA and ELX/TEZ/IVA analyses preferred by the Committee following ACM2.
	Calibrated PEx rate ratio		EAG comment
PEx rate ratio in patients treated with CFTRm aged ≥12 years (uncalibrated and calibrated)	[redacted]		Appropriate. Direct trial estimate from Ramsey 2011 in IVA-treated patients with a *G551D* mutation through Week 24.[5] The EAG notes this estimate is more optimistic than the Week 48 estimate from the same publication, but using the Week 24 estimate is aligned with the primary endpoint of the trial, and with the time point used for ELX/TEZ/IVA in the same genotype, which the EAG considers appropriate. The EAG notes that two other trials, including non *G551D* mutations, contributed to the NMA for the acute treatment effect for IVA in the F/Gating population, but that PEx were not reported as an efficacy outcome in De Boeck 2014[6] and, although PEx were reported as a tertiary outcome in Moss 2015, a rate ratio was not reported, and the event rates were likely too low for a meaningful analysis.[7]
	PBO-adjusted WFAZ increment (95% CI)	Acute period duration (weeks)	EAG comment

Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age ≥12	[redacted]	8	Appropriate. Direct trial evidence from three IVA trials used in the company and EAG NMAs,[5-7] which may be conservative given the short follow-up period.
Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age 6-11	[redacted]	48	Appropriate. Direct trial evidence from Davies 2013.[1]
Acute increase in WFAZ by genotype and CFTRm for patients initiating treatment at age 2-5	[redacted]	24	Appropriate. Direct trial evidence from Davies 2016,[8] although the EAG notes this was a single-armed uncontrolled study. The EAG notes the effect estimate and standard deviation, 0.2 (0.3), are openly available from the trial publication.
	Acute period (weeks)	Annual rate (per pt-year)	EAG comment
Annual treatment discontinuation rate in patients initiating CFTRm at age ≥12	48	[redacted]	Appropriate. Calculated based on trial evidence from Ramsey 2011.[5] May be conservative as discontinuation includes [redacted]
Annual treatment discontinuation rate in patients initiating CFTRm at age 6-11	48	0.000	Appropriate. Calculated based on trial evidence from Davies 2013[1]
Annual treatment discontinuation rate in patients initiating CFTRm at age 2-5	24	0.065	Appropriate. Calculated based on trial evidence from Davies 2016[8]
	Post-acute period (weeks)	Annual rate (per pt-year)	EAG comment
Annual treatment discontinuation rate in patients initiating CFTRm at age ≥12	96	0.036	Appropriate. Calculated based on trial evidence from McKone 2014[9]

Annual treatment discontinuation rate in patients initiating CFTRm at age 6-11	96	0.043	Appropriate. Calculated based on trial evidence from McKone 2014[9]
Annual treatment discontinuation rate in patients initiating CFTRm at age 2-5	84	0.019	Appropriate. Based on clinical trial data from Rosenfield 2019.[10] The EAG notes that the report records 5 discontinuations; however, 2 of these were due to switching to commercial ivacaftor, 1 due to difficulty swallowing the tablet and one withdrawal due to inability to tolerate blood tests. Therefore only 1 discontinuation due to adverse events was included
	Compliance	Duration (weeks)	EAG comment
Compliance during acute period for patients initiating CFTRm treatment at age ≥12	[redacted]	48	Appropriate. Direct trial evidence available from the CSR for study 770-102
Compliance during acute period for patients initiating CFTRm treatment at age 6-11	[redacted]	48	Appropriate. Direct trial evidence in the CSR for study 770-103
Compliance during acute period for patients initiating CFTRm treatment at age 2-5	[redacted]	24	The EAG did not have access to the CSR to validate this number and could not identify it in the referenced study. However, the EAG notes that it is line with estimates for other treatments used in younger age groups

Abbreviations: ACM, appraisal committee meeting; CFTR, cystic fibrosis transmembrane conductance regulator; CS, company submission; CSR, clinical study report; EAG, external assessment group; ECM, established clinical management; IVA, ivacaftor; IVA/TEZ/ELX, ivacaftor/tezacaftor/elexacaftor and ivacaftor; NMA, network meta-analysis; PBO, Placebo; PEx, Pulmonary Exacerbations; ppFEV1, Percentage of predicted FEV1; WFAZ, weight-for-age z-score

1.3 Updated ICERs following model amendments and inclusion of IVA monotherapy

1.3.1 Pairwise versus ECM

Population	Absolute			Incremental			ICER
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LY, life year; QALY, quality adjusted life year; TEZ/IVA, tezacaftor/ivacaftor

1.3.2 Incremental ICERs versus previous treatment

The EAG notes that in the presentation of the incremental results for the F/Gating population, the Company had not sorted treatments in terms of ascending costs, as is required for fully incremental analysis. Therefore, the EAG made this amendment in the presentation of their results, as shown below in Section 1.3.2 and 1.3.3.

Population	Absolute			Incremental			ICER
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LY, life year; QALY, quality adjusted life year; TEZ/IVA, tezacaftor/ivacaftor

1.3.3 Fully incremental ICERs with dominated/extendedly dominated treatments removed

Population	Absolute			Incremental			ICER
	Costs	QALY	LY	Costs	QALY	LY	
Committee preferences							
F/F genotype							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUM/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/MF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F/Gating							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F/RF							
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELX/TEZ/IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor; ICER, incremental cost effectiveness ratio; LUM/IVA, lumacaftor/ivacaftor; LY, life year; QALY, quality adjusted life year; TEZ/IVA, tezacaftor/ivacaftor

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