NICE National Institute for Health and Care Excellence

NICE guidance

Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation

Technology appraisal guidance

Published: 27 July 2016
www.nice.org.uk/guidance/ta398

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Lumacaftor–ivacaftor is not recommended, within its marketing authorisation, for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

1.2 This guidance is not intended to affect the position of patients whose treatment with lumacaftor–ivacaftor was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or the child or young person's parents or carers.

2 The technology

2.1 Lumacaftor–ivacaftor (Orkambi, Vertex Pharmaceuticals) is a systemic protein modulator. Lumacaftor is a corrector of the cystic fibrosis transmembrane conductance regulator (CFTR) and ivacaftor is a potentiator of the CFTR. Lumacaftor–ivacaftor has a marketing authorisation in the UK for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation (that is, have 2 copies of the mutation) in the CFTR gene. The recommended dose is 2 tablets (each tablet contains 200 mg lumacaftor and 125 mg ivacaftor) taken orally every 12 hours (a total daily dose of 800 mg lumacaftor and 500 mg ivacaftor).

2.2 The summary of product characteristics lists the following very common adverse reactions for lumacaftor–ivacaftor: abdominal pain, bacteria in sputum, diarrhoea, dizziness, dyspnoea, headache, nasal congestion, nasopharyngitis and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of lumacaftor–ivacaftor is £8,000 per 112-tablet pack (excluding VAT; company's evidence submission). The cost of a 1-year course of treatment is £104,000 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 5) considered evidence submitted by Vertex Pharmaceuticals and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company did a systematic review of the literature to identify studies on the clinical effectiveness and safety of lumacaftor–ivacaftor for treating cystic fibrosis in people who are homozygous for the F508del mutation. It identified 2 phase III randomised controlled trials, TRAFFIC and TRANSPORT, and 1 ongoing extension study, PROGRESS.

3.2 TRAFFIC and TRANSPORT were international multicentre (including 5 UK centres) double-blind, phase III placebo-controlled trials in people 12 years and over with cystic fibrosis who are homozygous for the F508del mutation. People were randomised in a 1:1:1 ratio to:

- lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily (TRAFFIC, n=183; TRANSPORT, n=185)
- a fixed-dose combination of lumacaftor 400 mg–ivacaftor 250 mg twice daily (TRAFFIC, n=182; TRANSPORT, n=187) or
- placebo (TRAFFIC, n=184; TRANSPORT, n=187).

People continued to have their usual cystic fibrosis management (standard of care) in all trial arms. In both TRAFFIC and TRANSPORT, people had treatment for 24 weeks and were then enrolled into the 96-week PROGRESS extension study if they completed treatment. Patients stopped treatment if they could not tolerate the study drug. For lumacaftor–ivacaftor, only data relating to the licensed dosage (fixed-dose combination of lumacaftor 400 mg–ivacaftor 250 mg twice daily) were presented in the company's submission.

3.3 People were eligible for TRAFFIC and TRANSPORT if they had a confirmed diagnosis of cystic fibrosis (defined as a sweat chloride value of 60 mmol/litre or more, or 2 cystic fibrosis-causing mutations and either chronic sinopulmonary

disease or gastrointestinal or nutritional abnormalities) and a forced expiratory volume in 1 second (FEV_1) of 40–90% of predicted normal. The company stated that the designs of the trials were almost identical, except that ambulatory electrocardiography screening was included in TRAFFIC and adolescent pharmacokinetic assessments were included in TRANSPORT. The company considered that the baseline characteristics in both trials were generally balanced across treatment arms. However, more people had inhaled antibiotics in the placebo arms (TRAFFIC, 66.3%; TRANSPORT, 72.7%) than in the lumacaftor–ivacaftor arms (TRAFFIC, 62.1%; TRANSPORT, 59.9%).

3.4 The primary outcome in TRAFFIC and TRANSPORT was the absolute change from baseline in percent predicted FEV_1 ($ppFEV_1$) at week 24, based on a mixed-effects model for repeated measures. The company noted that this was calculated by averaging the mean absolute change at weeks 16 and 24 to reduce variability. The analysis of efficacy outcomes was based on a 'full analysis set' population (that is, people who were randomised into the trials and had received at least 1 dose of the study treatment). All outcomes were assessed on day 1, day 15 and at weeks 4, 8, 16 and 24. The company noted that consistent and sustained improvements in $ppFEV_1$ were seen from as early as day 15 up until week 48 (that is, at week 24 of PROGRESS). People who had taken lumacaftor–ivacaftor plus standard of care for a total of 48 weeks had an absolute change from baseline in $ppFEV_1$ of 2.6%. The results for the primary outcome of TRAFFIC, TRANSPORT and a pre-specified pooled analysis are in table 1.

3.5 The company stated that the results (treatment effect) of its pre-specified subgroup analyses were consistent with the results for the overall population. It highlighted that 28 people having lumacaftor–ivacaftor plus standard of care had a $ppFEV_1$ value less than 40% at baseline, but the clinical benefit and safety profile seen in this group with severe lung dysfunction was comparable with the overall population.

Table 1 Mean absolute and relative change from baseline in $ppFEV_1$ at week 24

$ppFEV_1$	TRAFFIC	TRANSPORT	Pooled analysis

	LUM–IVA (n=182)	PBO (n=184)	LUM–IVA (n=187)	PBO (n=187)	LUM–IVA (n=369)	PBO (n=371)
Primary outcome: Absolute change from baseline in $ppFEV_1$ (%)						
Within-group change (SE)	**2.16 (0.53)**	−0.44 (0.52)	**2.85 (0.54)**	−0.15 (0.54)	**2.49 (0.38)**	−0.32 (0.38)
Mean difference (95% CI)	**2.6 (1.2 to 4.0)**		**3.0 (1.6 to 4.4)**		**2.8 (1.8 to 3.8)**	
Secondary outcome: Relative change from baseline in $ppFEV_1$ (%)						
Within-group change (SE)	**3.99 (0.92)**	−0.34 (0.91)	**5.25 (0.96)**	0.00 (0.96)	**4.64 (0.67)**	−0.17 (0.66)
Mean difference (95% CI)	**4.3 (1.9 to 6.8)**		**5.2[1] (2.7 to 7.8)**		**4.8 (3.0 to 6.6)**	
Secondary outcome: Response (≥5% increase in average relative change from baseline in $ppFEV_1$)						
Proportion of patients (%)	37	22	41	23	39	22
Odds ratio (95% CI)	**2.1 (1.3 to 3.3) p=0.002**		2.4 (1.5 to 3.7) p=0.001[2]		**2.2 (1.6 to 3.1) p<0.001**	

Abbreviations: CI, confidence interval; LUM–IVA, lumacaftor–ivacaftor; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SE, standard error.

The company did not report the mean baseline $ppFEV_1$ for each treatment arm.

[1] Taken from the company's response to clarification. Reported to be 5.3 in the company's original submission.

[2] p value ≤0.025; however, the company stated that it was not considered statistically significant within the framework of the testing hierarchy.

Bold text indicates statistically significant result.

3.6 Secondary outcomes were the frequency and severity of pulmonary exacerbations, and changes in BMI. The company stated that lumacaftor–ivacaftor reduced the rate of pulmonary exacerbations and the need for hospitalisation and intravenous antibiotics compared with placebo (see table 2). It also noted that lumacaftor–ivacaftor improved a person's BMI

compared with placebo (see table 3).

Table 2 Company's analysis of pulmonary exacerbations data

Pulmonary exacerbations[1]	TRAFFIC		TRANSPORT		Pooled analysis	
	LUM–IVA (n=182)	PBO (n=184)	LUM–IVA (n=187)	PBO (n=187)	LUM–IVA (n=369)	PBO (n=371)
Total number of exacerbations at week 24 (event rate per 48 weeks)						
Number (rate)	73 (0.71)	112 (1.07)	79 (0.67)	139 (1.18)	152 (0.70)	251 (1.14)
Rate ratio	0.66 (p=0.02)[2]		0.57 (p<0.001)[2]		**0.61 (p<0.001)**	
Number of exacerbations needing hospitalisation at week 24 (event rate per year)						
Number (rate)	17 (0.14)	46 (0.36)	23 (0.18)	59 (0.46)	40 (0.17)	105 (0.45)
Rate ratio	**0.38 (p=0.0008)**		**0.39 (p=0.0002)**		**0.39 (p<0.0001)**	
Number of exacerbations needing IV antibiotics at week 24 (event rate per year)						
Number (rate)	33 ([3])	62 ([3])	31 (0.23)	87 (0.64)	64 (0.25)	149 (0.58)
Rate ratio	**(p=0.0050)** [3]		**0.36 (p<0.0001)**		**0.44 (p<0.0001)**	
Mean duration in days of pulmonary exacerbations						
Total	7.81	13.07	8.45	18.23	8.14	15.67
	p<0.0001		**p<0.0001**		**p<0.0001**	
Hospitalisation	NR	NR	NR	NR	2.48	7.64
IV antibiotics	NR	NR	NR	NR	3.79	10.13

Abbreviations: IV, intravenous; LUM–IVA, lumacaftor–ivacaftor; NR, not recorded; PBO, placebo.

[1] Estimated using a negative binomial regression model that included treatment, study, sex, age group at baseline, and ppFEV$_1$ severity at screening.

[2] p value ≤0.025; however, the company stated that it was not considered statistically significant within the framework of the testing hierarchy.

[3] The company stated that these rates could not be estimated because the negative binomial model did not converge.

Bold text indicates statistically significant result.

Table 3 Absolute change from baseline in BMI at week 24

BMI	TRAFFIC		TRANSPORT		Pooled analysis	
	LUM–IVA (n=182)	PBO (n=184)	LUM–IVA (n=187)	PBO (n=187)	LUM–IVA (n=369)	PBO (n=371)
Baseline (SD)	21.68 (3.169)	21.03 (2.956)	21.32 (2.894)	21.02 (2.887)	21.50 (3.034)	21.02 (2.918)
Within-group change (SE)	**0.32 (0.071)**	**0.19 (0.070)**	**0.43 (0.066)**	0.07 (0.066)	**0.37 (0.048)**	**0.13 (0.048)**
Mean difference (95% CI)	0.13 (−0.07 to 0.32)		**0.36 (0.17 to 0.54)**		**0.24 (0.11 to 0.37)**	

Abbreviations: CI, confidence interval; LUM–IVA, lumacaftor–ivacaftor; PBO, placebo; SD, standard deviation; SE, standard error.

Bold text indicates statistically significant result.

3.7 Health-related quality of life was measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the EuroQol-5 dimensions-3 levels survey (EQ-5D-3L); see table 4. CFQ-R is measured on a scale of 0–100, with higher scores representing better health. An absolute change of at least 4 points is considered a minimal clinically important difference for the CFQ-R respiratory domain. The company stated that people in the trials had very high baseline EQ-5D-3L values because they are born with cystic fibrosis and perceive their quality of life to be 'normal' (that is, equivalent to people without cystic fibrosis). As a result, people with cystic fibrosis score their health-related quality of life as

high, so statistically significant improvements in health-related quality of life are unlikely to be seen because of this ceiling effect. It noted that this is a challenge commonly reported in cystic fibrosis trials.

Table 4 Health-related quality-of-life data at week 24

Health-related quality of life	TRAFFIC		TRANSPORT		Pooled analysis	
	LUM–IVA (n=182)	PBO (n=184)	LUM–IVA (n=187)	PBO (n=187)	LUM–IVA (n=369)	PBO (n=371)
Cystic Fibrosis Questionnaire-Revised: respiratory domain						
Baseline (SD)	69.29 (17.4)	70.54 (16.03)	67.36 (18.5)	67.05 (18.4)	68.31 (18.0)	68.78 (17.3)
Within-group change (SE)	**2.60 (1.192)**	1.10 (1.161)	**5.66 (1.169)**	**2.81 (1.153)**	**4.10 (0.834)**	**1.88 (0.818)**
Mean difference (95% CI)	1.5 (−1.69 to 4.69)		2.9 (−0.27 to 5.98)		2.2 (−0.01 to 4.45)	
EuroQol-5 dimensions-3 levels survey (EQ-5D-3L)						
Baseline (SD)	0.9237 (0.104)	0.9217 (0.098)	0.9171 (0.10837)	0.9267 (0.10462)	Not reported by the company	
Within-group change (SE)	0.0006 (0.0074)	0.01 (0.0076)	0.0117 (0.00673)	0.0108 (0.00683)		
Mean difference (95% CI)	0.0095 (−0.0109, 0.0298)		−0.0009 (−0.0192, 0.0174)			

Abbreviations: CI, confidence interval; LUM–IVA, lumacaftor–ivacaftor; PBO, placebo; SD, standard deviation; SE, standard error.

Bold text indicates statistically significant result.

3.8 Adverse event data were available from the pooled analysis of TRAFFIC and TRANSPORT, and from PROGRESS (see table 5). The most common adverse events reported for lumacaftor–ivacaftor compared with placebo were cough (28.2% compared with 40.0%), diarrhoea (12.2% compared with 8.4%), dyspnoea (13.0% compared with 7.8%), haemoptysis (13.6% compared with 13.5%), headache (15.7% compared with 15.7%), increase in sputum production

(14.6% compared with 18.9%), infective pulmonary exacerbation (35.8% compared with 49.2%), nasopharyngitis (13.0% compared with 10.8%), nausea (12.5% compared with 7.6%) and upper respiratory tract infection (10.0% compared with 5.4%). No deaths were reported in either TRAFFIC or TRANSPORT, and 1 death was reported in PROGRESS, which was considered unrelated to treatment.

Table 5 Summary of adverse event data

Number of people (%)	Pooled analysis (24 weeks)		PROGRESS (0–48 weeks): LUM–IVA (n=544)
	LUM–IVA (n=369)	PBO (n=370)	
Any AE	351 (95.1)	355 (95.9)	532 (97.8)
Any grade 3 or 4 AE	45 (12.2)	59 (15.9)	100 (18.4)
At least 1 serious AE	64 (17.3)	106 (28.6)	159 (29.2)
Stopping treatment because of AE	17 (4.6)	6 (1.6)	34 (6.3)
Abbreviations: AE, adverse event; LUM–IVA, lumacaftor–ivacaftor; PBO, placebo.			

Cost effectiveness

3.9 The company submitted an individual patient-level microsimulation model that compared lumacaftor–ivacaftor plus standard of care with standard of care alone in people 12 years and older with cystic fibrosis who are homozygous for the F508del mutation. The company used a 4-week cycle length for the first 2 years and yearly thereafter. It did the economic analysis from an NHS and personal social services perspective and chose a lifetime time horizon. Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied.

3.10 Baseline characteristics (age, sex, weight-for-age z-score and $ppFEV_1$) were taken from 1,097 people in TRAFFIC and TRANSPORT who had $ppFEV_1$ data available at baseline. Statistical bootstrapping methods were used to randomly create a group of 1,000 people (see table 6). Baseline diabetes and infection status were taken from the UK Cystic Fibrosis Registry, and every person was assumed to have pancreatic insufficiency. Each person's data were run through

the company's model twice (that is, once for lumacaftor–ivacaftor plus standard of care, and once for standard of care alone). The company ran its economic model for 6 replications on the group of 1,000 people and used different random numbers for each replication.

Table 6 Baseline characteristics

Characteristic	Mean of total trial population (n=1,097)	UK Cystic Fibrosis Registry
Age (years)	25.5	19.6
Male	50.6%	Not reported
BMI	21.2	Not reported
Percent predicted forced expiratory volume in 1 second (ppFEV$_1$)	60.6%	75%

3.11 Survival was estimated using a 2-part calculation in the company's model:

- Firstly, the age-specific background mortality was derived from UK Cystic Fibrosis Registry data (2013). The company fitted a series of parametric curves to a Kaplan–Meier analysis of 6,082 cystic fibrosis patients (all genotypes) divided into groups based on their year of birth (ranging from 1980 to 2008). The company simulated patient-level data based on digitised curves and the number of patients in each group using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull functions. The company stated that the curves estimated from the generalised gamma, Gompertz and Weibull functions provided the best statistical fit. In the base-case analysis, the company used the Weibull function because it considered it provided the most valid long-term survival projections based on visual inspection and clinical expert opinion (that is, an estimated median survival of 40.8 years, with approximately 0% alive by 80 years).

- Secondly, the age-specific mortality was adjusted to take into account 9 clinical and patient characteristics that the company considered as predictors of survival based on a Cox proportional hazards model published by Liou et al. (2001): ppFEV$_1$, pulmonary exacerbations, age, sex, weight-for-age z-score, pancreatic sufficiency, diabetes, infection with *Burkholderia cepacia* and *Staphylococcus aureus*. These clinical and patient characteristics were updated at the end of each cycle, and subsequently used to adjust the underlying survival function.

3.12 The company stated that the ppFEV$_1$ of people having lumacaftor–ivacaftor plus standard of care increased by 2.8% by week 16 and was maintained until week 24 in its economic model, to reflect the changes seen in TRAFFIC and TRANSPORT. However, the ppFEV$_1$ of people having standard of care alone was assumed to remain unchanged over the first 24 weeks of the company's economic model. After week 24 in the model, ppFEV$_1$ declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV$_1$ was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Decline in ppFEV$_1$ was not age dependent for lumacaftor–ivacaftor plus standard of care based on TRAFFIC, TRANSPORT and PROGRESS using a mixed-model analysis (see table 7). The company stated that it also included a lower bound ppFEV$_1$ of 15% to avoid unrealistically low values. The company's model also included pulmonary exacerbations needing intravenous antibiotics and hospitalisation, and modelled a person's BMI based on weight-for-age z-scores using data from TRAFFIC and TRANSPORT (see table 7). The company also assumed that 24.7% of people with a ppFEV$_1$ below 30% had a lung transplant. Post-lung transplant mortality was assumed to be 15.2% in the first year, and 6.1% for each subsequent year based on 6,766 adults with cystic fibrosis in the UK who had a lung transplant between 1990 and 2012.

Table 7 Summary of the company's ppFEV$_1$, exacerbation, and weight-for-age z-score inputs

Input		LUM–IVA plus SoC	SoC
ppFEV$_1$	From week 16–24	Baseline +2.8%	Baseline
	Annual change after week 24	Age <18: −0.68% Age 18–24: −0.68% Age ≥25: −0.68%	Age <18: −2.34% Age 18–24: −1.92% Age ≥25: −1.45%
Annual rate of pulmonary exacerbations		Predicted, conditional on ppFEV$_1$ and age, multiplied by 0.442	Predicted, conditional on ppFEV$_1$ and age
Weight-for-age z-scores	First 24 weeks	Baseline +0.068	Baseline
	After 24 weeks		

Abbreviations: LUM–IVA, lumacaftor–ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SoC, standard of care.

3.13 The drug costs for lumacaftor–ivacaftor were based on the list price (£2,000 per week) and were assumed to reduce by 89% after 12 years because of patent expiry (see section 4.18). In the company's economic model, approximately 6.8% of people having lumacaftor–ivacaftor stopped treatment during the first 24 weeks to reflect TRAFFIC and TRANSPORT, and after 24 weeks their $ppFEV_1$ declined at the rate estimated for standard of care alone. The company assumed that after 24 weeks, no more people stopped treatment with lumacaftor–ivacaftor. It included an adherence rate of 90% for lumacaftor–ivacaftor, but noted that the adherence rate in the trials was 96.5%. The company's costs for managing cystic fibrosis were dependent on lung function and were based on a retrospective 24-month study in 8 UK specialist centres of 200 people with cystic fibrosis who are homozygous for the F508del mutation. Hospitalisation costs for pulmonary exacerbations were assumed to reduce by 61% for people having lumacaftor–ivacaftor plus standard of care, based on the rate ratio of pulmonary exacerbations needing hospitalisation in TRAFFIC and TRANSPORT. The company included adverse reactions that were reported in more than 5% of people having lumacaftor–ivacaftor plus standard of care compared with standard of care alone, costed as a GP visit. It also included costs associated with lung transplant and monitoring (liver function tests).

3.14 To estimate the health-related quality of life in the economic model, the company used a multivariate mixed-model repeated measures regression analysis to model the relationship between EQ-5D utility values, lung function ($ppFEV_1$) and pulmonary exacerbations reported in TRAFFIC and TRANSPORT. Therefore, the utility for a given patient varied throughout the time horizon of the company's economic model. The company did not apply any utility decrements for adverse events other than pulmonary exacerbations. Utility values for lung transplant were taken from Whiting et al. (2014) and the weighted-average utility for people post-transplant was estimated to be 0.81.

3.15 Table 8 presents a summary of the company's base-case and probabilistic cost-effectiveness results for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. Table 9 presents a summary of the health outcomes predicted by the company's base-case analysis.

Table 8 Summary of company's base-case and probabilistic results

	LUM–IVA plus SoC	SoC	Increment
Base-case analysis			
Life years	13.78	10.32	3.46
QALYs	12.38	8.92	3.45
Costs	£1,131,202	£377,632	£753,570
ICER (£/QALY)			£218,248
Probabilistic sensitivity analysis			
Life years	13.82	10.34	3.48
QALYs	12.42	8.94	3.49
Costs	£1,125,946	£377,152	£748,794
ICER (£/QALY)			£214,838
Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; QALY, quality-adjusted life year; SoC, standard of care.			

Table 9 Summary of health outcomes predicted by company's base-case analysis

Outcome	LUM–IVA plus SoC	SoC	Increment
Projected median survival (years)	43.84	36.15	7.69
Undiscounted life years	24.52	15.05	9.47
Mean $ppFEV_1$ cumulative change	−13.51	−21.89	8.37
Mean years with $ppFEV_1$ ≥70%	4.08	1.14	2.94
Mean years with $ppFEV_1$ 40–70%	17.10	8.84	8.26
Mean years with $ppFEV_1$ 30–40%	2.58	2.66	−0.08
Mean years with $ppFEV_1$ <30%	0.77	2.42	−1.65
Annual rate of pulmonary exacerbation	0.46	1.24	−0.78

Percent having lung transplant	1.82%	6.80%	–4.98%
Mean years until lung transplant	46.49	19.34	27.14
Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SoC, standard of care.			

3.16 The company presented the results of a univariate sensitivity analysis and several scenario analyses. The univariate sensitivity analysis suggested that the base-case incremental cost-effectiveness ratios (ICERs) were most sensitive to the rate of $ppFEV_1$ decline for lumacaftor–ivacaftor, the discount rate and costs of managing cystic fibrosis. The company presented the results of several scenario analyses (see table 10) and subgroup analyses (see table 11).

Table 10 Company's scenario analyses

Scenario	LUM–IVA plus SoC		SoC		ICER (£/QALY)
	Total cost	Total QALYs	Total cost	Total QALYs	
Base case	£1,131,202	12.38	£377,632	8.92	£218,248
Discount rate 1.5%	£1,381,148	16.56	£467,146	10.83	£159,678
Rate of $ppFEV_1$ decline (LUM–IVA): +20%	£1,121,358	12.04	£377,632	8.92	£238,795
Rate of $ppFEV_1$ decline (LUM–IVA): –20%	£1,140,078	12.76	£377,632	8.92	£199,003
Rate of $ppFEV_1$ decline (SoC): Canadian cystic fibrosis population	£1,131,202	12.38	£350,697	8.07	£181,366
PE rate: all events	£1,114,588	12.09	£377,632	8.92	£233,018
Utility values: TRAFFIC and TRANSPORT by $ppFEV_1$ strata	£1,131,202	12.52	£377,633	9.25	£230,769
Utility values: Tappenden et al.	£1,131,202	11.09	£377,632	7.97	£241,109
Utility values: Acaster et al.	£1,131,202	9.52	£377,632	6.86	£283,458
Stop treatment at rate of 1.9% post 24 weeks	£1,092,338	12.27	£377,633	8.92	£213,910

Survival curve: Gompertz	£939,058	10.00	£292,406	7.18	£228,830
Adherence: 96.5%	£1,185,593	12.38	£377,633	8.92	£234,000
Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; PE, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; QALYs, quality-adjusted life years; SoC, standard of care.					

Table 11 Company's subgroup analyses by baseline $ppFEV_1$

Subgroup	LUM–IVA plus SoC		SoC		ICER (£/QALY)
	Total cost	Total QALYs	Total cost	Total QALYs	
Baseline $ppFEV_1$ >40%	£1,176,340	13.07	£393,337	9.40	£213,336
Baseline $ppFEV_1$ <40%	£745,575	5.76	£231,284	4.05	£300,688
Baseline $ppFEV_1$ >70%	£1,366,094	17.72	£493,464	13.34	£199,481
Baseline $ppFEV_1$ <70%	£1,053,685	10.48	£334,864	7.30	£225,907
Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; QALY, quality-adjusted life years; SoC, standard of care.					

Evidence review group comments on clinical effectiveness

3.17 The ERG stated that the company's systematic literature review was of reasonable quality and all relevant randomised controlled trials were identified.

3.18 The ERG stated that TRAFFIC and TRANSPORT were generally of good quality. It was aware that the expert statements NICE received suggested they were the largest trials of a cystic fibrosis therapy to date. The ERG's clinical adviser also considered that the trial populations were generalisable to people in clinical practice in England.

3.19 The ERG stated that because both trials included people with mild to moderate cystic fibrosis (that is, $ppFEV_1$ of 40–90% at screening), the clinical evidence may not be generalisable to people with severe cystic fibrosis, or people with very mild cystic fibrosis.

3.20 The ERG stated that the company's method used to pool the results from TRAFFIC and TRANSPORT was likely to be appropriate, but insufficient details were provided by the company for the ERG to determine this.

3.21 The ERG's clinical adviser noted that estimating the mean absolute change from baseline $ppFEV_1$ at week 24 by averaging the mean absolute change at weeks 16 and 24 was common in cystic fibrosis trials and considered acceptable.

3.22 The ERG's clinical adviser stated that absolute changes in $ppFEV_1$ were more clinically relevant than relative changes, and that an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important. The ERG concluded that although lumacaftor–ivacaftor plus standard of care had statistically significant effects on key outcomes compared with standard of care alone, it was unclear how clinically significant they were.

3.23 The ERG noted that because the company's trials were short, the long-term effects of lumacaftor–ivacaftor were uncertain.

Evidence review group comments on cost effectiveness

3.24 The ERG stated that the company's model appeared to capture the important features of cystic fibrosis.

3.25 The ERG stated that it was not possible to compare the baseline characteristics of the company's trial population with the subgroup of people included in the Cystic Fibrosis Registry who are homozygous for the F508del mutation and with a $ppFEV_1$ of 40–90%. As a result, it was unclear whether the differences in mean age and $ppFEV_1$ were because of different characteristics among the subtypes of cystic fibrosis or the result of differences between the trial population and the relevant UK cystic fibrosis population (see table 6). The ERG further highlighted that most of the natural history parameters in the company's model were informed by data for the whole UK cystic fibrosis population and not by data for the population with cystic fibrosis who are homozygous for the F508del mutation. Therefore, the ERG concluded that any differences between the modelled and real populations, and the impact this may have on efficacy and cost effectiveness, should be considered when interpreting the company's results.

3.26 The ERG acknowledged that the company had highlighted the challenges of estimating survival from the Cystic Fibrosis Registry:

- There is selection bias with groups born earlier, because of a lack of available follow-up data earlier in their lifetime, which may artificially inflate survival rates.
- Observed survival in groups born more recently is relatively immature, making long-term extrapolation potentially unreliable.

3.27 The ERG highlighted that using the absolute difference in $ppFEV_1$ by averaging across the 16-week and 24-week measurements was more favourable for lumacaftor–ivacaftor than using the 24-week measurement alone.

3.28 The ERG stated that short-term benefits were assumed to persist over much longer time horizons in the company's model because the long-term benefit of lumacaftor–ivacaftor on $ppFEV_1$ was based on 48-week data. The ERG further considered that using different and non-randomised data sets for the long-term extrapolations may bias the estimates for each treatment group.

3.29 The ERG noted that the company had not provided any long-term evidence to support the assumptions around the benefits of lumacaftor–ivacaftor on pulmonary exacerbations (maintained for as long as people stayed on treatment) and weight-for-age z-score (maintained for the remainder of a person's life irrespective of whether they stopped treatment). Therefore these were associated with uncertainty.

3.30 The ERG highlighted that the company assumed the impact of lumacaftor–ivacaftor on pulmonary exacerbations was independent from, rather than partially caused by, its effect on $ppFEV_1$. The ERG was aware that the company's clinical experts verified this assumption, but the ERG noted that the company risked double counting the benefits of treatment.

3.31 The ERG considered that no robust rationale was provided by the company for the assumed price reduction after 12 years (see section 3.13). The ERG stated that the company's disease management costs were taken from a population that included people with a different mutation (G551D) and not only the F508del mutation as specified by the company.

3.32 The ERG considered that the company's assumption that pre-transplant health-

related quality of life depended only on ppFEV$_1$ and pulmonary exacerbations may not be justified if other treatment-related factors affect health-related quality of life (for example, adverse events with lumacaftor–ivacaftor).

3.33 The ERG explored the impact of applying a conservative assumption in the company's economic model. The assumption was that after the time horizon of the trial, the effect of lumacaftor–ivacaftor on pulmonary exacerbations was based solely on any differences in ppFEV$_1$ (see section 3.30). This analysis explored by the ERG estimated incremental costs of £704,645 and an incremental quality-adjusted life year (QALY) gain of 2.59, with an estimated ICER of £272,265 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone.

3.34 The ERG also presented an exploratory analysis that included the following changes (see table 12):

- Setting the adherence rate to 96.5% rather than 90% so that the same adherence rate is used for both effectiveness and cost data (see section 3.13).
- People could stop lumacaftor–ivacaftor treatment after 24 weeks. After this time, the rate for people stopping treatment was assumed to be 1.9% annually, in line with a rate used by the company in its scenario analysis.
- The mean absolute change in ppFEV$_1$ from baseline was based on the 24-week data alone rather than the average of the 16-week and 24-week data (that is, replacing an absolute increase of 2.8% [see section 3.12] with an absolute increase of 2.45%). The absolute increase of 2.45% was estimated by the ERG from a graph in the company's submission showing the mean absolute change in ppFEV$_1$ from baseline at various time points of the trials.

Table 12 Summary of ERG's exploratory analysis

	LUM–IVA plus SoC	SoC	Increment
Life years	13.56	10.32	3.24
QALYs	12.14	8.92	3.22
Costs	£1,092,269	£377,632	£714,637
ICER (£/QALY)	–		£221,992

Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; QALYs, quality-adjusted life years; SoC, standard of care.

3.35 The ERG presented a sensitivity analysis around the company's assumed price reduction using the exploratory analysis model (see table 13).

Table 13 Summary of the ICERs for the ERG's sensitivity analysis of generic pricing

		Percent price reduction for generic medicine				
		89%	80%	70%[1]	60%[1]	50%[1]
Time until generic alternative becomes available	10 years	£203,100	£215,971	£230,272	£244,573	£258,874
	12 years	£221,992[2]	£232,953	£245,132	£257,311	£269,490
	15 years	£244,675	£253,342	£262,972	£272,602	£282,232
	20 years	£271,764	£277,692	£284,279	£290,865	£297,452
	Never	£330,385[3]	£330,385[3]	£330,385[3]	£330,385[3]	£330,385[3]

[1] Costs were calculated by extrapolating costs from the 89% and 80% scenarios.

[2] ERG's exploratory analysis (see section 3.34, table 12).

[3] The company's base-case incremental cost-effectiveness ratio increased from £218,248 to £349,337 per QALY gained when the price reduction for lumacaftor–ivacaftor was removed.

3.36 The ERG also presented a sensitivity analysis exploring the impact of applying the lower and upper bound of the 95% confidence interval for the annual ppFEV$_1$ decline estimated from weeks 4–48 in the company's trials for people having lumacaftor–ivacaftor (see table 14).

Table 14 Summary of ERG's sensitivity analysis around the annual decline in ppFEV$_1$ in people having lumacaftor–ivacaftor

	LUM–IVA plus SoC	SoC	Increment
Lower bound of 95% confidence interval (1.58% ppFEV$_1$ decline per year after 24 weeks in people having lumacaftor–ivacaftor)			
Life years	11.80	10.32	1.48
QALYs	10.41	8.92	1.49
Costs	£1,061,163	£377,632	£683,532
ICER (£/QALY)	–		£459,045
Upper bound of 95% confidence interval (−0.16%[1] ppFEV$_1$ decline per year after 24 weeks in people having lumacaftor–ivacaftor)			
Life years	16.07	10.32	5.76
QALYs	14.73	8.92	5.81
Costs	£1,164,047	£377,632	£786,415
ICER (£/QALY)	–		£135,464

Abbreviations: ICER, incremental cost-effectiveness ratio; LUM–IVA, lumacaftor–ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; QALY, quality-adjusted life years; SoC, standard of care.

[1] The upper bound of 95% confidence interval for annual ppFEV$_1$ decline indicated a slight improvement with lumacaftor–ivacaftor.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of lumacaftor–ivacaftor, having considered evidence on the nature of cystic fibrosis in people who are homozygous for the F508del mutation and the value placed on the benefits of lumacaftor–ivacaftor by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee heard from the clinical and patient experts about the nature of cystic fibrosis. It understood from the patient experts that cystic fibrosis is a progressive, debilitating, life-limiting and unpredictable condition. The committee was aware that cystic fibrosis in people homozygous for the F508del mutation was classified as severe disease (see section 4.11), and it understood that the lumacaftor–ivacaftor combination is indicated specifically for this population because of its mechanism of action, that is, lumacaftor is a corrector and ivacaftor is a potentiator of the CFTR gene (see section 2.1). The committee heard from the patient and clinical experts that the goals of therapy include maintaining lung function, reducing pulmonary exacerbations, maintaining a healthy BMI, improving health-related quality of life and reducing the treatment burden. It heard from the patient experts that cystic fibrosis can impair a person's social life and ability to work, and significantly affects the lives of their families and carers. A patient expert highlighted that because of the unpredictable nature of the condition, it was difficult to make plans for the future and this has a substantial impact on psychological wellbeing (for example, causing symptoms of stress, anxiety and depression). The committee concluded that cystic fibrosis has a major impact on the quality of life of patients and their carers.

4.2 The committee discussed the current treatment options and management of cystic fibrosis. It understood from the clinical experts that there was no single standard of care. Treatment is determined according to each person's needs, because current options manage the symptoms and complications associated with cystic fibrosis rather than the cause of the condition. The patient experts highlighted that managing cystic fibrosis is relentless and can take up 2 or more hours of the person's time each day. The person may have to take up to 50 tablets every day and may need frequent hospital admission. A patient expert explained that having intravenous antibiotics for chest infections was

one of the worst aspects of managing the condition because it usually meant hospitalisation for long periods of time, causing significant disruption. The committee heard from the clinical experts that a substantial number of people with pulmonary exacerbations who need supportive treatment cannot be admitted to hospital in a timely manner because specialist cystic fibrosis centres in England have limited capacity and cannot cope with demand. The clinical experts explained that it was frustrating not to be able to admit all people with a clinical need for supportive treatment. The committee concluded that oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers.

4.3 The committee discussed how lumacaftor–ivacaftor would be used in clinical practice. It was aware that lumacaftor–ivacaftor has a marketing authorisation in the UK for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation, that is, approximately 50% of people with cystic fibrosis. It understood from the clinical experts that if lumacaftor–ivacaftor was available in the NHS, it would likely be prescribed to all people whose disease is suitable, within 12 months. Most people would continue to have standard of care, as needed. The committee concluded that lumacaftor–ivacaftor would be considered as an adjunct to standard of care for treating cystic fibrosis in people homozygous for the F508del mutation.

Clinical effectiveness

4.4 The committee discussed the clinical evidence from the TRAFFIC and TRANSPORT trials. It noted that the company's trials did not include mannitol dry powder as part of standard of care. It was aware that NICE's technology appraisal guidance on mannitol dry powder for inhalation for treating cystic fibrosis recommended mannitol as an option for some adults. The committee heard from the clinical experts that only a small number of people are treated with mannitol dry powder in clinical practice and the standard of care treatments in the trials were generally appropriate. The committee also understood from the clinical experts that the trial populations broadly represent people who would be offered lumacaftor–ivacaftor in England. However, it noted a key issue highlighted by the evidence review group (ERG) that the trial results may not be generalisable to people with very mild or severe cystic fibrosis because the inclusion criteria required people to have a percent

predicted forced expiratory volume in 1 second ($ppFEV_1$) of 40–90%. The committee noted a consultation comment that stated that the severity of cystic fibrosis was not defined by $ppFEV_1$, but depended on the type of mutation present and other modifying environmental and physiological factors. The clinical experts and commissioning representatives stated that it would be inappropriate to restrict treatment in clinical practice until a person's lung function declined to a $ppFEV_1$ of 90%. This was because they considered that these patients would have substantial capacity to benefit from treatment. The committee concluded that the results from TRAFFIC and TRANSPORT were generalisable to most patients in routine clinical practice in England.

4.5 The committee discussed the company's methods for analysing outcomes in TRAFFIC and TRANSPORT. It was aware that the company presented the results from TRAFFIC and TRANSPORT in a pre-specified pooled analysis. The committee agreed with the ERG that the company's methods for pooling were likely to be appropriate, and were acceptable to use in its decision-making. It noted that the primary outcome of TRAFFIC and TRANSPORT, the change from baseline to week 24 in $ppFEV_1$, was calculated as an average of week 16 and week 24 results to reduce variability. The committee considered that the company's approach did not truly reflect the treatment effect after 24 weeks of treatment because $ppFEV_1$ changed over time. The committee was aware that the European public assessment report stated that the company's primary analysis method (that is, a mixed-effects model for repeated measures) takes into account the variability, and therefore it was not considered appropriate to reduce it by time point averaging. The committee also highlighted that the company's data showed that there was an underlying trend in the mean absolute change in $ppFEV_1$ from baseline over time in the company's trials. Therefore, estimating the results of the primary outcome of TRAFFIC and TRANSPORT based on an average of week 16 and week 24 results rather than week 24 results alone could introduce bias, and favoured lumacaftor–ivacaftor. The committee also noted that other key secondary outcomes, including weight-for-age z-score and pulmonary exacerbations, were reported at week 24 and these data were included in the cost-effectiveness analysis. The committee concluded that it would have been more appropriate for the company to estimate the absolute change from baseline in $ppFEV_1$ based on the 24-week data alone.

4.6 The committee discussed the results of $ppFEV_1$ outcomes from TRAFFIC,

TRANSPORT and PROGRESS. It noted that the mean absolute change in $ppFEV_1$ from baseline to week 24 ranged from approximately 2.45% to 2.8%, depending on whether the outcome was based on 24-week data alone or an average of 16-week and 24-week data respectively. Furthermore, the committee highlighted that the company's pooled analysis for each of the $ppFEV_1$ outcomes was statistically significant, but the trials were powered on the basis of detecting an absolute difference of 5% or more in $ppFEV_1$ for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in $ppFEV_1$ because of the heterogeneous nature of the condition. A patient expert stated that an absolute increase of 2.8% in $ppFEV_1$ may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. The committee noted that the absence of an agreed minimum clinically important difference would not prevent it from being able to make a recommendation for lumacaftor–ivacaftor. It was aware that the observed (and subsequently extrapolated) benefits of lumacaftor–ivacaftor on $ppFEV_1$ were taken into account in the company's cost-effectiveness analysis (see sections 4.12–4.13). The committee heard from the clinical experts that the general size of the effect seen for lumacaftor–ivacaftor was lower than the absolute acute improvement in $ppFEV_1$ seen with other treatments for cystic fibrosis directed against mutations conferring a similar severity of disease. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in $ppFEV_1$ was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The committee concluded that longitudinal changes rather than acute changes in $ppFEV_1$ were more clinically relevant for assessing long-term outcomes of cystic fibrosis, and both the observed and extrapolated benefits of lumacaftor–ivacaftor on $ppFEV_1$ were taken into account in the company's cost-effectiveness analysis.

4.7 The committee discussed the pulmonary exacerbation outcomes from TRAFFIC, TRANSPORT and PROGRESS. It noted that the company's pooled analysis of TRAFFIC and TRANSPORT suggested that lumacaftor–ivacaftor as an add-on therapy to standard of care reduced:

- the total number of pulmonary exacerbations by 39%

- pulmonary exacerbations needing hospitalisation by 61% and
- pulmonary exacerbations needing intravenous antibiotics by 56%.

The committee heard from the clinical experts that pulmonary exacerbations are associated with long-term decline in ppFEV$_1$, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant. It noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres (see section 4.2). The committee understood from a patient expert that reducing pulmonary exacerbations is the most important aspect of managing their condition. This is because of the unpredictable onset of exacerbations and their potential to cause irreversible lung damage. The committee concluded that the reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for managing cystic fibrosis.

4.8 The committee discussed the health-related quality-of-life data collected in TRAFFIC and TRANSPORT. It commented that modest improvements in health-related quality of life with lumacaftor–ivacaftor plus standard of care compared with standard of care alone were seen when assessed by the Cystic Fibrosis Questionnaire-Revised (CFQ-R), but no differences were seen when assessed by the EuroQol-5 dimensions-3 levels survey (EQ-5D-3L). The committee heard from a patient expert that they believe health-related quality of life in people with cystic fibrosis is lower than that of people without cystic fibrosis. However, both the clinical and patient expert explained that people with cystic fibrosis may perceive their health-related quality of life to be equivalent to that of people without cystic fibrosis because they have never known any other health state. The committee was aware from the clinical experts that other treatments for cystic fibrosis directed against mutations conferring a similar severity of disease had shown clinically significant changes in health-related quality of life when measured by the disease-specific CFQ-R. The committee stated that it would have expected to see a difference in health-related quality of life between the 2 treatment groups in the company's trial because of the differences in the rate of pulmonary exacerbations. The clinical experts stated that the health-related quality of life of people in hospital is often low, not only because of physical symptoms, but also because hospital treatment can be isolating, which can have a psychological impact. The committee recognised the difficulty of

valuing health states in chronic conditions of an unpredictable nature because a person's health-related quality of life is generally their current health on the day of assessment rather than at the time of an event (for example, during a pulmonary exacerbation), and it was not always assessed over the longer term. However, the committee highlighted that the company had not provided qualitative empirical evidence to support that the EQ-5D was inappropriate, as recommended in NICE's guide to the methods of technology appraisal (2013). The committee also understood from the clinical experts that they considered that the 5 dimensions of the EQ-5D questionnaire generally captured most of the important effects of cystic fibrosis. It was also aware that only small changes in health-related quality of life were seen when using the disease-specific CFQ-R in the company's trials, and therefore the lack of sensitivity to showing changes in health-related quality of life in people treated with lumacaftor–ivacaftor was not limited to the generic EQ-5D-3L. The committee stated that the standard method of using the general population's valuation of descriptions of health-related quality of life to generate utility values was appropriate. The committee concluded that there was no evidence to suggest that the EQ-5D was inappropriate and it generally captured the effects of having cystic fibrosis and its treatment. It further concluded that these effects were therefore incorporated in the company's cost-effectiveness estimates.

4.9 The committee considered the safety data from TRANSPORT, TRAFFIC and PROGRESS. It noted that the proportion of patients with adverse events was similar between those taking lumacaftor–ivacaftor plus standard of care and standard of care alone. The committee commented that grade 3 or 4 adverse events, and serious adverse events, were reported more frequently in people taking standard of care alone than lumacaftor–ivacaftor plus standard of care. A patient expert highlighted that people appreciate that lumacaftor–ivacaftor is taken orally, and any treatment that can reduce the burden and unpleasant side effects of intravenous antibiotics would be welcomed. The committee concluded that lumacaftor–ivacaftor is generally well tolerated.

Cost effectiveness

4.10 The committee considered the company's economic model, the ERG's critique and the ERG's exploratory analyses. It agreed with the ERG that the company's economic model captured the important features of cystic fibrosis. The committee noted that, when available, the company had applied the baseline

characteristics of its trial populations to the modelled population rather than using published sources. The committee highlighted that data sources such as the Cystic Fibrosis Registry were not limited to the population homozygous for the F508del mutation. The committee was aware that there are over 1,000 known cystic fibrosis mutations. It understood from the clinical experts that there were key differences in the severity of the condition between cystic fibrosis mutations (for example, some mutations result in little or no cystic fibrosis transmembrane conductance regulator [CFTR] protein function and in others, there is some residual function), but the trial populations were generalisable to the clinical population in England (see section 4.4). The committee concluded that the company's economic model structure and the baseline characteristics of the modelled population were relevant to the management of cystic fibrosis and the clinical population homozygous for the F508del mutation in England.

4.11 The committee discussed the company's methods for estimating survival. It commented that using a Weibull function to model the age-specific background mortality seemed reasonable. The committee acknowledged that most predictors of mortality in people with cystic fibrosis were captured by the Cox proportional hazards model published by Liou et al. (2001). However, it understood from the clinical experts that Liou excluded a major predictor of lung function and mortality in people with cystic fibrosis, that is, chronic *Pseudomonas* infection. The committee was aware from the company's evidence submission that there were 13 other sources that the company could have used to take into account the clinical and patient characteristics that predict survival. It considered that the company's submission had not sufficiently explained how it identified Liou as the most appropriate source. The committee noted that the company's survival analyses were based on the whole cystic fibrosis population rather than the population homozygous for the F508del mutation. The committee heard from the clinical experts that up to 20% of people in the Cystic Fibrosis Registry have mild disease, and that cystic fibrosis in people homozygous for the F508del mutation was classified as severe. The committee concluded that, overall, the company's methods for estimating survival seemed valid but there was uncertainty about how the differences in outcomes between the whole cystic fibrosis population and the population with the F508del mutation would affect the cost-effectiveness results.

4.12 The committee discussed the company's methods for estimating the treatment

effect of lumacaftor–ivacaftor on $ppFEV_1$. It commented that all people having lumacaftor–ivacaftor had an absolute increase in $ppFEV_1$ of 2.8% from 0–24 weeks in the company's economic model, irrespective of whether they stopped treatment during this initial period. The committee recalled that an absolute increase of 2.45% in $ppFEV_1$ was more robust based on the 24-week data alone (see sections 4.5–4.6). It also heard from the clinical experts that most people who stopped lumacaftor–ivacaftor in clinical practice had felt worse soon after coming off treatment. The committee considered that the company's approach had potentially overestimated the initial benefit of lumacaftor–ivacaftor treatment on $ppFEV_1$. It highlighted that there was also considerable uncertainty associated with how the company modelled the decline in $ppFEV_1$ after 24 weeks. The committee noted that the data from the company's trials showed that the treatment effect of lumacaftor–ivacaftor on $ppFEV_1$ peaked at 8 weeks, but the company chose to model the decline based on data from 4 weeks onwards. Therefore, the company's data used to estimate the decline in $ppFEV_1$ with lumacaftor–ivacaftor included a period in which $ppFEV_1$ was still improving. The committee noted that the company's sensitivity analysis for the decline in $ppFEV_1$ was based on an arbitrary range. However, it was aware that the ERG had presented the results of a sensitivity analysis using the 95% confidence intervals for the decline in $ppFEV_1$ in people having lumacaftor–ivacaftor from the trials (which also incorporated the absolute increase in $ppFEV_1$ of 2.8% from 0–24 weeks). It noted that the ERG's sensitivity analysis showed that the incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. The committee discussed the decline in $ppFEV_1$ for people having standard of care alone, and noted that basing it on a large, observational study was generally appropriate. However, it was aware that there were other observational studies available for modelling the decline in $ppFEV_1$ for standard of care alone. The company had not sufficiently explained why it considered that the US and Canadian study was more relevant to clinical practice and the clinical population in England than the other data sets available. The committee stated that the lack of clear selection criteria for choosing this study increased the uncertainty around the company's results because the relative rate of decline in $ppFEV_1$ for lumacaftor–ivacaftor plus standard of care compared with standard of care alone had a considerable impact on the ICER. The committee commented that because extrapolations for $ppFEV_1$ decline were based on different, non-randomised studies for each treatment group, it would have been

appropriate for the company to explore the impact on the ICER using the $ppFEV_1$ decline for standard of care alone based on the 24-week trial data. The committee concluded that the uncertainty in the company's method for estimating changes in $ppFEV_1$ has not been appropriately explored, and the methods used were likely to have overestimated the benefits of lumacaftor–ivacaftor treatment.

4.13 The committee discussed whether the decline in $ppFEV_1$ was age dependent. It understood from the clinical experts that younger populations, such as adolescents, generally have a higher rate of $ppFEV_1$ decline compared with older populations. The committee highlighted that in the company's economic model, the decline in $ppFEV_1$ was approximately 2% or more per year for people younger than 24 years in the standard of care alone group. However, it heard from the clinical experts that the average rate of decline in $ppFEV_1$ was generally 1–2% per year for all people with cystic fibrosis, and that a decline in $ppFEV_1$ of 2% or more per year reflected rapidly declining lung function. The committee agreed that it was plausible that the decline in $ppFEV_1$ was age dependent for people having lumacaftor–ivacaftor plus standard of care or standard of care alone. Therefore, the company's approach of applying age dependence to the rate of $ppFEV_1$ decline only in the standard of care alone group potentially overestimated the relative benefits of lumacaftor–ivacaftor treatment in the younger age groups. Furthermore, the committee agreed that the annual rate of decline in $ppFEV_1$ could be overestimated in the standard of care alone group. The committee concluded that the rate of $ppFEV_1$ decline was age dependent for all people with cystic fibrosis, irrespective of treatment.

4.14 The committee discussed the company's methods for estimating the treatment effect of lumacaftor–ivacaftor on pulmonary exacerbations. It stated that it would have been more appropriate for the company to apply the rate ratio for all pulmonary exacerbations rather the rate ratio specifically for pulmonary exacerbations needing intravenous antibiotics or hospitalisation. It noted that this would not only reflect the observed rate and definition of pulmonary exacerbation in the trials, but would take into account that all pulmonary exacerbations affect health-related quality of life. The committee was aware from the company's scenario analyses that choosing the rate ratio for pulmonary exacerbations needing intravenous antibiotics or hospitalisation, rather than the overall rate ratio, resulted in a more favourable ICER for lumacaftor–ivacaftor. The committee acknowledged that the model chosen by

the company from the literature to relate ppFEV$_1$ to the number of pulmonary exacerbations was based on pulmonary exacerbations needing hospitalisation or intravenous antibiotics. However, the committee was aware that the company had used the number of pulmonary exacerbations needing hospitalisation or intravenous antibiotics in the Liou et al. (2001) survival model too. It understood from the ERG that the Liou model was estimated from data relating to all pulmonary exacerbations. Therefore, the ERG considered that the company may have overestimated the survival benefit for lumacaftor–ivacaftor by including only pulmonary exacerbations needing hospitalisation or intravenous antibiotics. The committee highlighted that the company had been inconsistent in its approach to selecting pulmonary exacerbation data for its model. The committee concluded that the treatment effect of lumacaftor–ivacaftor on pulmonary exacerbations used in the company's base-case analysis underestimated the ICER.

4.15 The committee discussed the company's methods for estimating the treatment effect of lumacaftor–ivacaftor on BMI. It understood from the clinical experts that the company's assumption that people having lumacaftor–ivacaftor had a lifetime BMI benefit irrespective of stopping treatment was unlikely to be plausible in clinical practice. The committee acknowledged that the improvement in BMI with lumacaftor–ivacaftor was small. Therefore, it concluded that there was uncertainty associated with the treatment effect on BMI in the company's model, but was satisfied this would only have a small impact on the ICER.

4.16 The committee discussed whether it was plausible that the effect of lumacaftor–ivacaftor on ppFEV$_1$ was independent of its effect on pulmonary exacerbations, as modelled by the company. It heard from the clinical experts that the results from the company's trials potentially supported the effect of lumacaftor–ivacaftor on ppFEV$_1$ and pulmonary exacerbations being independent (that is, because of the small effect on ppFEV$_1$, but relatively large effect on pulmonary exacerbations). However, the clinical experts stated that in general, an increase in ppFEV$_1$ would be associated with a lower risk of exacerbation. Therefore, the committee understood from the clinical experts that in practice, there was some dependency between these outcomes but the degree to which they were related was difficult to quantify. The ERG considered that the company's approach may have led to the double counting of quality-of-life gains and mortality reductions in the modelling. The committee concluded

that it was uncertain how independent lumacaftor–ivacaftor's effects on ppFEV$_1$ and pulmonary exacerbations were, and the potential impact of this on the ICER should be taken into account in the decision-making.

4.17 The committee noted that the available trial data were for lumacaftor–ivacaftor treatment up to 48 weeks (that is, 24 weeks from TRAFFIC and TRANSPORT, and an additional 24 weeks from the company's interim analysis of the 96-week PROGRESS study), but the company assumed that people would take lumacaftor–ivacaftor indefinitely. It further noted that the treatment effect persisted over the time horizon of the company's economic model. Therefore, the committee concluded that the company should have explored a more cautious scenario that included a waning of the treatment effect because of the uncertain longer-term benefits of lumacaftor–ivacaftor.

4.18 The committee discussed the treatment cost of lumacaftor–ivacaftor used in the company's model. It noted that the company had assumed an arbitrary reduction of 89% in the price of lumacaftor–ivacaftor after 12 years because of patent expiry. The committee considered that there was no robust basis for making this assumption. The committee agreed that it had not considered price reductions resulting from the potential introduction of generics or biosimilars previously because this is speculative, and the timing and impact of their introduction is unknown. It highlighted that the cost of several resources included in the company's economic model could change over time. The committee also understood from the clinical experts that several treatments for cystic fibrosis were under development and were likely to be available in the next 12 years, further affecting the clinical and cost effectiveness of lumacaftor–ivacaftor over time. The committee appreciated the patient experts' view that having access to new medicines as soon as possible could be life changing for people living with cystic fibrosis because of the condition's unpredictable and life-limiting nature. The committee noted that NICE's guide to the methods of technology appraisal (2013), which is consistently applied across all diseases and conditions, stated that a reduced price should only be used when there is a nationally available price reduction. The committee concluded that the treatment costs associated with lumacaftor–ivacaftor treatment in the economic modelling had been substantially underestimated by the company.

4.19 The committee discussed the rates of adherence included in the company's

economic model and ERG's exploratory analysis. It noted that in the trials, the adherence rate was 96.5%, but the company had assumed an adherence rate of 90% in its economic model. The committee acknowledged that the adherence rate in clinical practice may be lower than seen in the trials, but agreed with the ERG that the impact of reduced adherence should be consistent for both costs and effects. The committee noted that adherence and efficacy are related, because if adherence goes down, so should efficacy. For this reason, the committee agreed that the adherence rate should come from the same data source used to determine efficacy. Efficacy in the model was derived from the trials; therefore, the committee indicated that this was the preferred source for the adherence rate. The committee concluded that there was uncertainty around the face validity of the assumptions on adherence but the adherence rate seen in the trials, which was consistent for both costs and effects, was preferred.

4.20 The committee discussed whether it was plausible that people would discontinue lumacaftor–ivacaftor treatment after 24 weeks. It was aware that in TRAFFIC, TRANSPORT and PROGRESS, approximately 13% of people discontinued lumacaftor–ivacaftor by week 48, but in the company's base-case analysis people could only stop treatment in the first 24 weeks. The committee acknowledged that the company's scenario analysis and ERG's exploratory analysis had arbitrarily assumed that 1.9% of people having lumacaftor–ivacaftor discontinued treatment per year after 24 weeks until the end of year 15 in the economic model. The committee noted that the company had not proposed any stopping criteria for lumacaftor–ivacaftor. It understood from the clinical experts that in clinical practice, people would only discontinue lumacaftor–ivacaftor because of adverse events or because they did not adhere to treatment, and not because of a change in ppFEV$_1$. Cystic fibrosis is a multi-organ disease, so treatment can have a beneficial effect beyond FEV$_1$. The committee agreed that in clinical practice, people would discontinue treatment after 24 weeks because of adverse events or because they did not adhere to treatment, and that it was reasonable to assume that the rate at which people discontinued treatment would reduce after the initial treatment period of 24 weeks. However, the committee emphasised that it remained concerned about the company's modelling and how the treatment effect was maintained indefinitely for BMI. The committee concluded that people could discontinue lumacaftor–ivacaftor after 24 weeks, but the rate of discontinuation was uncertain. It also concluded that the consequences on the treatment effect of

discontinuing treatment were inappropriately modelled in the company's base-case analysis, which potentially biased the ICER in favour of lumacaftor–ivacaftor.

4.21 The committee discussed the company's costs for managing cystic fibrosis. It was aware that these costs were based on a cystic fibrosis population including people who are homozygous for the F508del mutation or with a G551D mutation. The committee heard from the clinical experts that the costs of managing these types of cystic fibrosis were broadly similar. The committee highlighted that the hospitalisation cost was based on a pulmonary exacerbation lasting 21.7 days. It understood from the clinical experts that an average course of treatment for a pulmonary exacerbation episode was 12–14 days. The committee commented that it appeared that the company had also overestimated any cost savings from lumacaftor–ivacaftor treatment. It explained that this was a result of the company applying a rate ratio to the number of pulmonary exacerbations (treatment effect), and another reduction to the cost of hospitalisation by 61%, for people having lumacaftor–ivacaftor plus standard of care. The committee concluded that the company's disease management costs were taken from a relevant population but there was some uncertainty around the hospitalisation costs.

4.22 The committee noted that EQ-5D utility data were collected in the clinical trials of lumacaftor–ivacaftor (see section 4.8), and discussed how the company adjusted the utility values for ppFEV$_1$ and pulmonary exacerbations in its economic model. It appreciated that the company had included EQ-5D data, as preferred by NICE in its guide to the methods of technology appraisal (2013). The committee heard from the company that the average EQ-5D utility value at baseline was approximately 0.9, which provided little opportunity to demonstrate an improvement in health-related quality of life from lumacaftor–ivacaftor treatment. However, the committee stated that benefits in health-related quality of life can also be captured by avoiding any decrements in health-related quality of life (for example, by avoiding pulmonary exacerbations). It recalled that the clinical experts considered that the 5 dimensions of the EQ-5D questionnaire generally captured the important effects of cystic fibrosis. However, the committee was aware that most of the benefit of lumacaftor–ivacaftor in the company's economic model was from the extension of life-years gained, with little benefit from improved health-related quality of life. The committee heard from the ERG that the EQ-5D was not

sensitive to small changes in $ppFEV_1$ in an individual patient, but the EQ-5D was sufficiently sensitive to differences in cystic fibrosis severity as measured by $ppFEV_1$ at a population level. Therefore, the committee considered it was possible to capture any benefits from improving health-related quality of life. It was also aware that a study by Acaster et al. (2015) showed differences in health-related quality of life measured by the EQ-5D for 3 levels of cystic fibrosis severity as measured by $ppFEV_1$, and when these utility data were included in the company's economic model, the base-case ICER increased by £65,000 per QALY gained. The committee commented that the baseline characteristics of people in the Acaster study and the company's trials were sufficiently similar, but the health-related quality-of-life results from Acaster appeared to have more face validity than the results from the company's trials. The committee noted that the company's utility model showed an association between EQ-5D score and $ppFEV_1$, which suggests that differences between utility and cystic fibrosis severity as measured by $ppFEV_1$ existed. It also stated that it would have been more appropriate for the company's economic model to take account of age-related differences in utility values. Taking everything into account, the committee concluded that it was not convinced that health-related quality of life in the company's economic model had been valued with any certainty, and that this led to increased uncertainty around the ICER for lumacaftor–ivacaftor plus standard of care compared with standard of care alone.

4.23 The committee discussed the most appropriate discount rate for costs and health effects. It understood from the company's sensitivity analyses that the ICER was sensitive to the discount rate. The committee was aware from NICE's guide to the methods of technology appraisal (2013) that a non-reference case may be considered for treatments that restore people (who would otherwise die or have a very severely impaired life) to full or near full health, and when this is sustained over a very long period (normally at least 30 years). NICE's methods guide states that 'a discount rate of 1.5% for costs and benefits may be considered by the committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs'. The committee highlighted that people were not restored from very severely impaired life to full or near full health, as measured by the EQ-5D. It also agreed that there was considerable uncertainty around whether the treatment effect

of lumacaftor–ivacaftor would be maintained for a person's lifetime (see section 4.17). The committee concluded that a discount rate of 3.5% was appropriate for this technology appraisal.

4.24 The committee discussed the ICERs presented for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. It acknowledged that the company had used the data from its trials when available, which were recognised as the largest trials in cystic fibrosis to date, and used EQ-5D utility data as preferred by NICE. The committee agreed that the most plausible ICER should be based on:

- $ppFEV_1$ improvement from 24-week data alone
- $ppFEV_1$ decline for lumacaftor–ivacaftor calculated after the treatment effect peaked at week 8 rather than at week 4
- age dependency for $ppFEV_1$ decline applied to both treatment groups
- no price reduction applied to lumacaftor–ivacaftor after 12 years
- a 96.5% adherence rate (same for costs and effects)
- some people discontinuing treatment after 24 weeks
- a pulmonary exacerbation lasting 14 days rather than 21.7 days and
- a 3.5% discount rate for both costs and effects.

The committee also agreed that there was considerable uncertainty around:

- the estimates of relative effectiveness for $ppFEV_1$ decline
- the rapid rate of $ppFEV_1$ decline in the standard of care group
- how the treatment effect was modelled when people came off treatment and over the longer term (that is, no waning effect of treatment over time)
- how independent the effects of lumacaftor–ivacaftor on $ppFEV_1$ and on pulmonary exacerbations were
- the effect of using data for pulmonary exacerbations needing hospitalisation or intravenous antibiotics in the modelling rather than for all pulmonary exacerbations

- potential overestimation of cost savings associated with hospitalisation and
- the company's utility estimates.

The committee inferred from the company's scenario analyses that the ICER for lumacaftor–ivacaftor plus standard of care compared with standard of care alone would increase rather than decrease if the company had applied the committee's preferred assumptions and accounted for the uncertainty. It acknowledged that when the company's arbitrary price reduction (assuming the introduction of a future low-cost generic) for lumacaftor–ivacaftor was removed, the company's base-case ICER increased from £218,000 to £349,000 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.

4.25 The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company, there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal.

4.26 The committee discussed whether there are any potential equality issues. It acknowledged that NHS England has published a clinical commissioning policy for ivacaftor monotherapy, which is for people of 6 years and older who have 1 of 9 mutations. The committee noted that ivacaftor monotherapy does not have a marketing authorisation in the UK for treating cystic fibrosis homozygous for the F508del mutation, and this population was not covered by NHS England's clinical commissioning policy. The committee was aware that NHS England commissioning policy decisions should not be taken as setting precedent for future policy decisions. It noted a comment from the company that there is potential for inequality of access based on the subtype of a person's cystic fibrosis, if lumacaftor–ivacaftor was not recommended for treating cystic

fibrosis homozygous for the F508del mutation. The committee considered that this did not constitute an equality issue for any group protected by the equality legislation and that its recommendation was in line with NICE's guide to the processes of technology appraisal (2014) and guide to the methods of technology appraisal (2013). The committee concluded that its recommendation was fair and did not discriminate against any protected groups, and therefore no changes were needed.

4.27 The committee discussed whether lumacaftor–ivacaftor could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. In its submission, the company stated that lumacaftor–ivacaftor addresses an unmet need because it is the first treatment to specifically target the F508del mutation. The committee agreed that lumacaftor–ivacaftor offers people an oral treatment option that has the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. It recognised that this was particularly important to people with cystic fibrosis. The committee therefore acknowledged that lumacaftor–ivacaftor was a valuable new therapy for managing cystic fibrosis. It agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis (for example, maintaining employment and improved family life). The committee understood from the company's response to consultation that the company considered that all the evidence for lumacaftor–ivacaftor had not been taken into account. However, the committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality-of-life effects had not been captured in its economic modelling. It agreed that direct health effects for carers had not been taken into account in the company's economic model as considered appropriate in NICE's guide to the methods of technology appraisal (2013). However, the committee concluded that even if the company's economic model had taken into account these uncaptured direct health effects, given the very high ICER for lumacaftor–ivacaftor plus standard of care compared with standard of care alone, its recommendation would remain unchanged.

4.28 The committee was aware of NICE's position statement on the Pharmaceutical

Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TA398	Appraisal title: Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation	Section
Key conclusion		
Lumacaftor–ivacaftor is not recommended, within its marketing authorisation, for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The committee concluded that longitudinal changes rather than acute changes in ppFEV$_1$ were more clinically relevant for assessing long-term outcomes of cystic fibrosis. It also concluded that the reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for managing cystic fibrosis. The committee concluded that, even without including any of its preferred assumptions, the estimated incremental cost-effectiveness ratios (ICERs) were considerably higher than what is normally considered a cost-effective use of NHS resources.		1.1, 4.6, 4.7, 4.24
Current practice		
Clinical need of patients, including the availability of alternative treatments	Cystic fibrosis has a major impact on the quality of life of patients and their carers. Oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers.	4.1, 4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Lumacaftor–ivacaftor offers people an oral treatment option that has potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation.	4.27
What is the position of the treatment in the pathway of care for the condition?	Lumacaftor–ivacaftor would be considered as an adjunct to standard of care for treating cystic fibrosis in people homozygous for the F508del mutation.	4.3
Adverse reactions	Lumacaftor–ivacaftor is generally well tolerated.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee discussed the clinical evidence from the TRAFFIC, TRANSPORT and PROGRESS trials. TRAFFIC AND TRANSPORT were international multicentre (including 5 UK centres) double-blind, phase III placebo-controlled trials in people 12 years and over with cystic fibrosis who are homozygous for the F508del mutation. In both TRAFFIC and TRANSPORT, people had treatment for 24 weeks and were then enrolled into the 96-week PROGRESS extension study if they completed treatment.	4.4–4.9
Relevance to general clinical practice in the NHS	Results from TRAFFIC and TRANSPORT were generalisable to most patients in routine clinical practice in England.	4.4

Uncertainties generated by the evidence	Trial results may not be generalisable to people with very mild or severe cystic fibrosis because the inclusion criteria required people to have a percent predicted forced expiratory volume in 1 second ($ppFEV_1$) of 40–90%. It would have been more appropriate for the company to estimate the absolute change from baseline in $ppFEV_1$ based on the 24-week data alone. Longitudinal changes rather than acute changes in $ppFEV_1$ were more clinically relevant for assessing long-term outcomes of cystic fibrosis. The committee recognised the difficulty of valuing health states in chronic conditions of an unpredictable nature because a person's health-related quality of life is generally their current health on the day of assessment rather than at the time of an event (for example, pulmonary exacerbation), and it was not always assessed over the longer term.	4.4–4.6, 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable	–
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in $ppFEV_1$ was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for managing cystic fibrosis.	4.6–4.7
Evidence for cost effectiveness		

Availability and nature of evidence	The committee considered the company's economic model, the evidence review group's (ERG) critique and the ERG's exploratory analyses.	4.10

Uncertainties around and plausibility of assumptions and inputs in the economic model	There was uncertainty about how the differences in outcomes between the whole cystic fibrosis population and the population with the F508del mutation would affect the cost-effectiveness results. There was considerable uncertainty around the selection and estimates of relative effectiveness for ppFEV$_1$ decline. The ppFEV$_1$ decline for lumacaftor–ivacaftor was calculated after the treatment effect peaked at week 8 rather than at week 4. There was a rapid rate of ppFEV$_1$ decline in the standard of care group. Age dependency for ppFEV$_1$ decline was only applied to the standard of care group. Data for pulmonary exacerbations needing hospitalisation or intravenous antibiotics were used in the modelling rather than data for all pulmonary exacerbations. The company's price reduction applied to lumacaftor–ivacaftor after 12 years was not appropriate. The adherence rate should be the same for costs and effects. The company's economic model should incorporate people discontinuing treatment after 24 weeks. The average length of a pulmonary exacerbation in clinical practice should be used (12–14 days). There was potential overestimation of cost savings associated with hospitalisations. There was uncertainty about how the treatment effect was modelled when people came off treatment and over the longer term (that is, no waning effect of treatment over time). It was not certain how independent the effects of lumacaftor–ivacaftor on ppFEV$_1$ and on pulmonary exacerbations were. The company's utility model estimates were uncertain (the committee was not convinced that health-related quality of life in the company's economic model had been valued with any certainty).	4.11–4.24

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Current measures of quality of life adequately captured the effects of having cystic fibrosis and of its treatment. The committee appreciated that the company had included EQ-5D data as preferred by NICE in its guide to the methods of technology appraisal (2013). The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality-of-life effects had not been captured in its economic modelling. It agreed that direct health effects for carers had not been taken into account. However, the committee concluded that even if the company's economic model had taken into account these uncaptured direct health effects, its recommendation would remain unchanged.	4.8, 4.22, 4.27
Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted that the company had not proposed any stopping criteria for lumacaftor–ivacaftor. It understood from the clinical experts that in clinical practice, people would only discontinue lumacaftor–ivacaftor because of adverse events or because they did not adhere to treatment, and not because of a change in $ppFEV_1$.	4.20
What are the key drivers of cost effectiveness?	The relative rate of decline in $ppFEV_1$ for lumacaftor–ivacaftor plus standard of care compared with standard of care alone had a considerable impact on the ICER. When Acaster et al. (2015) utility data were included in the company's economic model, the base-case ICER increased by £65,000 per QALY gained. When the company's arbitrary price reduction (assuming the introduction of a future low-cost generic) for lumacaftor–ivacaftor was removed, the company's base-case ICER increased from £218,000 to £349,000 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone.	4.12, 4.22, 4.24

Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that when the company's arbitrary price reduction (assuming the introduction of a future low-cost generic) for lumacaftor–ivacaftor was removed, the company's base-case ICER increased from £218,000 to £349,000 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.	4.24
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	–
End-of-life considerations	Not applicable	–
Equalities considerations and social value judgements	The committee concluded that its recommendation was fair and did not discriminate against any protected groups, and therefore no changes were needed.	4.26

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke
Technical Lead

Fay McCracken
Technical Adviser

Kate Moore
Project Manager

ISBN: 978-1-4731-1979-6

Accreditation