NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The company stated that lumacaftor–ivacaftor is intended to be considerd as an add-on therapy to standard of care. The use of mannitol dry powder is not reported as part of standard of care in the company's submission, but is recommended by NICE for a specific group of people with cystic fibrosis (see section 2). The ERG's clinical advisor stated that standard of care used in the trials was relevant to UK clinical practice.
  - What is the Committee's view on the omission of mannitol dry powder?
  - Do the components of standard of care in the trials reflect UK practice?
- The company's trials included people with percent predicted forced expiratory volume in 1 second (ppFEV$_1$) between 40–90%. Therefore, the ERG considered

that the clinical evidence may not be generlisable for people with 'end-stage' cystic fibrosis, or people with very mild cystic fibrosis at the beginning of the disease course.

  - Are the trial populations reflective and generalisable to people who are likely to be suitable for lumacaftor–ivacaftor in clinical practice?

- The company stated that the absolute change from baseline in $ppFEV_1$ at week 24 based was calculated by averaging the mean absolute change at weeks 16 and 24 to reduce variability. The ERG's clinical advisor noted this was common in cystic fibrosis trials and considered acceptable.
  - When intrepreting the absolute change from baseline in $ppFEV_1$, is the average of week 16 and week 24, or the average of week 24 alone, more appropriate?
- The absolute change from baseline in $ppFEV_1$ at week 24 was 2.8% in the pooled analysis for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The ERG's clinical advisor approximated that an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important.
  - How clinically significant are observed changes in effect on $ppFEV_1$?
- The company stated that lumacaftor–ivacaftor plus standard of care also reduced the rate of pulmonary exacerbations and improved a person's body mass index compared with standard of care alone.
  - How clinically significant are observed changes in effect on secondary outcomes?
- Mean baseline EQ–5D scores for people included in the trials were higher than 0,9. The company stated that people in the trials had very high baseline EQ-5D-3L values because patients are born with the condition and perceive their quality of life to be 'normal'. As a result, the company stated it was not possible to observe statistically significant improvements because of this ceiling effect, and is a challenge commonly reported in trials of cystic fibrosis.
  - Is the EQ–5D a valid instrument for assesing health-related quality of life in cystic fibrosis?
- Trial data for lumacaftor–ivacaftor was available up to 48 weeks. Treatment is anticipated to be life-long. What is the Committee's view on the uncertainty relating to the long-term treatment effect?

Cost effectiveness

- Baseline characteristics in the company's model were based on its trial populations. The ERG highlighted that there were differences in some baseline characteristics as reported by the UK cystic fibrosis registry (*n.b.* based on the whole cystic fibrosis population and not the F508del mutation population alone).
  - Are the baseline characteristics of the trial populations sufficiently similar to the popualtion likely to be treated with lumacaftor–ivacaftor in UK clinical practice?
- Long-term extrapolation of $ppFEV_1$ values are undertaken separately from different, non-randomised studies for lumacaftor–ivacaftor plus standard of care (PROGRESS; 0–48 week data) and standard of care alone (a large US and Canadian observational study in the whole cystic fibrosis population); see table 9.
  - Are the company's methods to estimating the long-term decline in $ppFEV_1$ in each treatment group sufficiently robust?
  - Is it appropriate that the decline in $ppFEV_1$ is age-dependent for standard of care, but not for lumacaftor–ivacaftor plus standard of care (see table 9)?
- The company estimated survival using a 2-part calculation: firstly, age-specific background mortality was derived from UK cystic fibrosis registry data (Weibull distribution chosen, median survival 40.8 years); secondly, the age-specific mortality was adjusted to take into account 9 clinical characteristics that predict survival based on a Cox proportional hazards model. The ERG highlighted that these natural history parameters were based on the whole cystic fibrosis population rather than the popualtion homozygous for the F508del mutation.
  - Is the Weibull function the most appropriate distribution?
  - Are there other clinical and patient characteristics that may predict survival?
  - Are there any differences between the modelled and UK clinical practice populations that may impact the efficacy and thus cost effectiveness?
- The company assumed that the impact of lumacaftor–ivacaftor on pulmonary exacerbations was independent from, rather than partially caused by, its effect on $ppFEV_1$. The ERG noted that this risked double counting the benefits of treatment.
  - Is it clinically plausible that the impact of treatment on pulmonary exacerbations is independent from the effect on $ppFEV_1$?

- The company assumed that people could only stop lumacaftor–ivacaftor during the first 24 weeks of treatment. The ERG explortory analysis assumed that people could stop lumacaftor–ivacaftor treatment after 24 weeks, and used the rate between weeks 24–48 from PROGRESS (13.5% annually), and an annual rate of 1.9% hereafter.
  - Is it plausible that people will continue to stop treatment after 24 weeks?
- The company assumed that the price of lumacaftor–ivacaftor reduced by 89% after 12 years in its economic model because of patent expiry. The ERG considered that no robust rationale was provided. Is the inclusion of a price reduction appropriate?
- The company's costs for manging cystic fibrosis were based on: a population including people with G551D mutation, and; the measured reduction in pulmonary exacerbations needing hospitalisation from the trials was applied to all hospital costs while people remained on treatment.
  - Are the company's costs sufficiently robust for capturing the differences in managing people with cystic fibrosis homozygous for the F508del mutation?
- The company included an adherence rate of 90% for lumacaftor–ivacaftor. The ERG preferred that the adherence rate observed in the trials (96.5%), so that the same adherence rate is used for both effectiveness and cost data.
  - Is it reasonable for the company to assume adherence is not equal to 100%?
  - Is a rate of 90% or 96.5% more appropriate?
- The company estimated health-related quality of life based on $ppFEV_1$ and pulmonary exacerbations only. The ERG considered that this may not be justified if other treatment-related factors affect health-related quality of life.
  - Is the company's approach for estimating utility values appropriate?
  - Are there other treatment-related factors that affect quality of life? For example, are there significant differences in adverse events between groups?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of lumacaftor in combination

with ivacaftor within its marketing authorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with cystic fibrosis who are homozygous for the F508del mutation	People aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Population in line with marketing authorisation	Clinical evidence presented specifically included people with mild to moderate cystic fibrosis; that is, with ppFEV$_1$ at screening of 40–90%.
Intervention	Lumacaftor and ivacaftor combination therapy	Lumacaftor and ivacaftor combination therapy plus standard of care	Appropriate to consider lumacaftor–ivacaftor as an adjunct to standard of care	
Comparator(s)	Established clinical management without lumacaftor and ivacaftor combination therapy (such as, best supportive care including but not limited to, mannitol dry powder for inhalation, inhaled mucolytics, nebulised hypertonic saline, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and oral, nebulised and intravenous antibiotics)		Comparator in line with final scope, referred to 'standard of care'	The use of mannitol dry powder is not reported as part of standard of care in the company's submission. Mannitol dry powder is the only specified comparator treatment recommended by NICE (TA266) – although its marketing authorisation is not identical to lumacaftor–ivacaftor's. The ERG's clinical advisor stated that standard of care used in the clinical trials is relevant to UK clinical practice.

Outcomes	• mortality • lung function • body mass index • respiratory symptoms • pulmonary exacerbations • frequency and severity of acute infections • need for hospitalisation and other treatments • adverse effects of treatment • health-related quality of life.		Implications of all these outcomes are discussed in the submission.	Outcomes presented mostly match those in NICE's final scope. The frequency and severity of NICE scoped outcomes of acute infections, and respiratory symptoms, are not discussed directly in the company's submission. Some acute infections and respiratory symptoms are reported in the adverse events, but these do not record the severity of the events.
Subgroups	If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.	Results of pre-planned subgroup analyses are presented. *n.b.* scenario analyses exploring the cost-effectiveness by baseline lung function for lumacaftor–ivacaftor plus standard of care compared with standard of care were also presented by company (see pages 39–40 of the company's response to clarification).	None.	None.

2 The technology and the treatment pathway

2.1 There are currently no treatment options available that specifically target the F508del mutation. Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease. Treatments can be broadly classified as: nutritional repletion (for example, pancreatic enzymes and nutritional supplements); relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators); treatment of acute infections; suppression of chronic infection; suppression of inflammation (for example, steroids, high dose ibuprofen) and lung transplantation.

2.2 During the development of NICE technology appraisal guidance 266, the Committee heard from the clinical experts that, after treatment with rhDNase, a patient would be offered either mannitol or hypertonic saline. The clinical specialists stated that approximately 40% of patients in the UK are treated with hypertonic saline. NICE technology appraisal guidance 266 recommends mannitol dry powder for inhalation as an option for treating cystic fibrosis in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and, whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate.

Table 2 Lumacaftor–ivacaftor

Marketing authorisation	"…for the treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene"
Administration method and dosage	Orally administered as a fixed-dose combination product and should be taken with fat-containing food. The recommended dose is 2 tablets every 12 hours containing a fixed-dose combination of 200 mg lumacaftor and 125 mg ivacaftor. Please see SmPC for dose adjustments for 'special populations'.
Monitoring requirements	It is recommended that liver function tests (ALT, AST and bilirubin) are conducted before starting lumacaftor–ivacaftor therapy and then at 1, 3, 6, 9 and 12 months during the first year of treatment and annually

	thereafter. For people with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered.
Cost	List price: £2000 per 28 film-coated tablets (weekly dosage). Annual cost (list price): £104,000 per patient.

See summary of product characteristics (SmPC) for on adverse reactions and contraindications.

Note: People aged 6 or more with 1 of 9 mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D) have routine access to ivacaftor monotherapy (see NHS England clinical commissioning policy); there are about 380 people in England that meet this criteria.

3 Comments from consultees

3.1 The professional groups stated that cystic fibrosis is predominantly treated by multidisciplinary teams in specialist centres. Professional and patient groups highlighted that lumacaftor–ivacaftor is the first therapy that specifically targets the F508del mutation. The patient groups stated that the current treatment options only manage the symptoms and complications of cystic fibrosis, and involve a large burden of daily treatments and frequent hospital visits. Approximately 46% of adults spend more than 3 hours each day on their treatment regime. A professional group noted that lumacaftor–ivacaftor may reduce the need for some of the current treatments, such as intravenous antibiotics for pulmonary exacerbations which can also be associated with unpleasant side effects. However, the professional groups considered that people with cystic fibrosis would still need to continue taking a significant number of therapies in conjunction with lumacaftor–ivacaftor.

3.2 Approximately 52% of people with cystic fibrosis have 2 copies of the F508del mutation (referred to as homozygous F508del). The professional groups commented that the F508del mutation was a severe mutation causing progressive lung disease and premature death, with a median survival of 40 years. The patient groups stated that the condition generally deteriorates with age. This consequently increases the frequency of exacerbations and complications (such as cystic fibrosis-related diabetes and osteoporosis). Patient groups noted that the availability of treatments that increased lung function, reduced pulmonary exacerbations, helped

maintain a healthy body mass index, reduced the treatment burden, and increased life expectancy, are of major importance.

3.3 The patient groups further highlighted that cystic fibrosis is an unpredictable condition that often has a substantial negative impact on quality of life, activities of daily living and a person's ability to plan for the future. A patient group stated that despite 70% of people with cystic fibrosis being in employment, the condition negatively affects a patient's financial situation because of the need for frequent trips to specialist centres, a reduced ability to secure full-time employment and the need for a high calorie diet. Several patient groups commented that because people with cystic fibrosis need a high fat and high calorie diet, the pressure to gain weight can generate emotional stress. People whom struggle to gain weight may need to take food via a gastric tube and this can impact their self-esteem. Symptoms of stress, insecurity, anxiety and depression are higher in both people with cystic fibrosis and their carers, with a prevalence 2–3 times higher compared with the general population.

3.4 Professional groups agreed that no additional education or training would be needed for staff delivering cystic fibrosis services. The professional groups noted that people receiving lumacaftor–ivacaftor would be closely monitored for clinical improvement and adherence in clinical practice, but no additional staff or infrastructure would be needed in the cystic fibrosis specialist centres because the delivery of care would be largely unchanged. However, a professional group acknowledged that routine liver function tests are needed for people receiving lumacaftor–ivacaftor, particularly in the first year (see section 2), and that additional sweat and eye tests may also be needed in clinical practice.

3.5 Professional groups considered that variation in clinical practice has been minimised because of the availability of published clinical guidelines and shared knowledge between multidisciplinary teams.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. It identified 2 phase III randomised controlled trials (RCTs), TRAFFIC and TRANSPORT, and 1 ongoing extension study, PROGRESS, of people who completed TRAFFIC and TRANSPORT.

4.2 TRAFFIC and TRANSPORT were international multicentre (including 5 UK centres) double-blind phase III placebo-controlled trials in people aged 12 years and over with cystic fibrosis homozygous for the F508del mutation. Patients 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 receive their usual cystic fibrosis management in all trial arms. In both the TRAFFIC and TRANSPORT trials, people were treated for 24 weeks and were then enrolled into the 96-week PROGRESS extension study if they completed treatment. Patients stopped treatment if they did 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.

4.3 Patients were eligible for inclusion in the TRAFFIC and TRANSPORT trials if they had a confirmed diagnosis of cystic fibrosis (defined as a sweat chloride value of 60 mmol/L or more, or 2 cystic fibrosis-causing mutations and either chronic sinopulmonary disease or gastrointestinal/ nutritional abnormalities) and a forced expiratory volume in 1 second between 40–90% of predicted normal. The company stated that the designs of the trials were almost identical, with the exception of the

inclusion of ambulatory electrocardiography screening (TRAFFIC only) and adolescent pharmacokinetic assessments (TRANSPORT only). The company considered that the baseline characteristics in both trials were generally balanced across treatment arms. However, the percentage of people receiving inhaled antibiotics was relatively larger in the placebo arms (TRAFFIC, 66.3%; TRANSPORT, 72.7%) compared with the lumacaftor–ivacaftor arms (TRAFFIC, 62.1%; TRANSPORT, 59.9%). For more information around the trials methods and characteristics of participants, please see pages 34–47 of the company's submission.

ERG comments

4.4 The Evidence Review Group (ERG) stated that company's systematic literature review was of reasonable quality and all relevant RCTs were identified.

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

4.6 The ERG stated that because both trials included people with mild to moderate cystic fibrosis (that is, ppFEV$_1$ between 90% and 40% at screening), the clinical evidence may not be generalisable for people with 'end-stage' cystic fibrosis, or people with very mild cystic fibrosis at the beginning of the disease course.

Clinical trial results

4.7 The primary outcome in TRAFFIC and TRANSPORT was the absolute change from baseline in percent predicted forced expiratory volume in one second (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. 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) was used to analyse the efficacy outcomes. 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 observed from as early as day 15 up until week 48 (that is, at week 24 of PROGRESS), with people who had received lumacaftor–ivacaftor plus standard of care for a total of 48 weeks experiencing 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 presented in table 3. For more details, please see pages 49–50 of the company's submission.

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

Table 3 Mean absolute and relative change from baseline in $ppFEV_1$ at week 24 (see tables 2–3 and 12, company's response to clarification)

$ppFEV_1$	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, 4.0)**		**3.0 (1.6, 4.4)**		**2.8 (1.8, 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, 6.8)**		**5.2[1] (2.7, 7.8)**		**4.8 (3.0, 6.6)**	
Secondary outcome: Response (≥5% increase in average relative change from baseline in $ppFEV_1$)						
No. of patients	37	22	41	23	39	22
Odds ratio (95% CI)	**2.1 (1.3, 3.3) p=0.002**		2.4 (1.5, 3.7) p=0.001[2]		**2.2 (1.6, 3.1) p<0.001**	

Abbreviations: CI, confidence interval; LUM–IVA, lumacaftor–ivacaftor; No., number; PBO, placebo; $ppFEV_1$, percent predicted forced expiratory volume in one second; SE, standard error.

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

[1] reported to be 5.3 in the company's original submission (see table 15, page 50)

[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.

4.9 Secondary outcomes reported the frequency and severity of pulmonary exacerbations, and changes in body mass index. 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 4). It also noted that lumacaftor–ivacaftor improved a

person's body mass index compared with placebo (see table 5). For more details, please see pages 50–58 of the company's submission.

Table 4 Company's analysis of pulmonary exacerbations data (see tables 16, 18–20 in the company's submission)

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	[3] **(p=0.0050)**		**0.36 (p<0.0001)**		**0.44 (p<0.0001)**	
Mean duration in days of pulmonary exacerbations						
Total	7.81	13.07	9.45	18.23	8.12	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; 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 5 Absolute change from baseline in body mass index at week 24 (see table 13, page 47 of the company's submission and table 4, page 7 of the company's response to clarification)

Body mass index	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, 0.32)		**0.36 (0.17, 0.54)**		**0.24 (0.11, 0.37)**	

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

Bold text indicates statistically significant result.

4.10 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 6. 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 as a minimal clinically important difference for the CFQ-R respiratory domain. The company also stated that people in the trials had very high baseline EQ-5D-3L values because patients are born with the condition and perceive their quality of life to be 'normal' (that is, equivalent to people without cystic fibrosis). As a result, patients with cystic fibrosis score their health-related quality of life high, so it was not possible to observe statistically significant improvements in health-related quality of life because of this ceiling effect. It noted that this is a challenge commonly reported in trials of cystic fibrosis.

Table 6 Health-related quality of life data at week 24 (see pages 2–4 and 7–8, company's response to clarification)

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, 4.69)		2.9 (-0.27, 5.98)		2.2 (-0.01, 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.

ERG comments

4.11 The ERG stated that the company's method used to pool the results from TRAFFIC and TRANSPORT was likely to be appropriate but sufficient details were not provided by the company to undertake an unequivocal critique.

4.12 The ERG's clinical advisor 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.

4.13 The ERG's clinical advisor stated that absolute changes were more clinically relevant than relative changes in $ppFEV_1$, and that an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important. The ERG concluded that while 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 the observed changes in effect were.

4.14 The ERG noted that the short-term nature of the company's trials meant that the long-terms effects of lumacaftor–ivacaftor were uncertain.

Adverse effects

4.15 Adverse event data was available from the pooled analysis of TRAFFIC and TRANSPORT, and from PROGRESS (see table 7). The most common adverse events reported for lumacaftor–ivacaftor compared with placebo were cough (35.8% compared with 49.2%), 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. For more details, please see pages 61–69 of the company's submission, and pages 47–52 of the ERG report).

Table 7 Summary of adverse event data (table 19, page 48 of the ERG report)

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.			

ERG comments

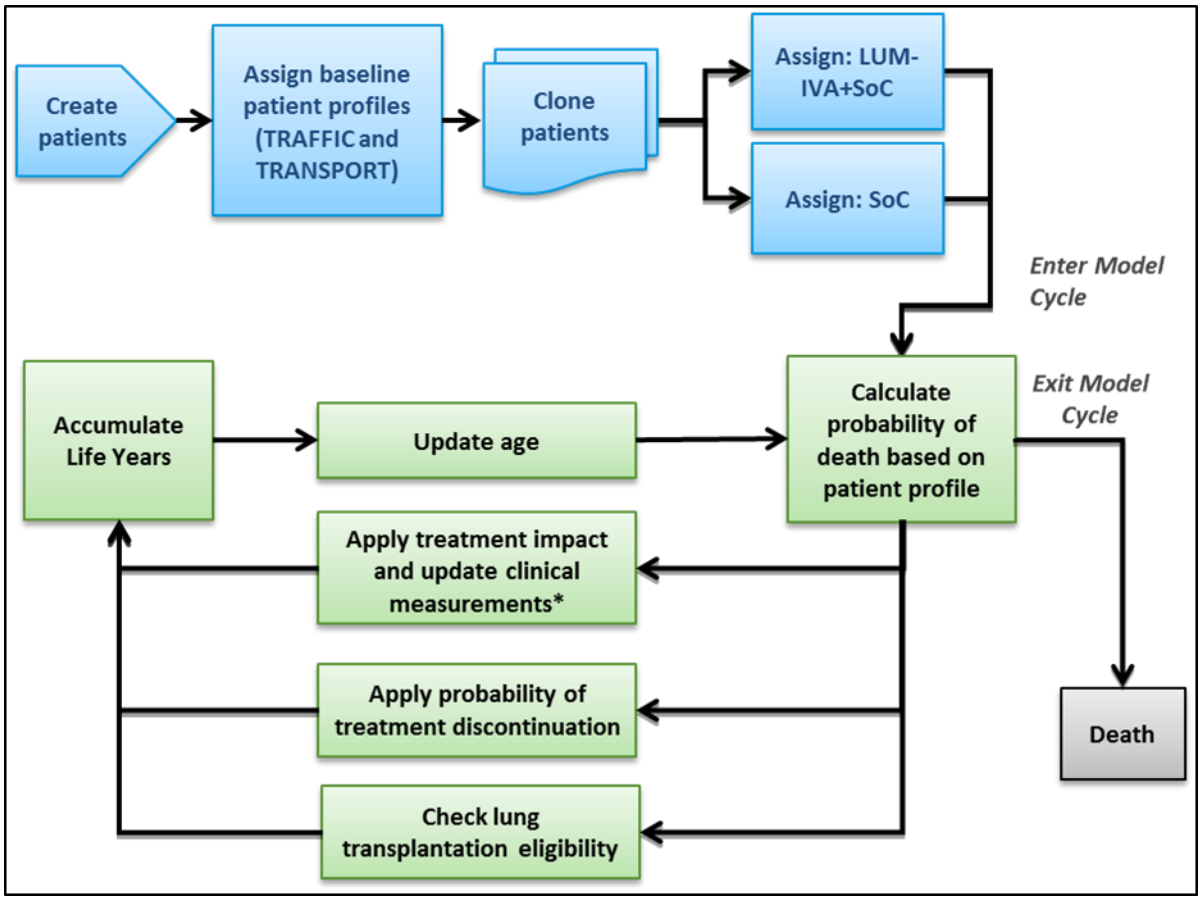
4.16 The ERG stated that it was unclear why more people appeared to be included in the safety set (n=544) than the company suggested were enrolled (n=517) in the PROGRESS extension study.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted an individual patient level microsimulation model that compared lumacaftor–ivacaftor plus standard of care with standard of care alone in people aged 12 years and older with cystic fibrosis homozygous for the F508del mutation (see figure 1). The company used a 4-week cycle length for the first 2 years and yearly thereafter. The company conducted 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.

Figure 1 Company's schematic for its patient level simulation model (see figure 11, page 82 of the company's submission)



ERG comments

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

Model details

5.3 Baseline characteristics (age, sex, weight-for-age z-score and baseline ppFEV$_1$) were taken from 1097 people in TRAFFIC and TRANSPORT who had ppFEV$_1$ data available at baseline. Bootstrapping methods were used to randomly create a cohort of 1000 people (see table 8). Baseline diabetes and infection status were taken from the UK cystic fibrosis registry, and every person was assumed to be pancreatic insufficient. Each person was run through the company's model twice (that is, once for

lumacaftor–ivacaftor plus standard of care and once for standard of care alone).

Table 8 Baseline characteristics (see table 37, pages 84–85 of the company's submission)

Characteristic	Mean of total trial population (n=1097)	UK cystic fibrosis registry
Age (years)	25.5	19.6
Male	50.6%	Not reported
Body mass index	21.2	Not reported
Percent predicted forced expiratory volume in one second ($ppFEV_1$)	60.6%	75%

5.4 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 6082 cystic fibrosis patients (all genotypes) grouped into several birth cohorts ranging from 1980 to 2008. The company simulated patient-level data based on digitised curves and the number of patients in each birth cohort 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 function 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 and approximately 0% were alive by 80 years).
- Secondly, the age-specific mortality was adjusted to take into account 9 clinical and patient characteristics that predict 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, burkholderia cepaci 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.

For further details, please see pages 89–95 of the company's submission.

5.5 The company stated that the ppFEV$_1$ of people receiving lumacaftor–ivacaftor plus standard of care increased by 2.8 percentage points by week 16 and was maintained until week 24 in its economic model to reflect the changes observed in TRAFFIC and TRANSPORT. However, the ppFEV$_1$ of people receiving standard of care alone was assumed to remain unchanged over the first 24 weeks of the company's economic model. After week 24, the ppFEV$_1$ declined, and was age-dependent for standard of care alone based on a large US and Canadian observational study of 4161 adults and 1359 children, and based on TRAFFIC, TRANSPORT and PROGRESS for lumacaftor–ivacaftor plus standard of care using a mixed model analysis (see table 9). The company stated it also included a lower bound ppFEV$_1$ of 15% to avoid unrealistically low values. The company's model also included the pulmonary exacerbations needing intravenous antibiotics and hospitalisation, and modelled a person's body mass index based on weight-for-age z-scores using data from TRAFFIC and TRANSPORT (see table 9). The company also assumed that 24.7% of people with a ppFEV$_1$ below 30% received a lung transplant. The post-lung transplantation rate of mortality was assumed to be 15.2% in the first year, and 6.1% for each subsequent year based on 6766 adults with cystic fibrosis in the UK who had a lung transplant between 1990 and 2012. For further details, please see pages 85–89 of the company's submission.

Table 9 Summary of the company's $ppFEV_1$, exacerbation, and weight-for-age z-score inputs (see table 40, page 88 of the company's submission)

Input		LUM–IVA plus SoC	SoC
$ppFEV_1$	From week 16–24	Baseline	Baseline +2.8%
	Annual change after week 24	Age <18: -2.34% Age 18–24: -1.92% Age ≥25: -1.45%	Age <18: -0.68% Age 18–24: -0.68% Age ≥25: -0.68%
Annual rate of pulmonary exacerbations		Predicted conditional on $ppFEV_1$ and age	Predicted conditional on $ppFEV_1$ and age, multiplied by 0.442
Weight-for-age z-scores	First 24 weeks	Baseline	Baseline + 0.068
	After 24 weeks		

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

5.6 The drug cost for lumacaftor–ivacaftor were based on the list price (£2000 per week) and assumed to reduce by 89% after 12 years because of patent expiry. Approximately 6.8% of people receiving lumacaftor–ivacaftor stopped treatment during the first 24 weeks in the company's economic model 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 further people stopped treatment with lumacaftor–ivacaftor. The company 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 based on a retrospective 24-month study of 200 people with cystic fibrosis homozygous for the F508del mutation in 8 UK specialist centres (see table 10). Hospitalisation costs for pulmonary exacerbations were assumed to reduce by 61% for people receiving lumacaftor–ivacaftor plus standard of care based on the rate ratio of pulmonary exacerbation needing hospitalisation in TRAFFIC and TRANSPORT. The company also included costs associated with lung transplantation, monitoring (liver

function tests) and for adverse reactions which were reported in more than 5% of people receiving lumacaftor–ivacaftor plus standard of care compared with standard of care alone and costed at GP Visit. For further information, please see pages 119–121 of the company's submission.

Table 10 Company's disease management costs (see table 16, page 23 of the company's response to clarification)

$ppFEV_1$	**Category**	**LUM–IVA plus SoC**	**SoC**
$ppFEV_1$ >70%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ 40–69%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ <40%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]

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

5.7 To estimate the health-related quality of life in the economic model, the company the 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 of 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 transplantation were taken from Whiting et al. (2014) and the weighted-average utility for people post-transplantation was estimated to be 0.81. For more details, please see pages 106–108 of the company's submission.

ERG comments

5.8 The ERG stated that because it was not possible to compare the baseline characteristics of the company's trial population with the subgroup of the people included in the cystic fibrosis registry with cystic fibrosis homozygous for the F508del mutation and a ppFEV$_1$ between 40% and 90%, it was unclear whether the differences in mean age and ppFEV$_1$ were a consequence of different characteristics between the subtypes of cystic fibrosis or the result of discrepancies between the trial population and the relevant UK cystic fibrosis population (see table 8). 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 from data for cystic fibrosis 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 thus cost effectiveness, should be considered when interpreting the company's results.

5.9 The ERG acknowledged that the company had highlighted the challenges associated with estimating survival from the cystic fibrosis registry:

- Selection bias of older cohorts because of a lack of available follow-up data earlier in their lifetime which may artificially inflate survival rates
- Observed survival in the more recent birth cohorts is relatively immature, making long-term extrapolation potentially unreliable.

5.10 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.

5.11 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

datasets for the long-term extrapolations may bias the estimates for each treatment group.

5.12 The ERG noted that company's assumption that the benefits of lumacaftor–ivacaftor on pulmonary exacerbations (maintained for as long as they stayed on treatment) and weight-for-age z-score (maintained for the remainder of a person's life irrespective of whether they stopped treatment or not) were not justified and therefore associated with uncertainty.

5.13 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 it risked double counting the benefits of treatment.

5.14 The ERG considered that no robust rationale was provided by the company for the assumed price reduction after 12 years (see section 5.6). The ERG stated that the company's disease management costs were taken from a population including a different mutation (G551D and not only the F508del mutation as specified by the company).

5.15 The ERG considered that the company assumption that pre-transplant health-related quality of life was dependent 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).

Company's base-case results and sensitivity analysis

5.16 Please see table 11 for 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 12 presents a summary of the health outcomes predicted by the company's base case analysis.

Table 11 Summary of company's base case and probabilistic results (tables 17 and 20, company's response to clarification)

	LUM–IVA plus SoC	SoC	Incremental
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 years; SoC, standard of care.

Table 12 Summary of health outcomes predicted by company's base case analysis (table 18, company's response to clarification)

Outcome	LUM–IVA plus SoC	SoC	Incremental
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 $ppFEV_1 \geq 70\%$	4.08	1.14	2.94
Mean years with $ppFEV_1$ between 70–40%	17.10	8.84	8.26
Mean years with $ppFEV_1$ between 40–30%	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 undergoing 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 one second; SoC, standard of care.

5.17 The company presented the results of univariate sensitivity analysis and several scenario analyses. The univariate sensitivity analysis suggested

that the base-case ICER were most sensitive to the rate of $ppFEV_1$ decline for lumacaftor–ivacaftor, the discount rate and costs for managing cystic fibrosis. The company presented the results of several scenario analyses (see table 13) and subgroup analyses (see table 14).

Table 13 Company's scenario analyses (pages 30–36 of the company's response to clarification)

Scenario	LUM–IVA plus SoC		SoC		ICER (£/QALY)
	Total cost	Total QALY	Total cost	Total QALY	
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 one second; SoC, standard of care.

Table 14 Company's subgroup analyses by baseline ppFEV$_1$ (pages 39–40 of the company's response to clarification)

Subgroup	LUM–IVA plus SoC		SoC		ICER (£/QALY)
	Total cost	Total QALY	Total cost	Total QALY	
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 one second; SoC, standard of care.

ERG comments

5.18 The ERG considered that the company's validation of the survival estimates suggested there was good agreement between the true and simulated data. For further details, please see pages 139–141 of the company's submission and pages 80–81 of the ERG report.

ERG exploratory analyses

5.19 The ERG explored the impact from applying a conservative assumption in the company's economic model that considered that after the time horizon of the trial, the effect of lumacaftor–ivacaftor treatment on pulmonary exacerbations was based solely on any differences in ppFEV$_1$ (see section 5.12). This analysis explored by the ERG estimated incremental costs of £704,645 and an incremental QALY gain of 2.59, with an estimated incremental cost-effectiveness ratio of £272,265 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone.

5.20 The ERG also presented an exploratory analysis that including the following changes (see table 15).

- 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 5.6).
- People could stop lumacaftor–ivacaftor treatment after 24 weeks. The rate for people stopping treatment between weeks 24–48 were taken from PROGRESS (13.5% annually), and was assumed to be 1.9% annually hereafter 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 time point data alone rather than the average of the 16-week and 24-week data (that is, replacing an absolute increase of 2.8% with an absolute increase of 2.45%; see section 5.10). This was estimated from the graph reproduced in the company submission.

Table 15 Summary of ERG's exploratory analysis (table 45, page 83 of ERG report)

	LUM–IVA plus SoC	SoC	Incremental
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; QALY, quality-adjusted life years; SoC, standard of care.

5.21 The ERG also presented a sensitivity analysis around the company's assumed price reduction using the exploratory analysis model (see table 16).

Table 16 Summary of the incremental cost-effectiveness ratios for the ERG's sensitivity analysis of generic pricing (table 48, page 84 of ERG report)

		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	£330,385	£330,385	£330,385	£330,385

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

[2] ERG's explortary analysis (see section 5.19, table 15)

Innovation

5.22 The company and experts considered that lumacaftor–ivacaftor was innovative because it was the first treatment to specifically target the F508del mutation. The company and a professional group also considered that measuring health-related quality of life is challenging in cystic fibrosis compared with other conditions such as cancer because people with chronic diseases adapt to the condition and subsequently self-report that they maintain quality of life (see section 4.10).

6 Equality issues

6.1 No equality issues were raised during the scoping workshop, or by patient and professional groups in their evidence submissions.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003954/WC500197613.pdf

"…age is a key determinant in the evaluation of disease severity and consequently treatment benefit. As such, the interpretation of efficacy data in adolescents needs to take into account the more complex clinical picture of the disease at this age."

"The studies have the same design, including a Screening Period, a Treatment Period of 24 weeks, and a Safety Follow-up of additional 4 weeks, which is in line with the relevant CHMP guideline and is considered in general adequate to the evaluation of treatment effect in the claimed indication. However, both pivotal trials included a very large number of study sites located in North America, Europe and Australia. Thus only a small proportion of potentially eligible patients could have been enrolled at each site, which hypothetically could have introduced bias in enrolment….treatment effect in both treatment arms does not seem to be driven by study sites with a low percentage of randomized patients."

"The inclusion and exclusion criteria allow the enrolment of a patient population that adequately represents the target patient population of the sought indication. Enrolment was limited to subjects with a FEV1> 40 and < 90 percent of predicted normal for age, sex and height at screening. This corresponds to patients with moderate-severe lung disease who on the basis of what is known for ivacaftor are more likely to respond to treatment."

"Standardization of concomitant therapy does not seem to have been done. As a consequence, results should be interpreted with caution sharp-cutting the background regimen."

"The SmPC advises that there is no experience of initiating treatment with lumacaftor/ivacaftor in patients having a pulmonary exacerbation and this is not advisable. This is considered appropriate by the CHMP."

"For endpoints on ppFEV1, the change from baseline to week 24 was calculated as an average of week 16 and week 24. This is not truly reflective of a treatment effect after 6 months of treatment and so the applicant was requested to provide analysis based on observations at week 24 alone."

"In the pivotal studies, the magnitude of treatment effect on the primary endpoint is smaller than the 5% difference on which the sample size calculations were based. Further, the statistical significance appears to be driven by the large sample size rather than a large effect size, and significance per se cannot be the only factor that supports the demonstration of efficacy. The analysis of responders further confirms the limited benefit of the combination therapy with only 30.8%-37% and 23-30% of patients in the two studies treated with the 600 mg LUM qb/IVA and 400 mg LUM q12h/IVA, respectively, showing an absolute gain in ppFEV1 over baseline of > 5%. Similar results are obtained when response to treatment is defined as >5% relative improvement in ppFEV1. Of note, there was a high rate of responders in the placebo groups, which may impact the interpretability of treatment effect."

"The extent of effect seen (1.68%-2.63%) is lower than anticipated 5% change. This is also lower than the reported 10-12% improvement with the only disease modifying treatment that has been authorised - ivacaftor in G551D patients. This extent of effect is closer to symptomatic treatment. Clinical benefit from an accrued benefit in FEV1 expanding with time from a 2% baseline can be of significance. The rate of decline of FEV1 in the population enrolled in the pivotal studies appears slower than what is documented from registry. Further the number of exacerbations is lower than in a general CF population and the number of patients who are considered to have rapidly progressive disease appears to be small in the study population. It is accepted that these are limitations that are expected in controlled clinical studies. Because of this limitation, the generalizability of the study results can be conclusively ascertained only in a post-marketing setting."

"No robust trends suggestive of meaningful differences between any of the subgroups were seen."

“Given the overall limited magnitude of beneficial effect seen on the primary endpoint, a longer follow up period is required to provide additional conclusive evidence on the long-term efficacy.”

“The results on the key secondary endpoints and other secondary endpoints were supportive of the conclusion from the primary endpoint including significant effects on clinical outcome endpoints related to exacerbations. The effects on CFQ-R and BMI have not been consistently significant across the studies and are not in themselves indicative of a clinically relevant benefit of the treatment. An absolute difference of 30-40% in the number of pulmonary exacerbations was observed in the active treatment arms compared to placebo in both pivotal trials which is accepted as clinically meaningful effect. The analysis of time to first pulmonary exacerbation, rate of severe pulmonary exacerbations requiring hospitalization and rate of pulmonary exacerbations requiring IV antibiotic therapy were all supportive of a clinically relevant treatment effect.”

“Several intervention strategies have been shown to reduce the number of acute exacerbations with comparable efficacy as the LUM/IVA combination therapy. Nevertheless, considering that the observed benefits are in addition to the benefits of standard of care, it is accepted that adequate evidence of clinically relevant and statistically significant effect on efficacy has been demonstrated.”

“Taking the overall evidence, it is concluded that adequate evidence of a significant and clinically relevant effect on efficacy has been demonstrated.”

“The combination of lumacaftor and ivacaftor in the treatment of these patients has been shown to be generally well tolerated, with few serious adverse events related to study medication.”

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lumacaftor in combination with ivacaftor within its marketing authorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation.

Background

Cystic fibrosis is an inherited disease caused by genetic mutations. The cystic fibrosis transmembrane conductance regulator (CFTR) gene normally creates a protein that regulates levels of sodium and chloride in cells. If the CFTR gene is defective, it leads to a build-up of thick, sticky mucus in the body's tubes and passageways. These blockages damage the lungs, digestive system and other organs, resulting in persistent cough, recurring chest and lung infections and poor weight gain. Cystic fibrosis is a progressive condition that limits life expectancy.

Cystic fibrosis affects over 10,000 children and young adults in the UK and has an incidence of 1 in 2500 live births. About 1 in 25 people are carriers of a faulty gene (or 'mutation') that can cause cystic fibrosis. For someone to be born with cystic fibrosis, they must inherit a faulty gene from both parents. There are over 1000 known mutations that can cause cystic fibrosis. The most common mutation is the F508del mutation and around 40–50% of people with cystic fibrosis carry 2 copies of the F508del mutation (termed 'homozygous').

There are currently no treatment options available that specifically target the F508del mutation. Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease. Treatments can be broadly classified as: nutritional repletion (for example, pancreatic enzymes and nutritional supplements); relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators); treatment of acute infections; suppression of chronic infection; suppression of inflammation (for example, steroids, high dose ibuprofen) and lung transplantation. NICE technology appraisal guidance 266 recommends mannitol dry powder for inhalation as an option for treating cystic fibrosis in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and, whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate.

The technology

Lumacaftor and ivacaftor combination therapy (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. It is orally administered as a fixed-dose combination product.

Lumacaftor and ivacaftor combination therapy does not currently have a marketing authorisation in the UK for treating cystic fibrosis. It has been studied in clinical trials compared with placebo in people aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation.

Intervention(s)	Lumacaftor and ivacaftor combination therapy
Population(s)	People with cystic fibrosis who are homozygous for the F508del mutation
Comparators	Established clinical management without lumacaftor and ivacaftor combination therapy (such as, best supportive care including but not limited to, mannitol dry powder for inhalation, inhaled mucolytics, nebulised hypertonic saline, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and oral, nebulised and intravenous antibiotics)
Outcomes	The outcome measures to be considered include: • mortality • lung function • body mass index • respiratory symptoms • pulmonary exacerbations • frequency and severity of acute infections • need for hospitalisation and other treatments • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 266, November 2012, 'Mannitol dry powder for inhalation for treating cystic fibrosis'. Review Proposal Date October 2015. Technology Appraisal No. 276, March 2013, 'Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis'. Review Proposal Date December 2015. Related Guidelines: Clinical Guideline in Preparation, 'Cystic fibrosis: diagnosis and management of cystic fibrosis'. Earliest anticipated date of publication February 2017.
Related National Policy	Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf Manual for prescribed specialised services, November 2014, 'Section 45: Cystic fibrosis services (all ages)'. NHS England. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Vertex Pharmaceuticals (lumacaftor, ivacaftor) Patient/carer group • Action for Sick Children • British Lung Foundation • Contact a Family • Cystic Fibrosis Trust • Genetic Alliance UK • Jewish Genetic Disorders UK • Muslim Council of Britain • National Children's Bureau • South Asian Health Foundation • Specialised Healthcare Alliance • Together for Short Lives Professional groups • Association of Genetic Nurses and Counsellors • Association of Respiratory Nurse Specialists • British Paediatric Respiratory Society • British Thoracic Society • British Society for Genetic Medicine • Chartered Society of Physiotherapists • Cystic Fibrosis Nurses Association • Primary Care Respiratory Society UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Paediatrics & Child Health • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • AbbVie (pancreatin) • Allergan Ltd UK (carbocisteine, nebulised hypertonic sodium chloride) • Essential Pharmaceuticals (pancreatin) • Janssen (pancreatin) • Merck Serono (pancreatin) • Pari Medical (nebulised hypertonic sodium chloride) • Pharmaxis (mannitol dry powder for inhalation) • Roche Products (dornase alfa) • Sanofi (carbocisteine) • Teva (carbocisteine) • Zentiva (carbocisteine) Relevant research groups • British Association for Lung Research • CF Unite

Appendix C

Consultees	**Commentators (no right to submit or appeal)**
• UK Genetic Testing Network UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS England • NHS Newark & Sherwood CCG • NHS West Leicestershire CCG • Welsh Government	• Cochrane Airways Group • Cochrane Cystic Fibrosis and Genetic Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research • UK Cystic Fibrosis Gene Therapy Consortium <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that markets comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cystic fibrosis (*F508del* mutation) - lumacaftor (with ivacaftor) [ID786]

Company evidence submission

November 2015

File name	Version	Contains confidential information	Date
ID786_vertex_cystic fibrosis (F508del mutation) - lumacaftor (with ivacaftor)_company evidence submission_ACIC_11112015	**1**	**Yes (ACIC)**	**11 / 11 / 15**

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
B. cenocepacia	*Burkholderia cenocepacia*
B. cepacia	*Burkholderia cepacia*
B. dolosa	*Burkholderia dolosa*
BMI	Body Mass Index
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic fibrosis questionnaire-revised
CFTR	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
ECFS	European Cystic Fibrosis Society
ECG	Electrocardiogram
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
EQ-5D-3L	EuroQol 5 Dimension 3 level
ERS	European Respiratory Society
FAS	Full Analysis Set
FDC	Fixed dose combination
FEV_1	Forced Expiratory Volume In One Second
GGT	Gamma-glutamyl transpeptidase
GP	General Practitioner
HR	Hazard ratio
HRQoL	Health-Related Quality Of Life
HUI2/3	Health Utility Index 2/3
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IV	Intravenous
IVA	Ivacaftor
kg	kilogram

LFTs	Liver function tests
LS	Least-squares mean
LUM	Lumacaftor
LUM-IVA FDC	Lumacaftor/ivacaftor fixed dose combination
LY	Life Year
M. abscessus	*Mycobacterium abscessus*
MCID	Minimal clinically important difference
mg	milligram
mmol/L	Millimoles Per Litre
MMRM	Mixed-effect model for repeated measures
N/A	Not Available
NBS	Newborn screening
NHS	National Health Service
NMF	New Medicines Fund
OP	Outpatient
P. aeruginosa	*Pseudomonas aeruginosa*
PAS	Patient Access Scheme
PD	Pharmacodynamic, Pharmacodynamics
PI	Pancreatic insufficiency
PK	Pharmacokinetic, Pharmacokinetics
$ppFEV_1$	Percent predicted forced expiratory volume in 1 second
PS	Pancreatic sufficiency
PSSRU	Personal Social Services Research Unit
q12h	Every 12 Hours
QALY(s)	Quality-adjusted life year(s)
QD	Daily
QWB	Quality of Well-Being
rhDNase	Recombinant human deoxyribonuclease
S. aureus	*Staphylococcus aureus*
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form-36 item
SMC	Scottish Medicines Consortium
SOC	System Organ Classification (for adverse events)
SoC	Standard of care
SPC	Summary of product characteristics
SS	Safety Set

TEAE	Treatment emergent adverse event
TNS	Tobramycin nebulizer solution
TSQM	Treatment satisfaction questionnaire for medication
ULN	Upper limits of normal
VAS	Visual Analogue Scale
Z-score	A standardised score that indicates how many standard deviations a data point is from the mean

1. Executive summary

Cystic fibrosis (CF) is a rare, chronically progressive, life-limiting, multi-system, genetic disease, caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein; a regulated ion channel in the apical membrane of epithelial cells that regulates the flow of chloride and other ions across the epithelium (1, 2).These defects arise from mutations in the *CFTR* gene that may be best classified by the severity of their effects on quantity and/or function of CFTR protein.

Patients' lives are interrupted and restricted every day by the disease. The clinical manifestations of CF and their management (e.g. routine daily treatment regimens) impose a significant health, quality of life, lost productivity and economic burden on patients and caregivers (3, 4). While CF is often characterised as a respiratory disorder, it affects multiple organ systems including the pancreas, gastrointestinal (GI) tract, liver, sweat glands, and reproductive system. CF significantly shortens life expectancy, with the UK median age at death being only 28 years in 2014 (5).

Key drivers for morbidity and mortality include:

- Inevitable decline in lung function (as measured by percent predicted forced expiratory volume in one second [$ppFEV_1$]) with each 1% reduction in $ppFEV_1$ increasing the risk of death over 5 years by 4% (6).
- Number of pulmonary exacerbations per year. Compared to having no exacerbations in a year, 1–2 exacerbations per year increases the risk of death 3-fold ($p<0.0001$) and 3 or more exacerbations per-year increases the risk of death 4.5-fold ($p<0.001$) (7).
- Poor nutritional status (low body mass index [BMI] and weight) (6, 7).

Of the more than 2,000 identified mutations of the *CFTR* gene, the most common is the *F508del*-CFTR mutation caused by the inheritance of two copies (one from each parent) of specific mutations in the *CFTR* gene. This results in both decreased quantity due to defective processing of the *F508del*-CFTR protein and impaired activity of the CFTR protein at the apical cell surface, due to low channel open probability. Patients with this mutation have a 14% higher risk for death compared to patients who have one copy of the mutation and a 25% higher risk for death than those who have no copies of the mutation (8).

The ideal goal of treatment is to delay the decline in organ function for as long as possible and avoid complications of the disease (2). In England, CF patients are currently managed with standard of care (SoC) treatments[a] which focus only on controlling symptoms of CF, but these do not address the underlying protein defect leading to the disease. Despite management with SoC, patients continue to have progressive loss of lung function at an annual $ppFEV_1$ decline of one to three percentage points per year (9, 10). As lung function declines, pulmonary exacerbations can become more frequent and the interval between these events may

[a] Including daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents.

shorten. Despite the availability of numerous CF medicines, the frequency of pulmonary exacerbations has not been reduced (11). These exacerbations have a significant impact on patient morbidity and mortality and increase the risk of future exacerbations, reductions in HRQoL, eventually the need for lung transplant, and ultimately death (10, 12-15).

Lumacaftor-ivacaftor (LUM-IVA) is provided as an oral fixed dose combination (FDC). Each tablet contains 200 mg of LUM and 125 mg of IVA with the recommended dose as two tablets, taken orally every 12 hours (4 tablets per day, total daily dose LUM 800 mg-IVA 500 mg) with fat-containing food. It is indicated for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Based on data available from the UK CF Registry and assumptions of CF genotype prevalence and patient age, it is estimated that only 2,748 patients are eligible for treatment with LUM-IVA in England.

The complementary mechanisms of action of both molecules is required to address both protein defects. LUM (a CFTR corrector) enhances stability and function of the protein, and improves quantity, by increasing processing and trafficking of the CFTR protein. IVA (a CFTR potentiator) modulates CFTR function, enhancing the gating channel open probability of the CFTR protein at the cell surface, thereby increasing chloride ion transport (16). The net result is increased quantity and quality of CFTR at the cell surface (16).

LUM-IVA has the potential to restore lung function and slow the rate of lung function decline. It is intended for use in conjunction with SoC and as such, the improvements seen in key clinical outcomes with LUM-IVA treatment during the Phase 3 studies are in addition to that which can be achieved at present with SoC alone. However, SoC is often time consuming and complex and may require a high level of expertise for both the patient and/or carer to administer.

A pooled analysis of the results from TRAFFIC and TRANSPORT (17), demonstrated that at 24 weeks, treatment with LUM-IVA resulted in consistent improvements in several clinically significant treatment measures agreed in previous appraisals by NICE of medicines for CF (TA266 and TA276) (18, 19). These benefits were seen across a variety of subgroups, defined according to various baseline characteristics and concomitant medications suggesting that all eligible patients will benefit from treatment with LUM-IVA (17, 20, 21).

- ***Rapid, consistent and sustained, statistically significant improvement in ppFEV$_1$:*** 2.8 percentage points absolute increase ($p<0.0001$), with a 4.8% relative improvement in ppFEV$_1$ ($p<0.0001$)
- ***Statistically significant improvements in all pulmonary exacerbation-related outcomes:***
    - 39% reduction in the annualised rate of pulmonary exacerbations ($p<0.0001$)
    - 61% reduction in the annualised rate of pulmonary exacerbations requiring hospitalisation ($p<0.0001$)
    - 56% reduction in the annualised rate of pulmonary exacerbations requiring IV antibiotics ($p<0.0001$)

    - Clinically and statistically significant reduction in the mean number of days with pulmonary exacerbations vs. placebo with 8.1 days in the LUM-IVA group versus 15.7 days in the placebo group (p≤0.0002)
- **Statistically *significant improvement in BMI:*** 0.24 kg/m^2 increase in BMI p=0.0004).

Patients who completed the pivotal studies were eligible to enrol in the ongoing extension study, PROGRESS (22): (96 weeks planned duration)

- ***All the above outcomes were sustained with up to 48 weeks of LUM-IVA treatment (TRAFFIC/TRANSPORT – 24 weeks and PROGRESS – 24 weeks), based on pre-planned interim analysis (22).***

The safety results from TRAFFIC and TRANSPORT, and the interim analysis of PROGRESS showed that LUM-IVA is generally well tolerated and addresses the treatment needs in patients with CF while maintaining an acceptable benefit/risk profile (17, 22).

As demonstrated by the pivotal Phase 3 studies and supportive data from PROGRESS, LUM-IVA addresses the primary goals of CF treatment by improving $ppFEV_1$, reducing pulmonary exacerbations and improving nutritional status as reflected by an improvement in BMI (absolute change), all of which are independent key drivers of morbidity and mortality in CF. The multi-factorial effects of the LUM-IVA systemic therapy reflect the benefits to the patient of treating and potentially modifying the underlying cause of CF.

Given the clinical findings, it is reasonable to suggest that LUM-IVA will have a positive impact on life expectancy and this is supported by the predictive modelling of LUM-IVA improvement of 9.4 years (mean undiscounted life years) in patients age 12 years and older who are homozygous for the *F508del* mutation. However, under standard cost analysis techniques survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms. The incremental cost effectiveness ratio (ICER) for LUM-IVA used in conjunction with SoC for indicated patients is £204,787 compared to SoC alone.

By targeting and potentially modifying the underlying cause of disease, LUM-IVA improves and sustains outcomes across multiple clinical parameters and represents a step-change targeted treatment for people with CF age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene; a population with a short life expectancy, high morbidity, and high unmet medical need.

1.1 Statement of the decision problem

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the final NICE scope
Population	People with CF aged 12 years and older who are homozygous[b] for the *F508del* mutation	Yes, the population considered in the submission is people with CF aged 12 years and older who are homozygous for the *F508del* mutation	N/A
Intervention	Lumacaftor and ivacaftor combination therapy	Yes, the intervention considered in the submission is lumacaftor (LUM) and ivacaftor (IVA) combination therapy	N/A
Comparator (s)	Established clinical management without lumacaftor and ivacaftor combination therapy (such as, best supportive care including but not limited to, mannitol dry powder for inhalation, inhaled mucolytics, nebulised hypertonic saline, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and oral, nebulised and intravenous antibiotics)	Yes, submission presents data for LUM-IVA in conjunction with patients' usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), referred to as standard of care [SoC] throughout the submission, vs. SoC alone	N/A
Outcomes	• Mortality • Lung function • Body mass index • Respiratory symptoms • Pulmonary exacerbations • Frequency and severity of acute infections • Need for hospitalisations and other treatments • Adverse effects of	Yes, implications of LUM-IVA treatment on all these outcomes are discussed in the submission	N/A

[b] Carry two copies of the *F508del* mutation.

	treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Yes, health-economic analyses in line with final scope	N/A
Subgroups to be considered	N/A	Results of pre-planned subgroup analyses are provided within the submission	N/A
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

Abbreviations: CF, cystic fibrosis.

1.2 Description of the technology being appraised

Table 2: The technology being appraised

UK approved name and brand name	Lumacaftor/ivacaftor (FDC) - Orkambi™
Marketing authorisation/CE mark status	Awaiting European marketing approval. CHMP positive opinion received 24th September 2015
Indications and any restriction(s) as described in the summary of product characteristics	Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
Method of administration and dosage	LUM-IVA is provided as FDC tablet. Each tablet contains 200 mg of LUM and 125 mg of IVA. The recommended dose is two tablets, taken orally every 12 hours (4 tablets per day, total daily dose LUM 800 mg-IVA 500 mg) LUM-IVA should be taken with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing

Abbreviations: CF, cystic fibrosis; *CFTR*, CF transmembrane conductance regulator; CHMP, Committee for medicinal products for human use; FDC, fixed-dose combination; IVA, ivacaftor; LUM, lumacaftor.

1.3 Summary of the clinical evidence

LUM 400 mg-IVA 250 mg treatment (every 12 hours) up to 48 weeks addresses the primary goals of CF treatment, demonstrated by the pivotal Phase 3 studies; improving ppFEV$_1$, reduction in pulmonary exacerbations and improved nutritional status, reflected by an improvement in BMI (absolute change), all of which are key drivers of mortality in CF. Given that improvements in each of these factors are known to independently predict survival in CF this is an early indication that continued LUM-IVA treatment is expected to positively impact life expectancy.

These clinical improvements in patients with CF age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene are demonstrated by the largest (1,108 patients enrolled in total), interventional, Phase 3 RCTs, conducted to date in this patient population (TRAFFIC and TRANSPORT) (see Appendix 3 – separate document), and is the basis of the integrated summary of efficacy, intended to evaluate the totality of the data.

Patients who completed these studies were eligible to rollover into the ongoing long-term extension study, PROGRESS (Study 105 – planned duration 96 weeks) providing up to 120 weeks of data for patients randomised to active treatment in the original studies.

LUM-IVA is intended for use in conjunction with usual CF care (SoC). In the LUM-IVA and placebo arms of the Phase 3 studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks), patients continued with their usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), for the duration of the studies. Thus, the improvements seen in key clinical outcomes with LUM-IVA treatment are incremental to that which can be achieved with SoC alone.

TRAFFIC and TRANSPORT study designs were almost identical, with the exception of inclusion of ambulatory electrocardiography (TRAFFIC only) and adolescent pharmacokinetic (PK) assessments (TRANSPORT only) for a subgroup of patients (17). The similarity of protocols for key outcome assessments allowed for a pre-specified pooled analysis of results from both studies, providing a robust dataset for analysis with larger patient numbers incorporated. The pooled analysis of TRAFFIC and TRANSPORT is the basis of the integrated summary of efficacy intended to evaluate the totality of the data and is reported for the LUM 400 mg-IVA 250 mg treatment group within this submission. Based on the pooled analysis, (24 weeks) LUM-IVA treatment resulted in (20):

- ***Rapid, consistent and sustained, statistically significant improvement in ppFEV$_1$:*** 2.8 percentage points absolute increase ($p<0.0001$), with a 4.8% relative improvement in ppFEV$_1$ ($p<0.0001$)
- ***Statistically significant improvements in all pulmonary exacerbation-related outcomes:***
    - 39% reduction in the annualised rate of pulmonary exacerbations ($p<0.0001$)
    - 61% reduction in the annualised rate of pulmonary exacerbations requiring hospitalisation ($p<0.0001$)
    - 56% reduction in the annualised rate of pulmonary exacerbations requiring IV antibiotics ($p<0.0001$)
    - Clinically and statistically significant reduction in the mean number of days with pulmonary exacerbations vs. placebo with 8.1 days in the LUM-IVA group versus 15.7 days in the placebo group ($p\leq0.0002$)
- **Statistically *significant improvement in BMI:*** 0.24 kg/m^2 increase in BMI $p=0.0004$).

The improvements in ppFEV$_1$, pulmonary exacerbations and BMI (absolute change) were consistent across subgroups in the pooled analysis, demonstrating that all patients (age 12 years and over who are homozygous for the *F508del* mutation), are expected to benefit from LUM-IVA treatment.

- ***All above outcomes were sustained with LUM-IVA up to 48 weeks of treatment, based on pre-planned interim analysis results, of the ongoing long-term extension study, PROGRESS***
    - Through a total of 48 weeks, LUM-IVA treatment demonstrated:
        - Improvement in ppFEV$_1$ was maintained
        - Lower pulmonary exacerbation rates were maintained
        - Steady improvement in BMI continued.

Additionally, the pattern of responses seen in the TRAFFIC and TRANSPORT studies for the active treatment groups, were repeated when patients who had received placebo were randomised to active treatment in the PROGRESS follow on study.

The safety results from TRAFFIC and TRANSPORT, and the pre-planned interim analysis of PROGRESS demonstrate that LUM-IVA is generally well tolerated (17, 23).

By targeting the underlying cause of the disease, LUM-IVA improves and sustains outcomes across multiple clinical parameters and represents a step-change treatment for people with CF age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene; a population with a short life expectancy, high morbidity, and high unmet medical need.

1.4 Summary of the cost-effectiveness analysis

An individual patient level microsimulation model was constructed to estimate incremental clinical outcomes, health outcomes, and costs of LUM-IVA + SoC versus SoC alone, from an NHS and PSSRU perspective. Model results were estimated over a lifetime horizon.

The model tracks disease progression focusing on nine clinical characteristics that have been found to impact survival in patients with CF; of these clinical characteristics LUM-IVA positively impacts $ppFEV_1$, pulmonary exacerbations, and weight-for-age z-score based on results of the TRAFFIC, TRANSPORT and PROGRESS studies. Study results were matched until week 24 in the model (end of the treatment period in the pivotal studies), and then extrapolated over a patient's lifetime based on available data for LUM-IVA after 24 weeks and published literature.

Clinical characteristics were used to estimate a patient's, health related quality of life (HRQoL), disease management costs and survival. HRQoL was estimated from TRAFFIC and TRANSPORT and disease management costs from a recent UK chart review of CF patients. The model provides estimates of treatment-specific outcomes (deaths, pulmonary exacerbations, lung transplants), median predicted survival, life-years (LYs), quality-adjusted life years (QALYs), and costs, as well as incremental cost-effectiveness ratios calculated as cost per QALY gained and cost per life-year saved, with costs and benefits discounted at 3.5%.

The economic impact of the disease is considerable, with significant cost linked to lost productivity. However under standard cost analysis techniques survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms. The model projects that the improvements in health outcomes with LUM-IVA, will lead to increases in median survival of 7.7 years and mean residual life expectancy of 9.4 years. The results found LUM-IVA + SoC to be associated with an ICER of approximately £204,787 per QALY gained versus SoC alone.

Table 3: Incremental cost-effectiveness results

Technology	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,084,725	13.78	12.38	£707,091	3.46	3.45	£204,787

2. The technology

2.1 Description of the technology

Approved name: Lumacaftor/ivacaftor (LUM-IVA), fixed-dose combination (FDC)

Brand name: Orkambi™

Mechanism of action: Lumacaftor-ivacaftor (LUM-IVA) fixed dose combination (FDC) is the first CF treatment that addresses the specific underlying defects in the CFTR protein in patients who are homozygous for the *F508del* mutation. LUM (a CFTR corrector) modulates and increases the quantity by improving trafficking of the CFTR protein and IVA (a CFTR potentiator) modulates function, enhancing the channel open probability of the CFTR protein at the cell surface, thereby increasing chloride ion transport (16).

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation status: LUM-IVA is awaiting European marketing approval, Committee for medicinal products for human use (CHMP) positive opinion was received on the 24th September 2015. Therefore, approval is expected at the end of November.

Anticipated launch date: December 2015.

Anticipated licensed indication: Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Anticipated contraindications (as per the draft SPC): Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 of the draft SPC.

Date of availability in the UK: December 2015

Summary of marketing authorisation draft assessment report:

The final CHMP report is currently not available. However, the main issues discussed during the EMA's assessment were:

- Clinical relevance of the combination induced treatment effect in the target population considering the magnitude of the effect on the primary endpoint
- Long-term maintenance of treatment effects
- Effects on pulmonary exacerbations
- Benefit with LUM-IVA in patients with rapidly progressive pulmonary disease
- Treatment benefits of LUM-IVA inferred from the pivotal studies as compared to the benefits of the currently used treatment options in these patients

Approval outside of the UK

The marketing status for LUM-IVA (worldwide) is outlined in Table 4.

.

Table 4: Marketing status worldwide

Country	Marketing Status	Proposed/Approved Marketing Indication
United States	NDA approved 02 July 2015	Treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
Europe	MAA positive opinion by CHMP 24 September 2015	Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
Canada	NDS submitted on 29 January 2015	Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
Australia	MAA Category 1, Type A Application submitted on 07 April 2015	Treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene

Abbreviations: CF, cystic fibrosis; *CFTR,* cystic fibrosis transmembrane conductance regulator gene; CHMP, Committee for Medicinal Products for Human Use; MAA, Marketing Authorisation Application; NDA, New Drug Application; NDS, New Drug Submission.

Other health technology assessments in the UK: The Scottish Medicines Consortium (SMC) are currently assessing LUM-IVA (submission date, November 2015).

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

Pharmaceutical formulation	Film-coated tablet. Pink, oval-shaped tablets printed with “2V125” in black ink on one side and plain on the other
Acquisition cost (excluding VAT) *	List price: £8,000 per 112 film-coated tablets (4 packs of 28 tablets, each for a 4-week treatment schedule)
Method of administration	Oral
Doses	Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor
Dosing frequency	The recommended dose is two tablets taken orally every 12 hours (4 tablets per day, total daily dose - lumacaftor 800 mg/ivacaftor 500 mg)
Average length of a course of treatment	Lifetime
Average cost of a course of treatment	List price: £104,000 per patient/per year
Anticipated average interval between courses of treatments	None
Anticipated number of repeat courses of treatments	Initial 4-week treatment schedule, followed by ongoing repeat 4-week treatment schedules
Dose adjustments	When initiating LUM-IVA (Orkambi) in patients taking strong CYP3A inhibitors, the dose should be reduced to one tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose) for the first week of treatment if starting or restarting treatment. For patients with moderate hepatic impairment (Child-Pugh Class B), a dose reduction to two tablets in the morning and one tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) is recommended. Lumacaftor/ivacaftor should be used with caution at a maximum dose of one tablet in the morning and one tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefit
Anticipated care setting	Secondary care / CF specialist clinics
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.	

2.4 Changes in service provision

Additional tests or investigations needed: See patient monitoring below.

Setting of care: Secondary care. Currently specialised treatments for CF are commissioned by NHS England and not via CCG funding routes.

Additional infrastructure: Existing infrastructure will be sufficient.

Patient monitoring: It is recommended that liver function tests (ALT, AST and bilirubin) are conducted before initiating LUM-IVA therapy and then at 1, 3, 6, 9 and 12 months during the

first year of treatment and annually thereafter (24). For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered (24). Given the progressive, multi-system nature of the disease it is envisaged that these requirements can be integrated with routine clinical monitoring to the greater part and thus will not impact significantly on established patient care pathways.

Concomitant therapies: LUM-IVA is intended to be used as adjunct to standard of care (SoC). In all arms of the Phase 3, pivotal studies (2 x LUM-IVA regimens and placebo), patients continued on their usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated) for the duration of the studies (24)..

2.5 Innovation

LUM-IVA is a highly innovative transformative medicine in an area of severe unmet medical need, providing the first treatment that addresses the underlying protein defect of the disease with the potential to reduce disease progression and increase life expectancy in patients who are homozygous for the *F508del* mutation in the *CFTR* gene.

The combined complimentary effect of lumacaftor and ivacaftor is increased quantity and function of *F508del*-CFTR protein at the apical cell surface, resulting in increased chloride ion transport (25). The collective clinical trial data suggest that this combination in patients homozygous for *F508del-CFTR* is important to effectively target the two protein defects that are associated with this mutation; processing and trafficking of CFTR protein to the cell surface, and channel gating for improved chloride transport at the cell surface.

LUM-IVA thus represents a step-change in the management of CF for this specific mutation (homozygous *F508del*) and represents an important treatment option for approximately 50% of all CF patients in England (approximately 2,748 patients).

3. Health condition and position of the technology in the treatment pathway

3.1 Cystic fibrosis

CF is a rare, chronically progressive, life-limiting, genetic disease. While CF is often characterised as a respiratory disorder, and indeed respiratory failure is the predominant cause of death, it affects multiple systems including the pancreas, gastrointestinal tract, liver, reproductive and sweat glands (26). CF significantly shortens life expectancy with the UK median age at death being 28 in 2014 (5).

Inevitable, progressive decline in lung function (measured as $ppFEV_1$), pulmonary exacerbations and poor nutritional status (low BMI and weight) are highly associated with survival and are key independent drivers of mortality in CF (6, 7). Therefore, the primary goals of treatment are maintaining lung function, reducing pulmonary exacerbations and improving nutritional status (11). These outcomes have been accepted as key treatment measures by NICE in previous appraisals of CF medicines (TA266 and TA276) (18, 19, 27).

Pulmonary exacerbations are one of the most significant clinical events in the progression of CF. A large Canadian population based cohort study, published in 2014, utilised hazards modelling to demonstrate that 1–2 exacerbations per year increases the risk of death almost 3-fold ($p<0.0001$), and 3 or more exacerbations per year increases the risk of death 4.5-fold

($p<0.001$) (7). Liou et al., (2001) found that each 1% reduction in $ppFEV_1$ increases the risk of death over 5 years by 4%, suggesting that every percentage point of lung function maintained has a significant clinical value for a patient with CF. Moreover, having one pulmonary exacerbation in a year is estimated to have the equivalent effect on 5-year survival, as a reduction in $ppFEV_1$ of 12 percentage points (6).

3.2 F508del – CFTR *mutation*

The underlying cause of CF is a mutation in the CF transmembrane conductance regulator (*CFTR*) gene, resulting in defective CFTR protein. Almost 2,000 mutations of the *CFTR* gene have been recognised, however the *F508del* mutation is the most prevalent (28, 29). Approximately 50% of patients with CF in the UK are homozygous for the *F508del* mutation (5), resulting in both decreased quantity due to defective processing of the *F508del*-CFTR protein and impaired activity of the CFTR protein at the apical cell surface due to low channel open probability (30).

The CFTR protein acts as a channel for the movement of chloride ions in and out of cells, which is essential for the salt and water balance on epithelial surfaces in multiple organs (31). The defective regulation of salt and water absorption and secretion in CF, leads to exocrine glands in the epithelia, producing abnormally thick secretions which continually damages many organs. As there is no effective long-term strategy for managing the consequences of CF on the lungs, CF mortality is typically characterised by lung deterioration and premature death by respiratory failure.

In addition to the defective processing of *F508del*-CFTR protein, the small amount that is delivered to the cell surface exhibits low channel open probability, and therefore only limited chloride ion transport occurs. Minimal chloride transport in these patients leads to a classical CF phenotype characterised by early onset pancreatic insufficiency, progressive loss of lung function, high rates of infection, and life-expectancy less than half that of the general population in England. Therefore, patients with CF who are homozygous for the *F508del* mutation require a therapy that can address the multiple defects in the CFTR protein and thus target the underlying cause of the disease.

3.3 Burden of disease

The chronic and severely debilitating nature of CF impacts not only patients, but also their families and carers. The effects of declining lung function and breathlessness can mean that routine daily physical activities become arduous tasks for patients. Mental health problems, including anxiety and depression are frequently reported in both patients and caregivers (32, 33). Aside from the physical and psychological impact of the disease, the treatment burden is substantial. Sawicki et al., (2009) found that adult patients with CF were taking up to 20 medications per day and spending an average of 108 minutes on their treatment (4).

In addition to the direct burden on patients, CF imposes a significant societal and economic burden. The disease has a negative impact on the ability of patients with CF to work and may result in time off work or missed educational opportunities. In a study of 254 patients with CF in the UK, 40% of patients reported that they had stopped a job due to CF (34). The substantial cost of productivity loss is highlighted in a separate UK study, which reports a £1.5 million cumulative lifetime productivity loss cost per patient with CF (35). However, this does not take into account either the parents or carers of CF patients and the negative impact on their lives and productivity. In addition to the direct burden on patients, CF

imposes a significant societal and economic burden. The disease has a negative impact on the ability of patients with CF to work and may result in time off work or missed educational opportunities. In a study of 254 patients with CF in the UK, 40% of patients reported that they had stopped a job due to CF (34). The substantial cost of productivity loss is highlighted in a separate UK study, which reports a £1.5 million cumulative lifetime productivity loss cost per patient with CF (35). However, this does not take into account the parents or carers of CF the patients and the negative impact on their lives and productivity.

A UK burden of illness study in patients with CF age 12 years and older, who are homozygous for *F508del* mutation (36), confirmed that resource utilisation, including medication use and hospitalisations were high in this group of patients. Over a 24-month period:

- 83% of patients experienced a pulmonary exacerbation
    - 75% of patients experiencing a pulmonary exacerbation had a hospitalisation
    - 78% of patients experiencing a pulmonary exacerbation were prescribed intravenous (IV) antibiotics
- 99% of patients were receiving pancreatic enzymes and a high proportion of patients were receiving antibiotics (oral 98% and nebulised 87%).

3.4 Unmet need

Irreversible structural lung damage is evident in early infancy, often in the absence of respiratory symptoms (37). Grasemann and Ratjen (2013) highlight the importance of early intervention to postpone or prevent the onset of lung disease in patients with CF (38). The importance of early intervention is recognised in England by the investment made in newborn screening, which identifies those with CF shortly after birth. While it is important to recognise the improvements in CF care over the past years, there has been little incremental effect on predicted survival. In 2010, the median age of death was 29 years vs 28 in 2014 (5). Moreover, despite management with SoC symptomatic therapies, patients still have progressive loss of lung function at an annual $ppFEV_1$ decline of one to three percentage points per year, and experience frequent pulmonary exacerbations (9, 10). As lung function declines, pulmonary exacerbations become more frequent and the clinically-important time between exacerbations gets shorter, allowing the patient less time to recover (39). The accelerating progression that characterises CF continues despite the use of numerous medicines that manage exacerbations once they occur (39). Pulmonary exacerbations have a significant impact on patient morbidity and mortality as they are associated with an accelerated decline in lung function, increased risk of future exacerbations, reductions in HRQoL, increased risk of death or need for a lung transplant (10, 12-15).

Patients who are homozygous for the *F508del* mutation in England are currently managed with SoC treatments[c] which focus on controlling symptoms of CF and do not address the progressive lung deterioration that typically leads to death in patients with CF. None of the currently available treatments address the underlying cause of this multi-organ disease. For

[c] Including daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents and daily physiotherapy.

some specific patients that qualify for strict criteria, lung transplantation is the only remaining option at present.

While individual CF specialist centres in England often have treatment guidelines, and the UK Cystic Fibrosis Trust has published a number of consensus documents on best practice in the management of CF (40); there is, however, currently no published NICE guidance. A guideline for the diagnosis and management of CF is under development by NICE that is due for publication in 2017. NICE has previously appraised the following SoC treatments for CF:

- TA276: Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (published March 2013)
- TA266: Mannitol dry powder for inhalation for treating cystic fibrosis (published November 2012)

3.5 Lumacaftor-ivacaftor

LUM-IVA FDC received positive CHMP opinion on the 24th September 2015 for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. LUM-IVA is provided as an oral FDC tablet. Each tablet contains 200 mg of LUM and 125 mg of IVA. The recommended dose is two tablets, taken orally every 12 hours (4 tablets per day, total daily dose LUM 800 mg-IVA 500 mg).

LUM-IVA is intended for use as an adjunct to SoC and as such, will not replace SoC treatments in clinical practice. In the LUM-IVA and placebo arms of the Phase 3 studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks), patients continued on their usual CF management e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated (termed SoC throughout this submission). Therefore, the improvements seen in key clinical outcomes with LUM-IVA in conjunction with SoC are in addition to that which was seen with placebo + SoC.

3.6 Equality

At present, CF patients aged 6+ years old with specified gating mutations have access to IVA monotherapy as an effective and generally well tolerated treatment for the underlying cause of their CF. CF patients aged 12+ who are homozygous for the *F508del* mutation deserve timely access to LUM-IVA as it represents a similar and appropriate treatment option for these patients.

4. Identification and selection of relevant studies

Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify available clinical literature for LUM monotherapy, IVA monotherapy, LUM-IVA combination therapy, and SoC therapies for patients with CF (randomised and non-randomised trials).

Although included in the systematic review, details of available SoC studies are not presented in this submission, because as previously described in the trial design sections,

the efficacy and safety of LUM-IVA was evaluated as an adjunct to SoC and compared to placebo in addition to SoC in the Phase 3 studies for LUM-IVA (TRAFFIC and TRANSPORT). Therefore, SoC are not appropriate comparators as the benefits of LUM-IVA are incremental to SoC.

The searches were conducted in a range of relevant electronic databases (outlined in Table 6), on the 29th July 2015 (EMBASE) and the 3rd August 2015 (Cochrane). Searches were restricted by date to the last 10 years (2005–2015)

The searches included terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) through the use of Boolean combination techniques. The use of explosion, free text and wild cards were used to ensure all relevant literature was captured in the search using the EMBASE indexing to automatically apply the limits. The search strategies are outlined in the Appendix (separate document).

Electronic searches were supplemented by hand searching the European Cystic Fibrosis Society (ECFS) conference proceedings (Table 6). The search was restricted by date (1st January 2015 – 31st July 2015).

Table 6: Databases searched and interfaces used in the systematic review

	Database	Interface	Date limits
Electronic database searches	Embase	EMBASE	1st January 2005 - 29th July 2015
	Medline	EMBASE	1st January 2005 - 29th July 2015
	Medline (R) In-Process	EMBASE	1st January 2005 - 29th July 2015
	Cochrane Database of Systematic Reviews	The Cochrane Library	1st January 2005 - 3rd August 2015
	Database of Abstracts of Reviews of Effects	The Cochrane Library	1st January 2005 - 3rd August 2015
	The Cochrane Central Register of Controlled Trials (CENTRAL)*	The Cochrane Library	1st January 2005 - 3rd August 2015
Conference proceedings	European Cystic Fibrosis Society	-	1st January 2015 - 31st July 2015

* Includes controlled-trial register.

To be included in the review, studies had to meet pre-defined eligibility criteria (outlined in Table 7).

Table 7: Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Cystic fibrosis (all mutations and all ages)	-
Intervention	• Ivacaftor • Lumacaftor • LUM-IVA	-
Comparators	SoC	SoC not used in current clinical practice
Outcomes	• BMI • FEV_1 • Pulmonary exacerbations • Sweat chloride levels • Weight • Z-score	-
Study design	• Observational • Randomised controlled studies	• Cross-over • Individual case study • Pilot • Retrospective/Post-hoc • Reviews/letters/comments • Time/dose comparison
Language	-	Non-English

Abbreviations: LUM-IVA, Lumacaftor + Ivacaftor; SoC, standard of care; BMI, body mass index; FEV_1, forced expiratory volume in one second

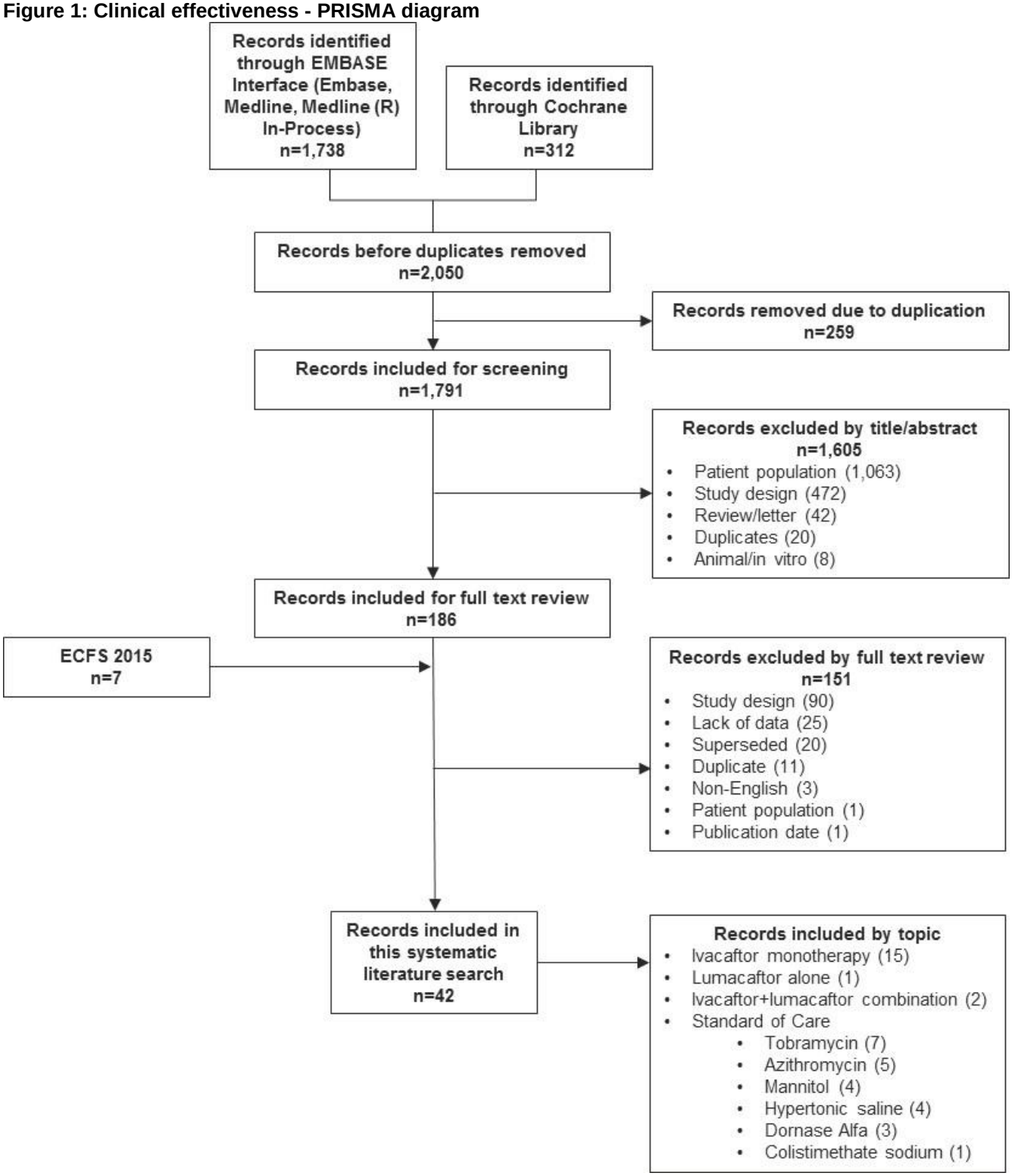
Duplicates were removed for all records obtained from the electronic database searches before a manual review of the titles and abstracts was undertaken using the predetermined eligibility criteria to identify studies to be considered for further review (1st pass). Full-text articles were obtained for those that met the inclusion. Full-text articles were then screened and included or excluded accordingly (2nd pass). Records not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion at 1st and 2nd pass.

Screening was performed by two independent reviewers and discrepancies were resolved by a third independent reviewer.

Following assessment and exclusion of studies based on title, abstract and full text, 42 studies were included in the final data set. The systematic review schematic is shown in Figure 1.

A list of excluded studies (IVA monotherapy, LUM monotherapy and LUM-IVA combination) is provided in the Appendix (separate document).

Figure 1: Clinical effectiveness - PRISMA diagram



The final included papers were then reviewed to identify those reporting data in the homozygous *F508del* mutation population. Four publications included in the systematic review reported on studies that are relevant to the indicated population, including five studies in the LUM-IVA clinical study programme, as follows:

- 1 of 15, IVA monotherapy publications – Flume et al., (2012) (41)
- 1 of 1, LUM monotherapy publications – Clancy et al., (2012) (42)
- 2 of 2, LUM-IVA publications – Boyle et al., (2014) (16), Wainwright et al., (2015) (17)
- 0 of 24, SoC publications (see Appendix 3 – separate document, Table (i)).

The separate search of the manufacturer's database identified six (Phase 2 and 3) studies included in the clinical study programme for LUM-IVA (Table 8).

The sixth study in the LUM-IVA clinical study programme, PROGRESS (Study 105) (23), (Table 8), is an ongoing long-term extension study of TRAFFIC (Study 103) and TRANSPORT (Study 104), which is currently unpublished and as such, was not identified by the systematic review. The primary reference for this study is therefore, the interim analysis, clinical study report (23).

4.2 List of relevant randomised controlled trials

The list of relevant RCTs for this submission, is provided in Table 8.

Table 8: List of relevant RCTs: LUM-IVA clinical study programme

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
Study 770-104 DISCOVER Phase 2	Patients with CF (≥12 years) homozygous for the *F508del-CFTR* mutation	IVA monotherapy	Placebo	Flume et al., (2012) (41)
Study 809-101 Phase 2	Patients with CF (≥18 years) homozygous for the *F508del-CFTR* mutation	LUM monotherapy	-	Clancy et al., (2012) (42)
Study 809-102 Phase 2	Patients with CF (≥18 years) homozygous for the *F508del-CFTR* mutation‡	LUM-IVA	-	Boyle et al., (2014) (16)
Study 103 TRAFFIC Pivotal Phase 3	Patients with CF (≥12 years) homozygous for the *F508del-CFTR* mutation	LUM-IVA	Placebo	Wainwright et al., (2015) (17)
Study 104 TRANSPORT Pivotal Phase 3	Patients with CF (≥12 years) homozygous for the *F508del-CFTR* mutation	LUM-IVA	Placebo	Wainwright et al., (2015) (17)
Study 105 PROGRESS Phase 3 ongoing extension study of TRAFFIC and TRANSPORT	Patients with CF (≥12 years) homozygous for the *F508del-CFTR* mutation	LUM-IVA	-	Interim analysis, Clinical study report (23)

‡With the exception of one group in cohort 2 which included patients heterozygous for the *F508del-CFTR* mutation.

The clinical study programme for lumacaftor and ivacaftor (LUM-IVA) FDC included, three Phase 2 studies, to assess the safety, pharmacokinetics, and signal of effect of IVA monotherapy (Study 770-104 [DISCOVER]) (41), LUM monotherapy (Studies 809-101 and 809-102) (16, 42), and LUM-IVA in combination (Study 809-102) (16) in subjects with CF who were homozygous for the *F508del-CFTR* mutation.

In addition, two pivotal, Phase 3 studies, TRAFFIC (Study 103 – 24 weeks) (17) and TRANSPORT (Study 104 – 24 weeks) (17) evaluated the efficacy and safety of LUM-IVA in patients with CF who were homozygous for the *F508del-CFTR* mutation (17).

Patients who completed TRAFFIC or TRANSPORT were eligible to rollover into the ongoing long-term extension study, PROGRESS (Study 105 – 96 weeks).

A summary of the Phase 2 studies, Study 770-104 (IVA monotherapy), Study 809-101 (LUM monotherapy) and Study 809-102 (LUM-IVA) is provided in section 4.2.1. The methodology and results for the Phase 3 studies are reported in detail (section 4.3 onwards).

4.2.1 Phase 2 studies

An outline of the methodology and results from the Phase 2 studies is provided in Table 9.

Results from Phase 2 studies demonstrated that neither LUM monotherapy nor IVA monotherapy had a clinically meaningful effect in patients with CF who are homozygous for the *F508del* mutation (16, 41, 42). Results from Study 809-102 demonstrated that combining LUM with IVA suggested a positive efficacy signal, and informed the dosing for the Phase 3 LUM-IVA studies (16).

Table 9: Summary of Phase 2 studies relevant to this submission

Study number (acronym)	Design	Intervention	Study length	Randomised N=	Patient population	Outcomes
770-104 (DISCOVER) (41)	Randomised, double-blind placebo-controlled	IVA 150 mg q12h	16 weeks (Part A) 96 weeks (Part B)[†]	140	Patients with CF (≥12 years) homozygous for the *F508del-CFTR* mutation	Primary: Safety Primary efficacy: Absolute change in $ppFEV_1$ Secondary: Absolute change in sweat chloride, weight and CFQ-R respiratory symptoms scale
Results	The incidence of AEs was similar across the groups. All AEs considered severe were reported in the IVA group. Conversely there was a higher incidence of SAEs in the placebo group, supporting the conclusion that treatment with IVA does not lead to safety concerns. No new safety events arose during the 40-week open-label extension. No clinically meaningful benefit was observed after 16 weeks of IVA monotherapy across a range of outcomes in this population. Furthermore, no clinical benefit was observed over the first 24 weeks of open-label treatment in Part B; therefore, Part B of the study was terminated early.					
809-101 (42)	Randomised double-blind, placebo-controlled, multi-dose finding	LUM 25 or 50 mg (Group A) LUM 100 or 200 mg (Group B)	28 days	89	Patients with CF (≥18 years) homozygous for the *F508del-CFTR* mutation	Primary: Safety Secondary: PK effect on *CFTR* function using sweat chloride, nasal potential difference. Evaluation of pulmonary function using spirometric measures including $ppFEV_1$, and evaluation of CFQ-R
Results	Primary: The type and incident of AEs were similar among LUM and placebo groups. Respiratory adverse events were the most commonly reported type of AE and led to discontinuation by one subject in each of the four active treatment arms. Eight AEs were considered severe. Secondary: PK data supported once-daily oral dosing regimen. PD data suggested that LUM improved CFTR function in at least one organ (sweat gland). LUM reduced elevated sweat chloride values in a dose-dependent manner (statistically significant in the 100 mg and 200 mg groups). There was no significant improvement in $ppFEV_1$ compared with baseline or placebo in any LUM group. There was no statistically significant improvement in CFTR function in the nasal epithelium, nor were there statistically significant changes in lung function or CFQ-R.					
809-102 (16)	Randomised	LUM monotherapy 200 mg qd for 14	56 days	62	Patients with CF	Primary: Change in

	double-blind, placebo-controlled, multicentre, multi-dose finding	days[±] followed by LUM 200 mg + IVA 150 mg or 250 mg q12h for 7 days (cohort 1) LUM monotherapy 200 mg, 400 mg, or 600 mg qd for 28 days followed by LUM 200 mg qd + IVA 250 mg q12h, LUM 400 mg qd + IVA 250 mg q12h, or LUM 600 mg qd + IVA 250 mg q12h for 28 days (cohort 2) LUM monotherapy 400 mg q12h for 28 days followed by LUM 400 mg q12h + IVA 250 mg q12h for 28 days (cohort 3)		(cohort 1) 109 (cohort 2) 15 (cohort 3)	(≥18 years) homozygous for the *F508del-CFTR* mutation[‡]	sweat chloride concentration during combination therapy and safety Secondary: Absolute change from baseline in $ppFEV_1$, sweat chloride concentration, change in CFQ-R
Results	Primary: For cohorts 2 and 3, mean sweat chloride concentration decreased significantly over the entire period in LUM-IVA groups (homozygous population) with the exception of the LUM 200 mg qd + IVA 150 mg q12h group Overall there was a similar proportion of AEs in LUM monotherapy, LUM-IVA and placebo. Treatment with higher doses of LUM monotherapy were associated with an increased risk of chest tightness. These symptoms were mild to moderate, two patients discontinued treatment. Secondary: Treatment with LUM monotherapy resulted in a dose-dependent decline in $ppFEV_1$. A statistically significant improvement in $ppFEV_1$ was observed in homozygous patients who received the higher doses of LUM-IVA combination (LUM 600 mg qd-IVA 250 mg q12h and LUM 400 mg q12h-IVA 250 mg q12h). Improvements in $ppFEV_1$ in the lower dose groups (LUM 200 or 400 mg qd-IVA 250 mg q12h) were not statistically significant. Patients who received LUM 600 mg qd and LUM 400 mg q12h reported increased respiratory symptoms during monotherapy compared with baseline followed by significant improvement in symptoms during LUM-IVA treatment.					

Abbreviations: AEs, adverse events; CF, cystic fibrosis; CFQ-R, cystic fibrosis questionnaire-revised; *CFTR*, CF transmembrane conductance regulator; IVA, ivacaftor; LUM, lumacaftor; PK, pharmacokinetics; $ppFEV_1$, forced expiratory volume in 1 second; q12h, every 12 hours; qd, daily.

[†]Patients who had achieved pre-specified levels of change in FEV_1 or sweat chloride were eligible for the open-label extension phase of the study.

[‡]With the exception of one group and some of the placebo patients in cohort 2 which included patients heterozygous for the *F508del-CFTR* mutation.

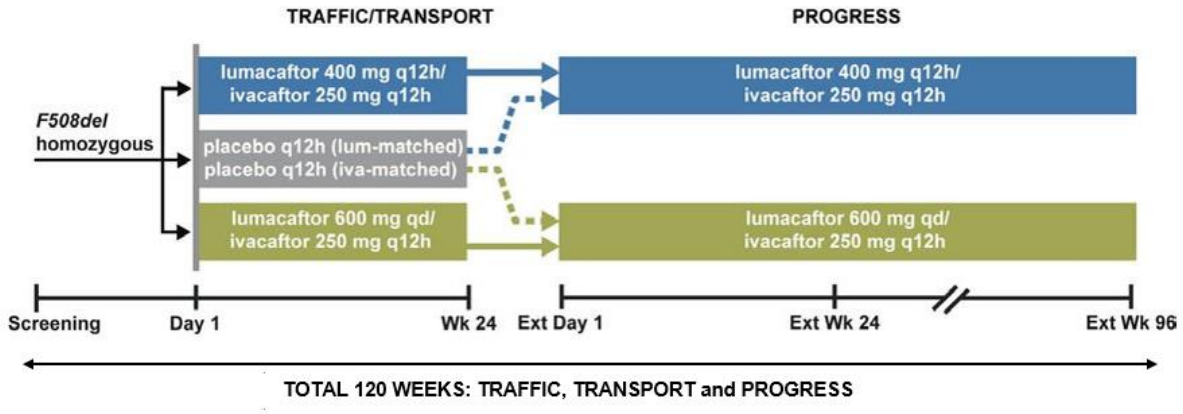
[±]In all cohorts LUM was given as monotherapy prior to the addition of IVA.

4.3 Summary of methodology of the relevant randomised controlled trials

The study design (Figure 2) and methods of analysis for the Phase 3, pivotal studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks) were almost identical, with the exception of inclusion of ambulatory electrocardiography screening (TRAFFIC only) and adolescent PK assessments (TRANSPORT only) (17). Therefore a pre-specified pooled analysis of results from both studies was conducted. The pooled analysis of TRAFFIC and TRANSPORT is the basis of the integrated summary of efficacy intended to evaluate the totality of the data and is reported for the LUM 400 mg-IVA 250 mg treatment group only within this submission[d]. Results are presented separately for TRAFFIC and TRANSORT and the pre-specified pooled analysis of TRAFFIC and TRANSPORT in section 4.7.

Patients who completed TRAFFIC or TRANSPORT were eligible to rollover into the ongoing long-term extension study, PROGRESS (Study 105 – 96 weeks), (Figure 2). A pre-planned interim analysis of PROGRESS was conducted after all patients in Part A (Treatment Cohort) completed the Week 24 study visit (i.e. up to 48 weeks of LUM-IVA treatment). The methodology of PROGRESS is presented in this section and interim results are presented in section 4.7.

Figure 2: Study design TRAFFIC, TRANSPORT and PROGRESS



[d] The pivotal studies included a LUM 600 mg once daily-IVA 250 mg every 12 hours arm, results are not reported within this submission as this dose of LUM-IVA is not included in the LUM-IVA licensed indication.

Table 10: Comparative summary of trial methodology

Trial number (acronym)	Study 103 (TRAFFIC) and Study 104 (TRANSPORT)	Study 105 (PROGRESS)
Location	187 sites in Europe (including 5 sites in the UK), North America and Australia	191 sites in Europe (including 5 sites in the UK), North America and Australia
Trial design	24 week, Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group	96 week, Phase 3, multicentre, parallel-group, double blinded with no placebo arm The study consists of 2 parts (Part A and Part B). Part A enrolled patients homozygous for the *F508del-CFTR* mutation who participated in TRAFFIC and TRANSPORT. Part A consists of a Treatment Cohort and an Observational Cohort. Part B enrolled patients heterozygous for the *F508del-CFTR* mutation (No further details will be presented for Part B as the heterozygous population is not included in the LUM-IVA licensed indication and therefore deemed not relevant to the submission)
Eligibility criteria for participants	• Male and female ≥12 years of age • Confirmed diagnosis of CF with sweat chloride ≥ 60mmol/L and chronic sinopulmonary disease OR gastrointestinal/ nutritional abnormalities • Homozygous for the *F508del* mutation in the *CFTR* gene • Stable CF disease • At screening, FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height[†]	*Treatment Cohort, Part A* • Patients who were receiving LUM-IVA or placebo at the end of treatment in TRAFFIC or TRANSPORT were eligible to enrol in Part A (Treatment Cohort) • Patients who were not receiving study drug at the end of treatment in TRAFFIC and TRANSPORT and had received Vertex approval for entry were also eligible to enrol in Part A (Treatment Cohort) • Patients who prematurely discontinued study drug treatment were not eligible for enrolment in Part A (Treatment Cohort) *Observational Cohort (Part A)* Patients who received at least 4 weeks of LUM-IVA (who were not eligible or elected to enrol in Part A

Trial number (acronym)	Study 103 (TRAFFIC) and Study 104 (TRANSPORT)	Study 105 (PROGRESS)
		(Treatment Cohort) were eligible to enrol in Part A (Observational Cohort)
Settings and locations where the data were collected	Specialist care centres in USA, Canada, Europe and Australia	Specialist care centres in USA, Canada, Europe and Australia
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	**Study drugs:** Patients were randomised in a 1:1:1 ratio to receive 1 of 3 treatments: • Treatment Arm A - LUM 600 mg qd-IVA 250 mg q12h. Provided as three LUM 200 mg-IVA 83 mg FDC tablets given in combination with two IVA 125 mg tablets (TRAFFIC n=183; TRANSPORT n=185)‡ • Treatment Arm B - LUM 400 mg q12h and IVA 250 mg q12h, provided as a LUM 200 mg-IVA 125 mg FDC tablet (TRAFFIC n=182; TRANSPORT n=187) • Treatment Arm C - matching placebo (TRAFFIC n=184; TRANSPORT n=187) **Concomitant medications:** In all arms of the studies patients continued on their usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated) regimen from 4 weeks prior to the start of study treatment through the end of study treatment (Week 24).	**Study drugs:** *Treatment Cohort (Part A)* Patients who received LUM-IVA combination in TRAFFIC or TRANSPORT continued to receive the same dosing regimen in a double-blind fashion for 96 weeks Treatment Arm 1 LUM 600 mg qd/IVA 250 mg q12h (n=334) or Treatment Arm 2 LUM 400 mg q12h/IVA 250 mg q12h (n=341) Patients who received placebo in TRAFFIC or TRANSPORT were randomised in a 1:1 ratio to Treatment Arm 1 (n=179) or Treatment Arm 2 (n=176) as described above Treatment Arm 1 LUM 600 mg qd/IVA 250 mg q12h Treatment Arm 2 LUM 400 mg q12h/IVA 250 mg q12h *Observational Cohort (Part A)* Patients in this cohort did not receive study drug. **Concomitant medications:** As per TRAFFIC and TRANSPORT
Primary outcomes (including scoring methods and timings of assessments)	**Primary outcome:** Absolute change from baseline in ppFEV$_1$ at Week 24 (calculated by	**Primary outcome (Part A, Treatment Cohort A):** Safety of long-term treatment of LUM-IVA based on AEs, clinical laboratory

Trial number (acronym)	Study 103 (TRAFFIC) and Study 104 (TRANSPORT)	Study 105 (PROGRESS)
	averaging the mean absolute change at Week 16 and Week 24). This approach was used as it was anticipated that it would reduce known variability, as compared with using the point estimate at Week 24 alone. **Scoring method:** Spirometry was performed according to the American Thoracic Society Guidelines. **Timing of assessments:** All visits were scheduled relative to the Day 1 Visit (first dose of study drug) Scheduled Clinic Visits: Day 1, Day 15, Week 4, 8, 16 and 24	values (serum chemistry, haematology, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry. The primary outcome is not applicable for Part A (Observational Cohort). **Scoring method (Part A, Treatment Cohort):** As outlined above for safety. **Timing of assessments (Part A, Treatment Cohort):** Scheduled Clinic Visits: Day 1, Day 15, Week 4, 8, 16, 24, 36, 48, 60, 72, 84 and 96
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	**Key secondary outcomes:** • Relative change in $ppFEV_1$ at Week 24 (average at Week 16 and Week 24) • Absolute change from baseline in BMI at Week 24 • Absolute change from baseline in the CFQ-R respiratory domain score at Week 24 • Response, defined as ≥5% increase in average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 24 • Number of pulmonary exacerbations from baseline through Week 24[±] **Other secondary and additional efficacy**	**Secondary efficacy outcomes (Part A, Treatment Cohort):** • Absolute change from baseline in $ppFEV_1$ • Relative change in $ppFEV_1$ • Absolute change from baseline in BMI • Absolute change from baseline in the CFQ-R respiratory domain score • Number of pulmonary exacerbations starting from the previous study • Time-to-first pulmonary exacerbation through including pulmonary exacerbations in the previous study (Part A only) • Risk of having at least one exacerbation including pulmonary exacerbations in the previous study • Absolute change from baseline weight • Absolute change in BMI z-score

Trial number (acronym)	Study 103 (TRAFFIC) and Study 104 (TRANSPORT)	Study 105 (PROGRESS)
	outcomes: • Absolute change in FEV_1 (in litres) at Week 24 • Number of pulmonary exacerbations requiring hospitalisation at Week 24 • Number of pulmonary exacerbations requiring IV antibiotics at Week 24 • Time-to-first pulmonary exacerbation through Week 24 • Risk of having at least one exacerbation at Week 24 • Number of days with pulmonary exacerbation at Week 24 • Number of days hospitalised for pulmonary exacerbation at Week 24 • Number of days on IV antibiotics for pulmonary exacerbations at Week 24 • Absolute change in weight at Week 24 • Absolute change in BMI z-score at Week 24 (patients 12–20 years old) • Absolute change from baseline in the EQ-5D-3L single utility index and VAS at Week 24 • Absolute change from baseline in the TSQ-M at Week 24 **Timing of assessments:** Scheduled Clinic Visits; Day 1, Day 15, Week 4, 8,	(<20 years old) **Additional efficacy outcomes (Part A, Treatment Cohort):** • Number of pulmonary exacerbations requiring hospitalisation • Number of pulmonary exacerbations requiring IV antibiotics **Timing of assessments (Part A, Treatment Cohort):** Scheduled Clinic Visits: Day 1, Day 15, Week 4, 8, 16, 24, 36, 48, 60, 72, 84 and 96

Trial number (acronym)	Study 103 (TRAFFIC) and Study 104 (TRANSPORT)	Study 105 (PROGRESS)
	16 and 24	
Pre-planned subgroups	Pre-planned subgroup analyses of the primary outcome and key secondary outcomes were conducted according to various baseline characteristics and concomitant medications	Pre-planned subgroup analyses of the primary outcome and key secondary outcomes were conducted according to various baseline characteristics and concomitant medications

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR; CF transmembrane conductance regulator; EQ-5D-3L, EuroQoL-5 Dimension-3 Level; FDC, fixed-dose combination; IV; intravenous; IVA, ivacaftor; LUM, lumacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; qd, once daily; q12h, every 12 hours; TSQ-M, treatment satisfaction questionnaire for medication; VAS, visual analogue scale.

† Mild to moderate CF.

‡ No further details will be presented for the LUM 600 mg-IVA 250 mg group as this dose is not included in the licensed indication and therefore is deemed not relevant to the submission.

± Pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) for any four or more of the following signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise; fatigue; or lethargy; temperature above 38ºC; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection

Source: Vertex Pharmaceuticals, data on file (23, 43, 44); Wainwright et al., (2015) (17).

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Table 11: Summary of statistical analyses in the RCTs

Trial number (acronym)	(TRAFFIC) Study 103 and (TRANSPORT) Study 104	(PROGRESS) Study 105
Hypothesis objective	To determine the efficacy of LUM-IVA in patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene as measured by $ppFEV_1$ The evaluation of safety was a secondary objective.	The primary objective of PROGRESS (Part A and Part B) is the evaluation of the long-term safety and tolerability (approximately 96 weeks) of LUM-IVA. Secondary objectives are as follows • Part A - evaluation of the long-term efficacy and durability of LUM-IVA for patients in the Treatment Cohort; and the evaluation of post-treatment safety and tolerability of LUM-IVA combination in the Observational Cohort
Statistical analysis	Full Analysis Set - all randomised patients who received at least 1 dose of study drug. The FAS was used for all efficacy analyses. Safety Set - all randomised patients who received at least 1 dose of study drug. The Safety Set was used for all safety analyses. The primary outcome was based on a MMRM. The within-group changes, including LS mean, 95% CI and p value were also obtained from this model. To address multiplicity resulting from having two active treatment arms, a Bonferroni correction was applied. A hierarchical testing procedure was used for the primary and key secondary outcomes at $\alpha = 0.025$ for each active treatment arm in each study. The test for treatment effect was considered statistically significant if the $p \leq 0.025$ at each step and all previous tests also met this level of significance. The testing hierarchy was as follows: 1. Absolute change from baseline in $ppFEV_1$ 2. Relative change from baseline in $ppFEV_1$ 3. Absolute change from baseline in	Full Analysis Set - all patients exposed to study drug was used for all efficacy summaries. Safety Set - all patients in Part A (Treatment Cohort) who were exposed to any amount of study drug was used for all safety summaries. For Part A (Observational Cohort), all summaries were based on all enrolled patients in the current study (TRAFFIC or TRANSPORT). For Part A (Observational Cohort), summaries were only provided for the disposition, demographic and baseline characteristics, and serious adverse events (SAEs). <u>Part A</u> For continuous variables, 2 separate mixed model repeated measures (MMRM) models were used to analyse the data from the placebo-controlled period of T&T and the first 24 weeks of Part A. For spirometry variables, the 24-week placebo-controlled period was analysed using an MMRM model including absolute change from T&T baseline in $ppFEV_1$ (including all measurements up to Week 24 [inclusive], both on-treatment

Trial number (acronym)	(TRAFFIC) Study 103 and (TRANSPORT) Study 104	(PROGRESS) Study 105
	BMI 4. Absolute change from baseline in CFQ-R respiratory domain score 5. Response defined as ≥5% increase in average relative change from baseline in ppFEV$_1$ 6. Number of pulmonary exacerbations Analysis of the key secondary outcomes were similar to that of the primary analysis of the primary outcome. If the testing hierarchy was broken, exploratory comparisons between active treatment and placebo were conducted for endpoints below the hierarchy and nominal p values were reported and should be evaluated in that context for biological plausibility and consistency. The hierarchical testing procedure was not used for the pre-specified pooled analyses. For the pooled analysis, the statistical methodology was prepared prior to unblinding of study results. The pooled analysis is the basis of the integrated summary of efficacy intended to evaluate the totality of the data and therefore no type 1 error control was used.	measurements and measurements after treatment discontinuation) as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for study (T&T), sex (male versus female), age group at baseline (<18 versus ≥18 years old), and ppFEV$_1$ severity at screening (<70 versus ≥70), and subject as a random effect was used to estimate the least squares (LS) mean of absolute change from baseline within each treatment at scheduled visits and then calculate the corresponding P values. For the subsequent 24-week period that corresponds to the first 24 weeks in Part A, baseline was defined as the last non-missing measurement before the first dose of active treatment. For subjects who were on active treatment in the previous study, baseline was baseline from T&T. For subjects on placebo who transitioned to active treatment in this study, baseline corresponded to the most recent non-missing measurement prior to receiving active treatment in this study. The other details of the model were the same as that for the placebo-controlled period. Continuous variables other than spirometry were analysed similarly, but were further adjusted for the baseline value of the dependent variable (e.g., analysis of absolute change in BMI included an additional adjustment for the baseline value of BMI). The number of pulmonary exacerbations using a negative binomial regression model that included treatment, study, sex, age group at baseline, and ppFEV$_1$ severity at screening. Time-to-first pulmonary exacerbation was analysed and plotted using the Kaplan-Meier approach. Both on-treatment events and events after treatment discontinuation were considered. The number of subjects with at least 1 pulmonary exacerbation

Trial number (acronym)	(TRAFFIC) Study 103 and (TRANSPORT) Study 104	(PROGRESS) Study 105
		was summarised. <u>Part B</u> Two separate MMRM models were used to analyse the data from the placebo-controlled period of the Study 102 C4 and the first 16 weeks of Part B. For spirometry variables, the 8-week placebo-controlled period was analysed using an MMRM model including absolute change from Study 102 C4 baseline in $ppFEV_1$ (including all measurements up to Week 8 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex (male versus female) and $ppFEV_1$ severity at screening (<70 versus ≥70), and subject as a random effect was used to estimate the LS mean of absolute change from baseline within each treatment at scheduled visits and then calculate the corresponding P values. On Day 1 and Day 7 of the placebo-controlled period, spirometry data were collected twice: predose and 4 hours postdose. Neither postdose measurements were included in this model. For the subsequent 16-week period that corresponded to the first 16 weeks in Part B, baseline was defined as the last non-missing measurement before the first dose of active treatment. For subjects who were on active treatment in the previous study, baseline was from Study 102 C4. For subjects on placebo who transitioned to active treatment in this study, baseline corresponded to the most recent non-missing measurement prior to receiving active treatment in this study. The other details of the model were the same as that for the placebo-controlled period. Continuous variables other than

Trial number (acronym)	(TRAFFIC) Study 103 and (TRANSPORT) Study 104	(PROGRESS) Study 105
		spirometry were analysed similarly, but were further adjusted for the baseline value of the dependent variable (e.g., analysis of absolute change in BMI included an additional adjustment for the baseline value of BMI). Analysis of safety data was conducted using the T&T Safety Set (Part A) and 102 C4 Safety Set (Part B). Only descriptive analyses of safety were performed (i.e., no formal between-treatment or within-treatment statistical testing was performed).
Sample size, power calculation	It was estimated that a sample size of 501 (167 patients for each treatment group) would have 99% power to detect a treatment difference of 5 percentage points in absolute change in ppFEV$_1$ between each of the active treatment groups and the placebo group, assuming a common standard deviation (SD) of 8 and a 10% drop out rate.	Approximately 1,122 patients were potentially eligible to be enrolled. With these 1,122 patients, a 95% CI of (0.391, 0.449) can be obtained assuming a 42% incidence of CF lung (preferred term for pulmonary exacerbations) in CF patients. This is considered adequate for the study objectives.
Data management, patient withdrawals	No imputation of missing data was performed.	No imputation of missing data was performed, unless specified.

Abbreviations: CI, confidence interval LS, least-squares; MMRM, mixed-effect model for repeated measures.
Source: Vertex Pharmaceuticals, data on file (23, 43, 44); Wainwright et al., (2015) (17).

4.5 Participant flow in the relevant randomised controlled trials

LUM-IVA is intended for use as an adjunct to SoC and as such, will not replace SoC treatments in clinical practice. In the LUM-IVA and placebo arms of the Phase 3 studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks), patients continued on their usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), for the duration of the studies. In this submission, the LUM-IVA arm of the pivotal studies is therefore referred to as LUM-IVA + SoC, and the placebo arm as placebo + SoC.

Data is presented for the LUM 400mg-IVA 250 mg (every 12 hours) arm throughout[e].

[e] The pivotal studies included a LUM 600 mg once daily-IVA 250 mg every 12 hours arm, results are not reported within this submission as this dose is not included in the licensed indication.

4.5.1 Patient disposition

Patient disposition data are shown in Table 12.

Table 12: Patient disposition: TRAFFIC, TRANSPORT (T & T) and PROGRESS (Part A, Treatment Cohort)

Disposition Reason	TRAFFIC		TRANSPORT		TRAFFIC/TRANSPORT Pooled		PROGRESS (Part A, Treatment Cohort)	
	LUM-IVA + SoC n (%)	Placebo + SoC n (%)	LUM-IVA + SoC n (%)	Placebo + SoC n (%)	LUM-IVA + SoC n (%)	Placebo + SoC n (%)	LUM-IVA + SoC n (%)	Placebo + SoC (T & T) to LUM-IVA +SoC n (%)
Randomised	187	187	189	187	376	374	341	176
Randomised but never dosed	5	3	2	0	7	3	1	0
Received at least one dose of study drug (Full Analysis Set)	182 (100)	184 (100)	187 (100)	187 (100)	369 (100)	371 (100)	340 (100)	176 (100)
Discontinued treatment Adverse event	10 (5.5) 6 (3.3)	4 (2.2) 4 (2.2)	15 (8.0) 11 (5.9)	5 (2.7) 2 (1.1)	25 (6.8) 17 (4.6)	9 (2.4) 6 (1.6)	31 (9.1) 9 (2.6)	18 (10.2) 10 (5.7)
Completed treatment	172 (94.5)	180 (97.8)	172 (92.0)	182 (97.3)	344 (93.2)	362 (97.6)	0	0
Treatment ongoing	-	-	-	-	-	-	309 (90.9)	158 (98.9)
Discontinued study	6 (3.3)	2 (1.1)	7 (3.7)	2 (1.1)	13 (3.5)	4 (1.1)	-	-
Completed study	176 (96.7)	182 (98.9)	180 (96.3)	185 (98.9)	356 (96.5)	367 (98.9)	-	-

Abbreviations: IVA: ivacaftor every 12 hours; LUM: lumacaftor every 12 hours.
Source: Wainwright et al., (2015) (17). Vertex Pharmaceuticals, data on file (23, 43, 44).
T & T, Placebo arm from Traffic and Transport were entered into treatment arm in PROGRESS

Table 13: Characteristics of participants in TRAFFIC, TRANSPORT and PROGRESS (Part A, Treatment Cohort)

Variable	TRAFFIC		TRANSPORT		Pooled TRAFFIC/TRANSPORT		PROGRESS (Part A, Treatment Cohort)	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371	LUM-IVA + SoC N = 340	Placebo + SoC (T & T) to LUM-IVA +SoC N = 176
Sex, n (%)								
Male	98 (53.8)	100 (54.3)	89 (47.6)	90 (48.1)	187 (50.7)	190 (51.2)	176 (51.8)	90 (51.1)
Female	84 (46.2)	84 (45.7)	98 (52.4)	97 (51.9)	182 (49.3)	181 (48.8)	164 (48.2)	86 (48.9)
Age (years)								
Mean (SD)	25.5 (10.09)	25.0 (10.80)	25.0 (9.03)	25.7 (10.02)	25.3 (9.56)	25.4 (10.41)	25.1 (9.33)	24.9 (10.10)
Range	12-57	12-64	12-54	12-55	12-57	12-64	12-57	12-64
Age groups (years) n (%)								
12 to <18	52 (28.6)	53 (28.8)	46 (24.6)	43 (23.0)	98 (26.6)	96 (25.9)	94 (27.6)	47 (26.7)
≥18	130 (71.4)	131 (71.2)	141 (75.4)	144 (77.0)	271 (73.4)	275 (74.1)	246 (72.4)	129 (73.3)
Race, n (%)								
White	176 (96.7)	183 (99.5)	185 (98.9)	186 (99.5)	361 (97.8)	369 (99.5)	335 (98.5)	174 (98.9)
Ethnicity, n (%)								
Not Hispanic or Latino	174 (95.6)	175 (95.1)	184 (98.4)	181 (96.8)	358 (97.0)	356 (96.0)	331 (97.4)	171 (97.2)
BMI (kg/m^2)								
Mean (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)	21.40 (2.936)	20.86 (2.761)
Range	14.6-29.8	14.4-32.2	14.8-31.4	14.1-29.7	14.6-31.4	14.1-32.2	14.6-31.4	14.1-27.6
$ppFEV_1$ at screening groups, n (%)								
<70	121 (66.5)	123 (66.8)	124 (66.3)	121 (64.7)	245 (66.4)	244 (65.8)	228 (67.1)	118 (67.0)
≥70	55 (30.2)	50 (27.2)	59 (31.6)	59 (31.6)	114 (30.9)	109 (29.4)	103 (30.3)	52 (29.5)

Variable	TRAFFIC		TRANSPORT		Pooled TRAFFIC/TRANSPORT		PROGRESS (Part A, Treatment Cohort)	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371	LUM-IVA + SoC N = 340	Placebo + SoC (T & T) to LUM-IVA +SoC N = 176
$ppFEV_1$ at baseline groups, n (%)								
<40	12 (6.6)	11 (6.0)	17 (9.1)	17 (9.1)	29 (7.9)	28 (7.5)	29 (8.5)	10 (5.7)
≥40 to <70	116 (63.7)	122 (66.3)	117 (62.6)	116 (62.0)	233 (63.1)	238 (64.2)	213 (62.6)	120 (68.2)
≥70 to <90	51 (28.0)	48 (26.1)	49 (26.2)	49 (26.2)	100 (27.1)	97 (26.1)	91 (26.8)	42 (23.9)
>90	1 (0.5)	0 (0.0)	2 (1.1)	3 (1.6)	3 (0.8)	3 (0.8)	3 (0.9)	2 (1.1)
Chronic CF therapy use at baseline, n (%)								
Bronchodilator	173 (95.1)	172 (93.5)	171 (91.4)	170 (90.9)	344 (93.2)	342 (92.2)	317 (93.2)	156 (88.6)
Dornase alfa	123 (67.6)	135 (73.4)	150 (80.2)	146 (78.1)	273 (74.0)	281 (75.7)	254 (74.7)	12.5 (71.0)
Inhaled antibiotic	113 (62.1)	122 (66.3)	112 (59.9)	136 (72.7)	225 (61.0)	258 (69.5)	208 (61.2)	116 (65.9)
Hypertonic saline	112 (61.5)	100 (54.3)	115 (61.5)	120 (64.2)	227 (61.5)	220 (59.3)	214 (62.9)	106 (60.2)
Inhaled c/steroid	109 (59.9)	113 (61.4)	103 (55.1)	107 (57.2)	212 (57.5)	220 (59.3)	193 (56.8)	105 (59.7)

Abbreviations: BMI, body mass index; CF, cystic fibrosis; IV; intravenous; IVA, ivacaftor; LUM, lumacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.
Source: Wainwright et al., (2015) (17). Vertex Pharmaceuticals, data on file (23, 43, 44).

4.6 Quality assessment of the relevant randomised controlled trials

A quality assessment for each RCT is provided in the Appendix (separate document).

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 Results: TRAFFIC (Study 103), TRANSPORT (104) and PROGRESS (Study 105)

LUM-IVA is intended for use as an adjunct to SoC and as such, will not replace SoC treatments in clinical practice. The pivotal studies reflect the intended use of LUM-IVA in clinical practice. In both the LUM-IVA and placebo arms of TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks), patients continued on their usual CF management (as clinically indicated) for the duration of the studies (43, 44). Thus, the improvements seen in key clinical outcomes with LUM-IVA treatment are in addition to that which can be achieved with stable CF medication regimens.

Patients who completed TRAFFIC or TRANSPORT were eligible to rollover into the ongoing long-term extension study, PROGRESS (Study 105 - 96 weeks) giving a total of 120 weeks data for those patients who remained on the active treatment arm.

A pre-planned interim analysis of PROGRESS was conducted after all patients in Part A (Treatment Cohort) completed the Week 24 study visit (up to 48 weeks of treatment, TRAFFIC/TRANSPORT - 24 weeks and PROGRESS - 24 weeks). The primary outcome in PROGRESS was safety, and efficacy outcomes were secondary. Results of the secondary efficacy outcomes from the pre-planned interim analysis for PROGRESS are also presented in this section (up to 48 weeks of treatment; TRAFFIC/TRANSPORT - 24 weeks and PROGRESS - 24 weeks).

4.7.1.1 Primary efficacy outcome: Absolute change from baseline in ppFEV$_1$ at week 24 (TRAFFIC and TRANSPORT) and week 24 – 48 (PROGRESS)

The difference between LUM-IVA + SoC and placebo + SoC with respect to the absolute change from baseline in ppFEV$_1$ at Week 24 (2.8 percentage points) was statistically significant in both studies and the pooled analysis (Table 14) (17). There was a consistent improvement in ppFEV$_1$ from as early as Day 15, (Figure 3). Improvements were rapid in onset and sustained through 24 weeks in the LUM-IVA + SoC group (17).

Table 14: Absolute change from baseline in ppFEV$_1$, FAS population

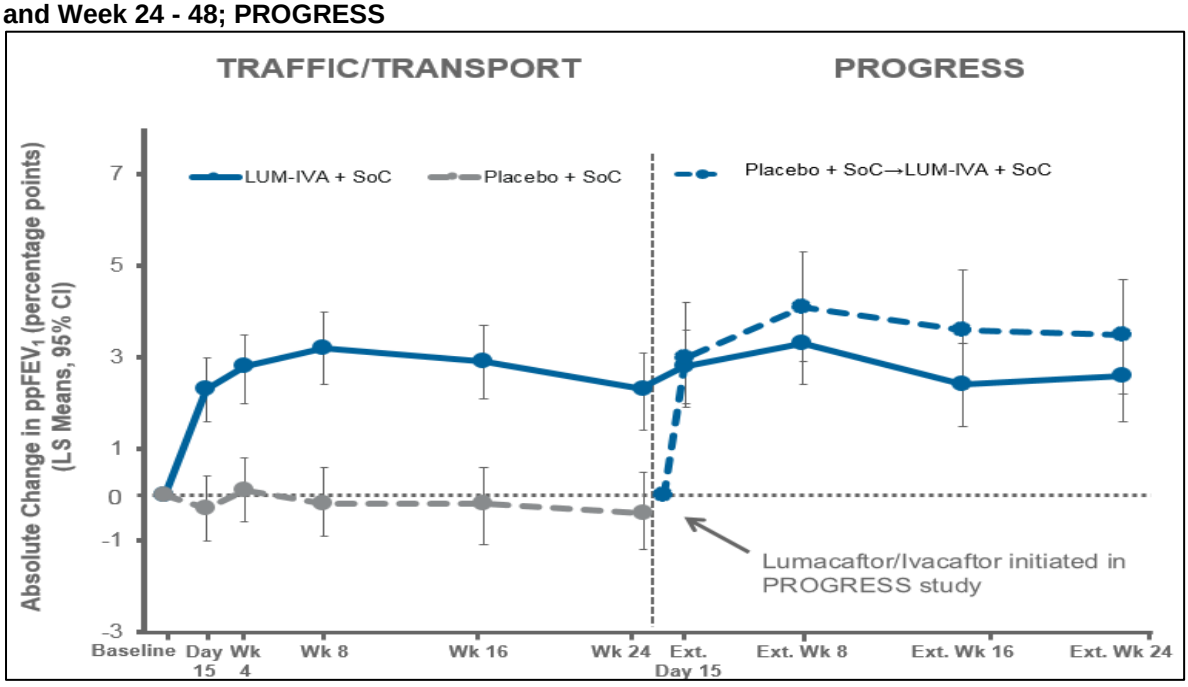
Absolute change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Mean treatment difference (95% CI)	**2.6 (1.2, 4.0) p<0.001**	-	**3.0 (1.6, 4.4) p<0.001**	-	**2.8 (1.8, 3.8) p<0.001**	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Bold text indicates statistical significance.

Source: Wainwright et al., (2015) (17).

Figure 3: Mean absolute change from baseline in ppFEV$_1$ at Week 24; TRAFFIC, TRANSPORT and Week 24 - 48; PROGRESS



Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LS, least-squares; LUM, lumacaftor 400 mg every 12 hours; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; SoC, standard of care.

Source: Adapted from Elborn et al., (2015) (22).

As seen in Figure 3, patients who received LUM-IVA + SoC in TRAFFIC and TRANSPORT maintained the improvement in ppFEV$_1$ through a total of up to 48 weeks of treatment (i.e. maintained through Week 24 study visit of PROGRESS) (22). The LS mean absolute change in ppFEV$_1$ at Week 24 of PROGRESS was 2.6 percentage points (p<0.0001), for the LUM-IVA + SoC group (23).

In both studies, and the pooled analysis, LUM-IVA + SoC resulted in improvements in $ppFEV_1$, regardless of age, sex, prior use of CF medications, and *P. aeruginosa* status (see Appendix, separate document) (17). As such, there are no patient subgroups that can be identified as better or worse responders based on $ppFEV_1$ in the Phase 3 studies. In the pooled analysis, 28 patients in the LUM 400mg-IVA 250mg (every 12 hours) group had $ppFEV_1$ values that had fallen to <40% of predicted at baseline, offering the opportunity to assess patients with more severe disease. The clinical benefit and safety profile observed with LUM-IVA + SoC in this group of patients with severe lung dysfunction was comparable to the overall population (17).

As highlighted earlier in the submission, inevitable progressive decline in lung function is a key driver of morbidity and mortality in patients with CF (6, 7). Preservation of lung function is the primary goal of treatment in patients with CF and is associated with reduced morbidity, improved survival, and can be associated with improved HRQoL. Liou et al., (2001) found that each 1% reduction in $ppFEV_1$ increases the risk of death over 5 years by 4%, demonstrating that every percentage point of lung function is important for a patient with CF (6). Lung function (as measured by $ppFEV_1$) typically declines at a rate of 1–3 percentage points per year in patients treated with SoC (45). The pooled analysis of TRAFFIC and TRANSPORT showed that treatment with LUM-IVA + SoC leads to a rapid, consistent, and sustained improvement in $ppFEV_1$ compared with placebo + SoC in patients age 12 years and older who are homozygous for the *F508del-CFTR* mutation, and the additional interim readout/analysis data from up to 24 weeks of the PROGRESS extension study showed that this improvement was sustained (22).

4.7.1.2 Relative change from baseline in $ppFEV_1$ at Week 24

Relative change in $ppFEV_1$ at Week 24 yielded statistically significant results in the LUM-IVA + SoC group in both studies and the pooled analysis (Table 15) (17).

Table 15: Relative change from baseline in $ppFEV_1$ at Week 24, FAS population

Relative change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Treatment difference (95% CI)	**4.3 (1.9, 6.8) p<0.001**	-	**5.3 (2.7, 7.8) p<0.001**	-	**4.8 (3.0, 6.6) p<0.001**	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Bold text indicates statistical significance.
Source: Wainwright et al., (2015) (17).

Patients who received LUM-IVA + SoC in TRAFFIC and TRANSPORT maintained the improvement in $ppFEV_1$ observed at 24 weeks through a total of up to 48 weeks of treatment in PROGRESS (i.e., maintained through extension Week 24 study visit of PROGRESS). The LS mean relative change in $ppFEV_1$ at Week 24 of PROGRESS was 4.7 percentage points (p<0.0001) for the LUM-IVA + SoC group (23).

4.7.1.3 Number of pulmonary exacerbations through week 24

In the pooled analysis, the rate of pulmonary exacerbations was significantly lower (39%) in the LUM-IVA + SoC group than in the placebo + SoC group (Table 16) (17).

Table 16: Number of pulmonary exacerbations through Week 24, TRAFFIC and TRANSPORT, FAS population

Pulmonary exacerbations	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (rate per 48 weeks)	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†	-	0.57 p<0.001†	-	**0.61 p<0.001**	-

Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
† p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy.
Bold text indicates statistical significance.
Source: Wainwright et al., (2015) (17).

Through 48 weeks of treatment with LUM-IVA + SoC in PROGRESS, the event rate per year (annualised rate) of pulmonary exacerbations (0.64) was significantly lower than the event rate observed in the placebo + SoC groups of TRAFFIC and TRANSPORT (p<0.001) (22) (Table 17). The event rate of 0.64 was consistent with the event rate of pulmonary exacerbations in weeks 0-24 in the LUM-IVA + SoC groups in TRAFFIC and TRANSPORT (0.61, pooled analysis) (22).

For patients who received placebo + SoC in TRAFFIC or TRANSPORT and were subsequently randomised to active treatment in PROGRESS, the annualised rate of pulmonary exacerbations after 24 weeks of active treatment (0.61) was also lower than the event rate observed with placebo + SoC treatment in TRAFFIC and TRANSPORT (46).

Table 17: Number of pulmonary exacerbations: Up to 48 weeks of active treatment, PROGRESS (pooled analysis)

Group	Number of patients with events	Number of events	Event rate/year (annualised rate)
TRAFFIC/TRANSPORT placebo + SoC (24 weeks)	152	237	1.19
LUM-IVA + SoC (TRAFFIC/TRANSPORT and PROGRESS (48 weeks)	146	249	0.64
Placebo + SoC to LUM-IVA + SoC (24 weeks)	48	61	0.61

Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Elborn et al., (2015) (22).

Number of pulmonary exacerbations was also assessed in a variety of subgroups defined according to various baseline characteristics and concomitant medications; the reduction in pulmonary exacerbations in the LUM-IVA + SoC group versus the placebo + SoC group was consistent across all subgroups, (see Appendix, separate document) (21). As such there are no patient subgroups that can be identified as better or worse responders based on number of pulmonary exacerbations in the Phase 3 studies.

4.7.1.4 Number of pulmonary exacerbations requiring hospitalisation at Week 24

Statistically significant reductions (61%) in the number of pulmonary exacerbations requiring hospitalisation were observed in the LUM-IVA group compared with placebo in TRAFFIC, TRANSPORT and the pooled analysis, respectively (Table 18), (Figure 4). The number (event rate per year) of pulmonary exacerbations requiring hospitalisations remained lower (0.19) through 48 weeks of treatment in PROGRESS, in the LUM-IVA + SoC group than the placebo group, in the previous studies (23).

Table 18: Number of pulmonary exacerbations requiring hospitalisation through Week 24, FAS population

Pulmonary exacerbations requiring hospitalisation	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	**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**	NA	**0.39 p=0.0002**	NA	**0.39 p<0.0001**	NA

Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, not applicable; SoC, standard of care.

[±] Figures are rounded to 2 decimal places

Bold text indicates statistical significance.

Source: Wainwright et al., 2015 (17); Vertex Pharmaceuticals, data on file (20).

4.7.1.5 Number of pulmonary exacerbations requiring IV antibiotics through Week 24

Statistically significant reductions (56%) in the number of pulmonary exacerbations requiring IV antibiotics were also observed in the LUM-IVA + SoC group versus placebo + SoC group (

Table 19), (Figure 4).

When patients who had received active treatment entered PROGRESS, the reduction in the number (event rate per year) of pulmonary exacerbations requiring IV antibiotics observed in TRAFFIC and TRANSPORT continued (0.26 through 48 weeks of treatment in PROGRESS) (23).

Table 19 Number of pulmonary exacerbations requiring IV antibiotics through Week 24, FAS population

Pulmonary exacerbations requiring IV antibiotics	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	**33 (no estimate*)**	62 (no estimate*)	**31 (0.23)**	87 (0.64)	**64 (0.25)**	149 (0.58)
Rate ratio[±]	**NA p=0.0050**	NA	**0.36 p<0.0001**	NA	**0.44 p<0.0001**	NA

Abbreviations: IV, intravenous; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, not applicable; SoC, standard of care.

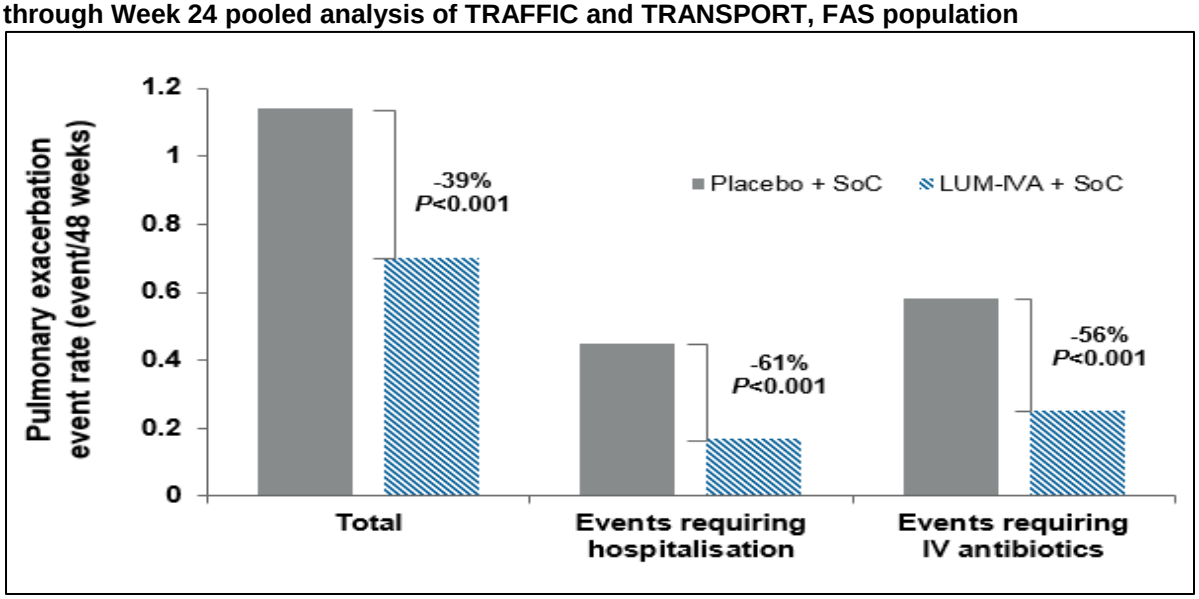
[±] Figures are rounded to 2 decimal places

Bold text indicates statistical significance.

* The event rate per year could not be estimated because the negative binomial distribution model did not converge.

Source: Wainwright et al., (2015) (17); Vertex Pharmaceuticals, data on file (20).

Figure 4: Rate of pulmonary exacerbations requiring hospitalisations and IV antibiotics through Week 24 pooled analysis of TRAFFIC and TRANSPORT, FAS population



Abbreviations: IV, intravenous; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

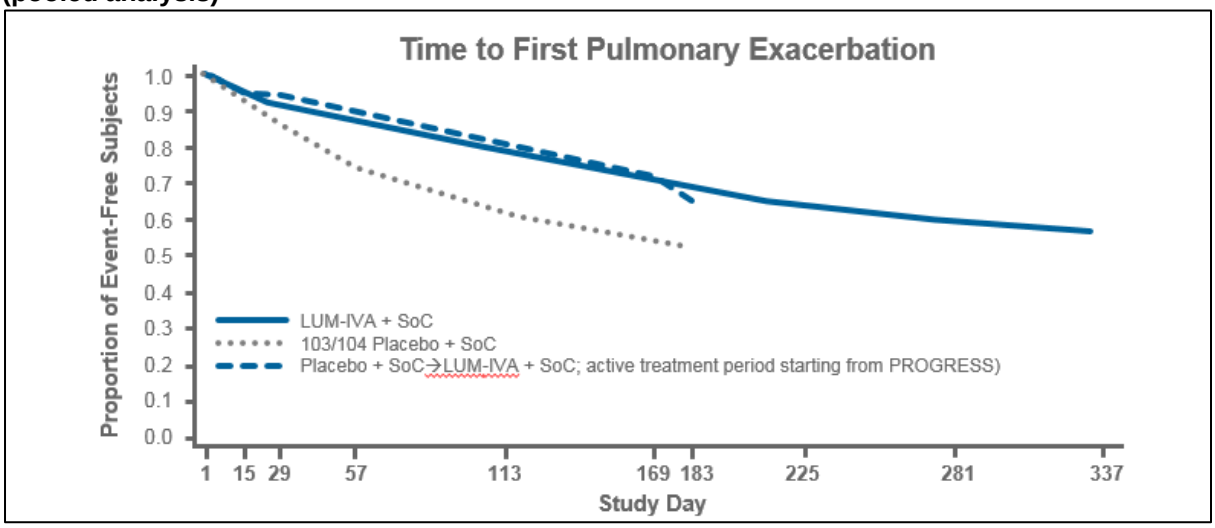
Source: Adapted from Wainwright et al., (2015) (17).

4.7.1.6 Time-to-first pulmonary exacerbation through Week 24

The proportion of patients who remained free from pulmonary exacerbations for a longer period of time was higher in the LUM-IVA + SoC group versus placebo + SoC group in the individual studies (TRAFFIC: rate ratio 0.69, p=0.0385 and TRANSPORT: rate ratio 0.53, p=0.0003) and was significantly higher in the pooled analysis (TRAFFIC and TRANSPORT (22).

Figure 5]).The estimated exacerbation-free probability, at Week 24 of PROGRESS (48 weeks of treatment), with LUM-IVA + SoC was 56.5% lower than the placebo + SoC group in the previous studies TRAFFIC and TRANSPORT (22).

Figure 5: Time to first pulmonary exacerbation: Up to 48 weeks of treatment, PROGRESS (pooled analysis)



Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Adapted from Elborn et al., (2015) (22).

4.7.1.7 Risk of having at least one exacerbation through Week 24

In both TRAFFIC and TRANSPORT, the risk of having at least one pulmonary exacerbation was lower in the LUM-IVA + SoC group compared with the placebo + SoC group in both studies (TRAFFIC: rate ratio; 0.64, p=0.0512 and TRANSPORT: rate ratio; 0.44, p=0.0002) (43, 44) and the pooled analysis (rate ratio; 0.5327, p<0.001).

4.7.1.8 Duration of pulmonary exacerbations at Week 24

Mean total durations of pulmonary exacerbations were shorter in the LUM-IVA + SoC group versus the placebo + SoC group, in TRAFFIC, TRANSPORT and the pooled analysis (

Table 20).

Table 20: Normalised total duration of pulmonary exacerbations, FAS population

Number of days with pulmonary exacerbation	**TRAFFIC**		**TRANSPORT**		**Pooled**	
	LUM-IVA + SoC N = 182	**Placebo + SoC N = 184**	**LUM-IVA + SoC N = 187**	**Placebo + SoC N = 187**	**LUM-IVA + SoC N = 369**	**Placebo + SoC N = 371**
n Mean (SD)	**55** **7.81** **(15.914)**	73 13.07 (22.269)	**54** **8.45** **(18.784)**	88 18.23 (26.858)	**109** **8.14** **(17.407)**	161 15.67 (24.791)
p value vs placebo + SoC	**p<0.0001**	NA	**p<0.0001**	NA	**p<0.0001**	NA

Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, not applicable; SD, standard deviation; SoC, standard of care.
Bold text indicates statistical significance.
Source: Vertex Pharmaceuticals, data on file (20).

Similar results were observed for the mean total durations of pulmonary exacerbations that required hospitalisation or IV antibiotic therapy in TRAFFIC, TRANSPORT and the pooled analysis. In the pooled analysis:

- Mean number of days patients were hospitalised for a pulmonary exacerbation was 2.48 days and 7.64 days in the LUM-IVA + SoC group and placebo + SoC group, respectively (p<0.0001).
- Mean number of days on IV antibiotic therapy for a pulmonary exacerbation was 3.79 days and 10.13 days in the LUM-IVA + SoC group and placebo + SoC group, respectively (p<0.0001).

Duration of pulmonary exacerbations was not included as an outcome in the PROGRESS study.

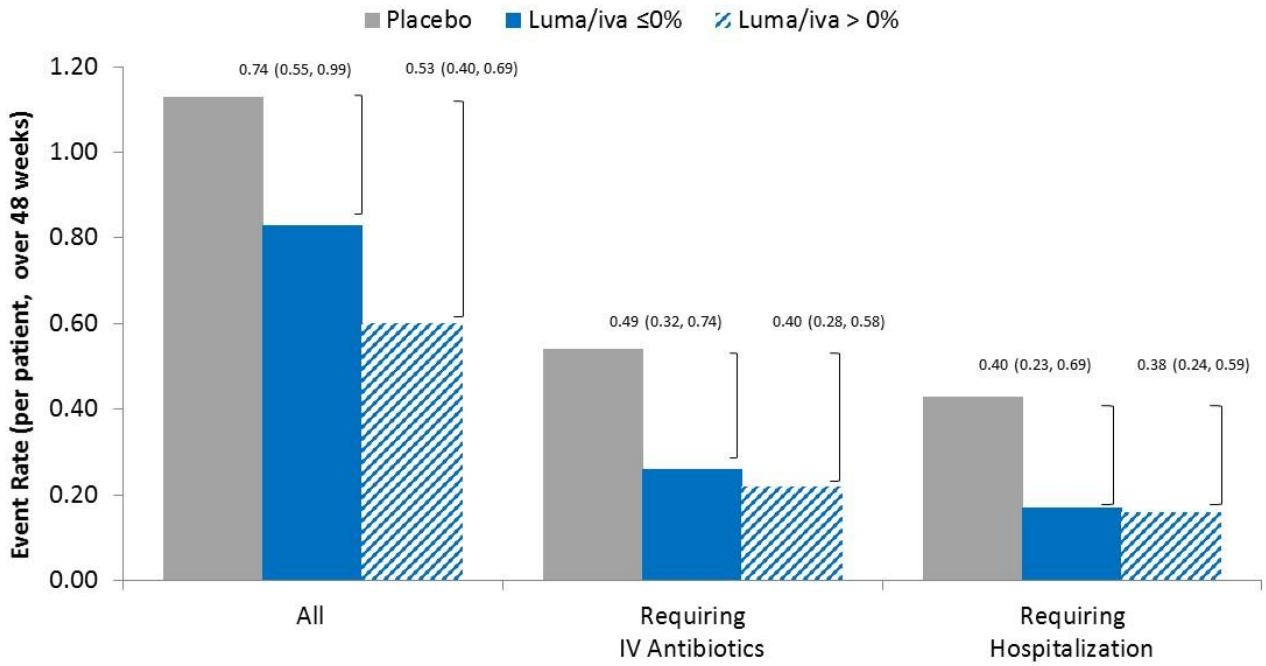
4.7.1.9 Summary of pulmonary exacerbation data

In summary, the pooled analysis of TRAFFIC and TRANSPORT, together with the additional 24-week interim readout/analysis data from the extension study PROGRESS, showed that treatment with LUM-IVA + SoC is associated with reduced rates of pulmonary exacerbations in total, as well as those requiring hospitalisation and/or IV antibiotics, and increased time to first pulmonary exacerbation, as compared with placebo + SoC in patients aged 12 years and older who are homozygous for the *F508del-CFTR* mutation.

Post-hoc analyses of pooled data from the TRAFFIC and TRANSPORT studies indicated that LUM-IVA + SoC treatment was associated with a reduction in pulmonary exacerbation-related events, including pulmonary exacerbations requiring hospitalisation and/or IV antibiotics, regardless of $ppFEV_1$ changes observed at study Day 15. (47). This analysis looked at the annualised event rates for pulmonary exacerbations in study participants grouped according to whether they had any improvement in $ppFEV_1$ from baseline to the Day 15 visit, no negative change (>0) or negative change in $ppFEV_1$ (≤0). Patients treated with LUM-IVA + SoC experienced fewer pulmonary exacerbations overall as compared with placebo + SoC, regardless of the observed change in $ppFEV_1$ at Day 15. Similarly, patients treated with LUM-IVA + SoC also experienced fewer pulmonary exacerbations requiring hospitalisations and/or IV antibiotics as compared with placebo + SoC, regardless of the initial changes in $ppFEV_1$ (47). Reductions in the rate of exacerbations versus placebo + SoC were significant across subgroups stratified by $ppFEV_1$ change, with the greatest reductions observed in exacerbations that required hospitalisation and/or IV antibiotic use (

Figure **6**) (47). This suggests that LUM-IVA + SoC may have a significant and meaningful impact on the rate of pulmonary exacerbations in patients who do not experience an increase in $ppFEV_1$ with LUM-IVA treatment and the multi-factorial clinical benefits of treatment are important to consider.

Figure 6: Pulmonary exacerbation rates by change from baseline to day 15 ppFEV$_1$ ≤0% vs. >0%, stratified by exacerbation type



Source: McColley et al., (2015) (47).

Reductions in pulmonary exacerbations are critical for patients with CF, as pulmonary exacerbations are significant and serious events leading to accelerated decline in lung function, increased risk of death (or need for a lung transplant) and increased risk of future exacerbations (14, 15). For these reasons, preventing or delaying exacerbations is a foremost goal in treating patients with CF. A recently conducted, burden of illness study, in patients age 12 years and older who are homozygous for the *F508del* mutation and not on LUM-IVA treatment, reported that over a 24-month period (36):

- 83% of patients experienced a pulmonary exacerbation
- 75% of patients experiencing a pulmonary exacerbation were hospitalised
- 78% of patients experiencing a pulmonary exacerbation were prescribed IV antibiotics.

LUM-IVA + SoC is associated with reduced rates of all pulmonary exacerbations, reduced rates of pulmonary exacerbations requiring hospitalisation and IV antibiotics, increased time to first pulmonary exacerbation, and a shorter average duration of pulmonary exacerbation as compared with placebo + SoC in patients age 12 years and older who are homozygous for the *F508del-CFTR* mutation. These clinically meaningful outcomes are of importance to patients and their carers, as the avoidance of these events improves long term prognosis.

4.7.1.10 Absolute change from baseline in BMI at Week 24

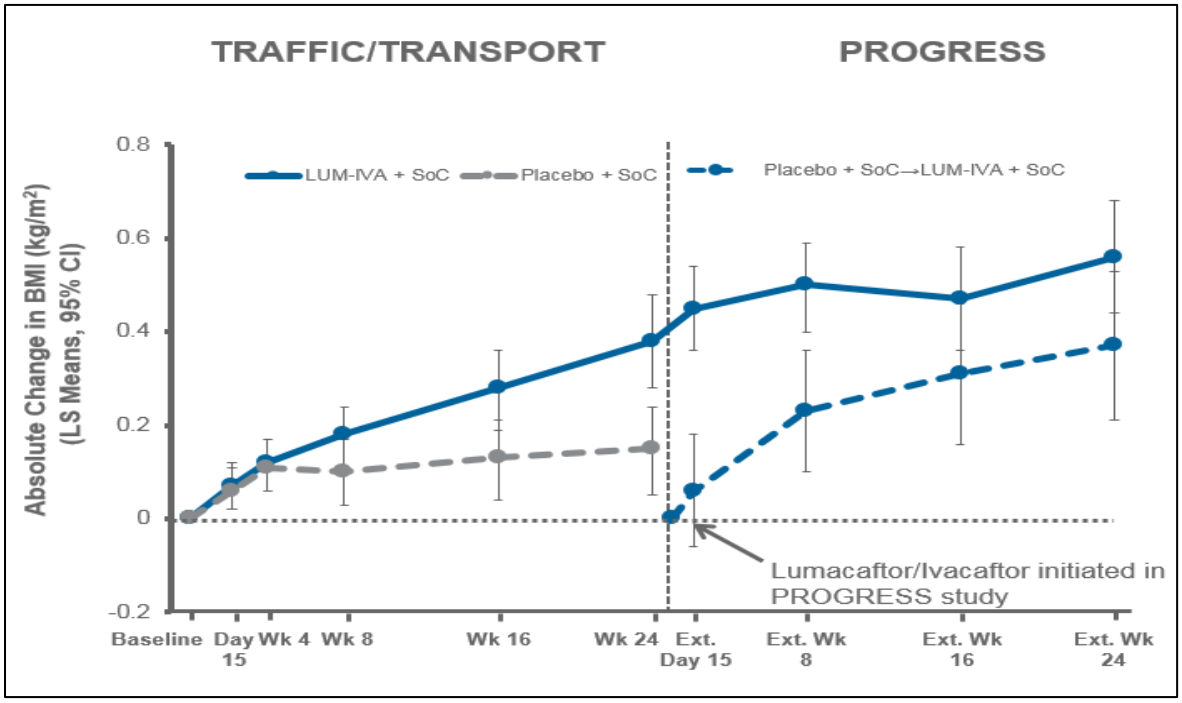
While absolute change from baseline in BMI at week 24 in TRAFFIC did not demonstrate a statistically significant change, in both TRANSPORT and the pooled analysis, patients in the LUM-IVA + SoC group had statistically significant improvements in BMI (Table 21), (Figure 7) (17).

Table 21: Absolute change from baseline in BMI at Week 24, FAS population

Absolute change (kg/m^2)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Treatment difference (95% CI)	0.13 (-0.07, 0.32) p=0.19	-	**0.36 (0.17, 0.54) p<0.001**	-	**0.24 (0.11, 0.37) p<0.001**	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Bold text indicates statistical significance.
Source: Wainwright et al., (2015) (17).

Figure 7: Absolute change from baseline in BMI at Week 24; TRAFFIC, TRANSPORT and PROGRESS



Abbreviations: BMI, body mass index, CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LS, least-squares; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Adapted from Elborn et al., (2015) (22).

As shown in Figure 7, when patients who had received active treatment entered PROGRESS, the improvements seen in BMI that were observed in TRAFFIC and TRANSPORT continued (22). The LS mean absolute change in BMI at Week 24 of PROGRESS was 0.56 kg/m^2 ($p<0.0001$) for the LUM-IVA + SoC group (23). This improvement in BMI was numerically larger than that observed at Week 24 of TRAFFIC and TRANSPORT (0.38 kg/m^2, $p<0.0001$) (23).

Patients who had received placebo in the previous studies demonstrated improvements in BMI upon receiving active treatment in PROGRESS. These improvements in BMI, throughout PROGRESS, were similar to those observed for the active treatment group (pooled analysis) from TRAFFIC and TRANSPORT.

The pooled analysis of TRAFFIC and TRANSPORT, and the additional 24-week interim analysis data from the PROGRESS extension study, showed that treatment with LUM-IVA

+ SoC is associated with significant and sustained improvement in BMI (17, 23). This is of great clinical significance as a low BMI is associated with reduced lung function, and poor nutritional status is an independent predictor of survival (48).

Low BMI was also assessed in a variety of subgroups defined according to various baseline characteristics and concomitant medications; the improvement in BMI (point estimates) in the LUM-IVA + SoC group versus the placebo + SoC group was consistent across all subgroups, (see Appendix, separate document) (21). This demonstrates there are no patient subgroups that can be identified as better or worse responders based on BMI in the Phase 3 studies.

4.7.1.11 Absolute change in weight and BMI z-score at Week 24

A similar pattern to that observed for absolute change from baseline in BMI at Week 24, was observed for absolute change from baseline in weight at Week 24 (Table 22).

Table 22: Absolute change from baseline in weight, FAS population (LUM-IVA + SoC)

Absolute change (kg)	TRAFFIC	TRANSPORT	Pooled
Treatment difference, LS mean	0.30	**0.95**	**0.62**
p value	p=0.2992	**p=0.0003**	**p=0.0013**

Abbreviations: LS, least-squares.
Bold text indicates statistical significance.
Source: Vertex Pharmaceuticals, data on file (20).

Additional analyses were conducted for a sub-set of patients <20 years of age, a similar pattern was observed for absolute change in BMI z-score at Week 24 (20).

At Week 24 of PROGRESS, improvements in weight were larger than those observed at Week 24 of the previous study for those receiving LUM-IVA + SoC in TRAFFIC/TRANSPORT and PROGRESS. The LS mean absolute change in weight was 2.1 kg (p<0.001) at Week 24 of PROGRESS in the LUM-IVA + SoC group (23).

4.7.1.12 Absolute change from baseline in the CFQ-R respiratory domain score at Week 24

CF has deleterious effects on the HRQoL of both patients and their caregivers. The vast majority of studies examining the disease burden have focussed on the impact of declining lung function and pulmonary exacerbations on HRQoL, demonstrating that pulmonary exacerbations in particular have a profound negative impact on patient HRQoL (13, 49-52).

While disease-specific measures, such as the Cystic Fibrosis Questionnaire-Revised (CFQ-R), assess some of the concepts relevant to patients with CF and as such are more suitable than generic measures to assess the effect of treatment on HRQoL, they still have limitations as they focus on symptomatic relief and may not capture the true value of medicines which address the underlying cause of CF.

The difficulty in assessing the HRQoL of patients with CF is accepted, particularly when using generic measures of HRQoL, such as EQ-5D, as patients are born with the disease and perceive their quality of life to be ‘normal’ (i.e. equivalent to people without CF). As a result, patients with CF score their HRQoL high as observed by Wahl et al. (53). Demonstrating quality of life gains with new therapies in patients with CF, is therefore

challenging. This was taken into consideration in the appraisal of mannitol for treating cystic fibrosis [TA266], where the Committee concluded that current measures of quality of life may not accurately capture the consequences of having cystic fibrosis and of its treatments.

CFQ-R is a CF-specific instrument that measures HRQoL, with a score ranging from zero to 100 points with higher scores representing better health. A difference of at least 4 points is considered the minimal clinically important difference (MCID) for the absolute change from baseline in the CFQ-R respiratory domain score at Week 24.

The pooled analysis of TRAFFIC and TRANSPORT showed a numerical improvement in the CFQ-R respiratory domain score in the LUM-IVA + SoC group as compared with the placebo + SoC group although the improvement was not statistically significant at Week 24 (Table 23). The difference between LUM-IVA + SoC and placebo + SoC in the CFQ-R respiratory domain score was statistically significant at all other time-points (Week 4, 8, 16) (Figure 8). When compared to baseline, patients treated with LUM-IVA + SoC achieved an MCID of over 4 points at all specified time-points in the study (17).

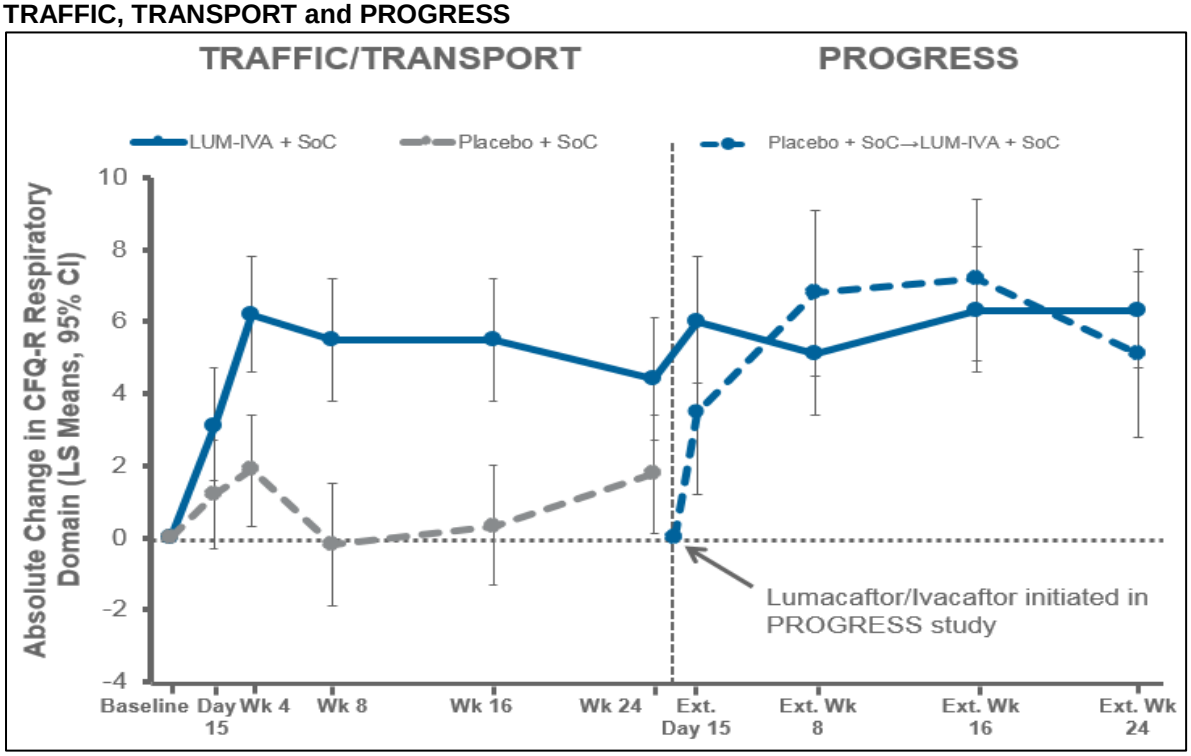
Table 23. Absolute change from baseline in CFQ-R respiratory domain score at Week 24, FAS population

Absolute change (points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Treatment difference (95% CI)	1.5 (-1.7, 4.7) p=0.36	-	2.9 (-0.3, 6.0) p=0.07	-	2.2 (0.0, 4.5) p=0.05	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Wainwright et al., (2015) (17).

As shown in Figure 8, improvements in the CFQ-R respiratory domain score were sustained through all study visits in PROGRESS through 48 weeks of treatment (22). The LS mean absolute change from baseline in the CFQ-R respiratory domain score at Week 24 of PROGRESS was 6.3 ($p<0.001$) for the LUM-IVA + SoC group (23). Patients that transitioned from placebo + SoC to LUM-IVA + SoC in PROGRESS demonstrated a similar improvement in CFQ-R when placed on active treatment.

Figure 8: Absolute change from baseline in the CFQ-R respiratory domain score at Week 24; TRAFFIC, TRANSPORT and PROGRESS



Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised; CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LS, least-squares; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Adapted from Elborn et al., (2015) (22).

4.7.1.13 Absolute change from baseline in the EQ-5D-3L at Week 24

No meaningful treatment differences were observed between the LUM-IVA + SoC and the placebo + SoC groups in both studies based on the single utility index analysis of the EQ-5D-3L. LUM-IVA + SoC resulted in favourable changes in the EQ-5D-3L visual analogue scale (VAS) score at Week 24. Statistically significant improvements in EQ-5D-3L scores were not observed in either study (20).

However, it is difficult to assess the HRQoL of patients with CF, particularly when using generic measures of HRQoL, such as EQ-5D, as patients are born with the disease and perceive their quality of life to be 'normal' (i.e. equivalent to people without CF). As a result, patients with CF score their HRQoL high. Demonstrating quality of life gains with new therapies in patients with CF is therefore challenging, as it is not possible to significantly improve HRQoL scores, representing a ceiling effect.

EQ-5D-3L was not included as an outcome in the PROGRESS study.

4.8 Subgroup analysis

Pre-planned subgroup analyses of the primary outcome and key secondary outcomes were conducted according to various baseline characteristics (age, sex, disease severity [measured by $ppFEV_1$ at screening and at baseline], *P. aeruginosa* infection status) and concomitant medications.

Results of the sub-group analyses for TRAFFIC and TRANSPORT (pooled) for $ppFEV_1$, pulmonary exacerbations, BMI and CFQ-R are presented in the Appendix (separate

document). Individual patient baseline characteristics were not identified as strong predictors of clinical response.

4.9 Meta-analysis

A meta-analysis was not required because the pivotal, Phase 3 studies (TRAFFIC and TRANSPORT) and the ongoing PROGRESS represent the totality of relevant available evidence on the clinical effectiveness of LUM-IVA. The similarity of the TRAFFIC and TRANSPORT protocols for key outcome assessments allowed for a pre-specified pooled analysis of results from both studies, providing a robust dataset to evaluate the totality of the data. Results of the pooled analysis are reported within this submission.

4.10 Indirect and mixed treatment comparisons

An indirect comparison or mixed treatment comparison was not required as the pivotal, Phase 3 studies (TRAFFIC and TRANSPORT) provided direct comparative evidence of the impact of LUM-IVA vs. the comparator (i.e. in both the LUM-IVA and placebo arms of the studies patients were permitted to continue with their usual CF management).

4.11 Non-randomised and non-controlled evidence

The clinical systematic literature review (section 4.1) included RCTs and non-RCTs. There were no non-RCTs identified for LUM-IVA.

4.12 Adverse reactions

4.12.1 TRAFFIC and TRANSPORT

4.12.1.1 Treatment-emergent adverse events

The safety profile for LUM-IVA has been well characterised by the clinical development programme. LUM-IVA is generally well tolerated by patients. Respiratory events (e.g. chest discomfort, dyspnoea, and respiration abnormal) were more common during initiation of LUM-IVA therapy. Clinical experience in patients with ppFEV$_1$ <40 is limited and additional monitoring of these patients is recommended during initiation of therapy (24).

Table 24 summarises the incidence of treatment-emergent AEs (TEAEs) in TRAFFIC, TRANSPORT and the pooled analysis. TEAEs are defined as events from the first dose of study drug to 28 days after the last dose of study drug. The majority of AEs were mild to moderate in intensity (17). No deaths were reported in either TRAFFIC or TRANSPORT (17).

Table 24: Incidence of TEAEs: TRAFFIC and TRANSPORT (Safety Set)

	TRAFFIC		TRANSPORT		Pooled Studies	
	LUM-IVA + SoC N = 182 n (%)	Placebo + SoC N = 184 n (%)	LUM-IVA + SoC N = 187 n (%)	Placebo + SoC N = 186 n (%)	LUM-IVA + SoC N = 369 n (%)	Placebo + SoC N = 370 n (%)
Any AE	174 (95.6)	174 (94.6)	177 (94.7)	181 (97.3)	351 (95.1)	355 (95.9)
At least one SAE	33 (18.1)	49 (26.6)	31 (16.6)	57 (30.6)	64 (17.3)	106 (28.6)
AEs leading to treatment discontinuation*	6 (3.3)	4 (2.2)	11 (5.9)	2 (1.1)	17 (4.6)	6 (1.6)

Abbreviations: AE, adverse event; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SAE, serious adverse event; SoC, standard of care.
Source: Wainwright et al., (2015) (17).

*Of the AEs leading to discontinuation in 2 or more patients in TRAFFIC and TRANSPORT, 4 patients had elevated creatinine kinases levels, 3 haemoptysis, 2 bronchospasm, 2 dyspnoea, 2 pulmonary exacerbations and 2 rash.

Table 25: Summary of TEAEs: TRAFFIC and TRANSPORT (Safety Set)

	TRAFFIC		TRANSPORT		Pooled Studies	
	LUM-IVA + SoC N = 182 n (%)	Placebo + SoC N = 184 n (%)	LUM-IVA + SoC N = 187 n (%)	Placebo + SoC N = 186 n (%)	LUM-IVA + SoC N = 369 n (%)	Placebo + SoC N = 370 n (%)
Most common AEs†						
Infective pulmonary exacerbation of CF	67 (36.8)	87 (47.3)	65 (34.8)	95 (51.1)	132 (35.8)	182 (49.2)
Cough	48 (26.4)	66 (35.9)	56 (29.9)	82 (44.1)	104 (28.2)	148 (40.0)
Headache	29 (15.9)	25 (13.6)	29 (15.5)	33 (17.7)	58 (15.7)	58 (15.7)
Increase in sputum production	25 (13.7)	23 (12.5)	29 (15.5)	47 (25.3)	54 (14.6)	70 (18.9)
Dyspnoea	17 (9.3)	14 (7.6)	31 (16.6)	15 (8.1)	48 (13.0)	29 (7.8)
Haemoptysis	30 (16.5)	24 (13.0)	20 (10.7)	26 (14.0)	50 (13.6)	50 (13.5)
Diarrhoea	24 (13.2)	13 (7.1)	21 (11.2)	18 (9.7)	45 (12.2)	31(8.4)

	TRAFFIC		TRANSPORT		Pooled Studies	
	LUM-IVA + SoC N = 182 n (%)	Placebo + SoC N = 184 n (%)	LUM-IVA + SoC N = 187 n (%)	Placebo + SoC N = 186 n (%)	LUM-IVA + SoC N = 369 n (%)	Placebo + SoC N = 370 n (%)
Nausea	14 (7.7)	11 (6.0)	32 (17.1)	17 (9.1)	46 (12.5)	28 (7.6)
Abnormal respiration (chest tightness)	14 (7.7)	9 (4.9)	18 (9.6)	13 (7.0)	32 (8.7)	22 (5.9)
Nasopharyngitis	26 (14.3)	20 (10.9)	22 (11.8)	20 (10.8)	48 (13.0)	40 (10.8)
Oropharyngeal pain	11 (6.0)	10 (5.4)	13 (7.0)	20 (10.8)	24 (6.5)	30 (8.1)
Upper respiratory tract infection	17 (9.3)	10 (5.4)	20 (10.7)	10 (5.4)	37 (10.0)	20 (5.4)
Nasal congestion	11 (6.0)	25 (13.6)	10 (5.4)	13 (7.0)	24 (6.5)	44 (11.9)

Abbreviations: AE, adverse event; CF, cystic fibrosis; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
† The most common AEs were defined as those that occurred in at least 10% of patients in any treatment group.
Source: Wainwright et al. (2015) (17).

4.12.1.2 Serious adverse events

The number of SAEs across the groups are reported in Table 24. The most commonly reported SAEs (reported in at least 3 patients) are outlined in Table 26.

Table 26: Serious adverse events pooled analysis: TRAFFIC and TRANSPORT (Safety Set)

Serious adverse event	LUM-IVA + SoC N = 369 n (%)	Placebo + SoC N = 370 n (%)
Infective pulmonary exacerbation of CF	41 (11.1)	89 (24.1)
Haemoptysis	5 (1.4)	3 (0.8)
Distal intestinal obstruction syndrome	2 (0.5)	5 (1.4)

Abbreviations: CF, cystic fibrosis; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Wainwright et al., (2015) (17).

4.12.1.3 Adverse events of special interest

Elevations in levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in the LUM-IVA + SoC group and the placebo + SoC group (17), (Table 27). SAEs related to abnormal liver function was not observed in the placebo + SoC

group and were reported for 3 patients in the LUM-IVA + SoC group. After discontinuation or interruption of LUM-IVA, liver function improved substantially and returned to baseline in the LUM-IVA + SoC group (17).

It is recommended that liver function tests (ALT, AST and bilirubin) are conducted before initiating LUM-IVA therapy and then at 1, 3, 6, 9 and 12 months during the first year of treatment and annually thereafter (24).

Table 27: Summary of liver function test elevations pooled analysis: TRAFFIC and TRANSPORT (Safety Set)

Parameter	LUM-IVA + SoC N = 369 n (%)	Placebo + SoC N=370 n (%)
ALT (U/L)		
>3x to ≤5xULN	8 (2.2)	15 (4.1)
>5x to ≤8xULN	1 (0.3)	1 (0.3)
>8xULN	1 (0.3)	0 (0.0)
AST (U/L)		
>3x to ≤5xULN	7 (1.9)	4 (1.1)
>5x to ≤8xULN	2 (0.5)	5 (1.4)
>8xULN	2 (0.5)	2 (0.5)
Total Bilirubin (µmol/L)		
>1.5xULN to ≤2xULN	0 (0.0)	5 (1.4)
>2xULN	1 (0.3)†	1 (0.3)
ALT or AST and Total Bilirubin		
ALT or AST >3xULN and Total Bilirubin >2xULN	1 (0.3)†	0 (0.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care; ULN, upper limits of normal.
† Elevations for this patient was noted at the local lab and was not captured in the clinical database.
Source: Elborn et al., (2014) (46).

4.12.2 PROGRESS (interim-analysis Week 24 of 96)

PROGRESS (Study 105 – 96 weeks) is an ongoing extension study of TRAFFIC and TRANSPORT designed to evaluate the safety and efficacy of long-term (120 weeks) LUM-IVA treatment in patients with CF age 12 years and older who are homozygous or heterozygous for the *F508del-CFTR* mutation (Figure 9). The primary outcome for this study is safety and as such the methods and safety results for PROGRESS are reported within this section.

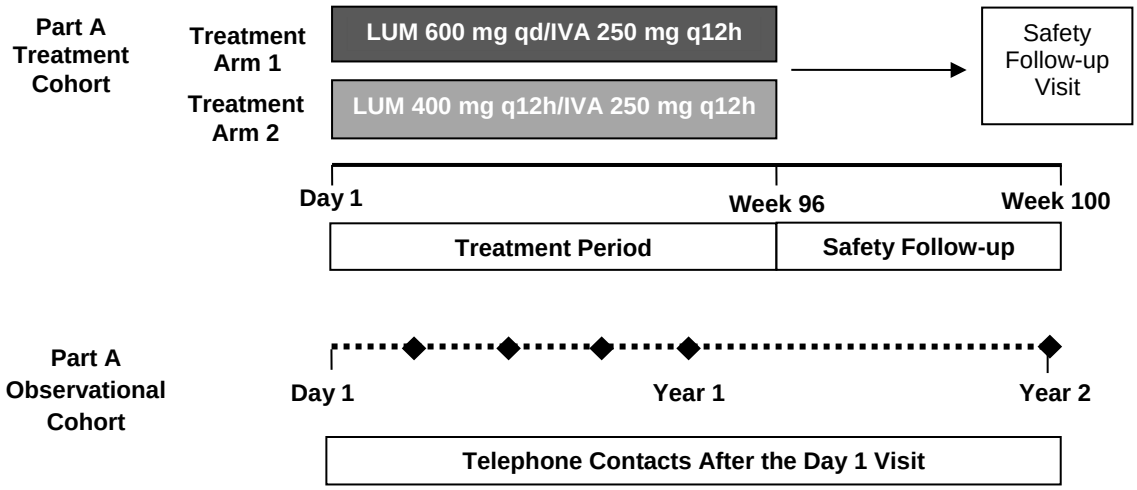
Interim results are presented for the pre-planned interim analysis, which were conducted after all patients in Part A (Treatment Cohort) completed the Week 24 study visit (up to 48 weeks of LUM-IVA + SoC treatment).

4.12.2.1 Primary outcome: Safety

LUM-IVA + SoC was generally well tolerated for up to 48 weeks of treatment with 93% of patients from T & T electing to enter the study. Overall, the incidence of AEs and SAEs during the active treatment period of PROGRESS (24 to 48 weeks of treatment) generally

did not exceed that reported in the preceding studies (TRAFFIC/TRANSPORT: weeks 0 to 24) (Table 28).

Figure 9 Study design chart: PROGRESS, Part A



Abbreviations: IVA, ivacaftor every 12 hours; LUM, lumacaftor every 12 hours (q12h); LUM, lumacaftor daily (qd).

Table 28: TEAEs by active treatment period, Part A, Safety Set

Active treatment period	0–24 weeks of treatment	24–48 weeks of treatment
LUM-IVA dosing regimen	**LUM-IVA + SoC N=544 n (%)**	**LUM-IVA + SoC N=508 n (%)**
Any AE	520 (95.6)	416 (81.9)
At least one SAE	103 (18.9)	84 (16.5)
AE leading to treatment discontinuation	27 (5.0)	7 (1.4)

Abbreviations: AE, adverse event; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SAE, serious adverse event; SoC, standard of care.
Source: Vertex Pharmaceuticals, data on file (23).

The most common AE in PROGRESS (weeks 24–48) was infective pulmonary exacerbation of CF (Table 29). The most common AEs leading to treatment discontinuation (i.e., those occurring in 5 or more patients during any treatment interval) were respiration abnormal, dyspnoea, increased blood creatinine phosphokinase, and infective pulmonary exacerbation of CF.

Table 29: TEAEs with an incidence of ≥5% active treatment period, Part A, Safety Set

Active treatment period	0–24 weeks of treatment	24–48 weeks of treatment
LUM-IVA dosing regimen	**LUM-IVA + SoC N=544 n (%)**	**LUM-IVA + SoC N=508 n (%)**
Infective pulmonary exacerbations of CF	187 (34.4)	160 (31.5)
Cough	150 (27.6)	107 (21.1)

Headache	75 (13.8)	23 (4.5)
Dyspnoea	72 (13.2)	29 (5.7)
Sputum increased	75 (13.8)	50 (9.8)
Haemoptysis	73 (13.4)	44 (8.7)
Respiration abnormal	54 (9.9)	26 (5.1)
Diarrhoea	61 (11.2)	23 (4.5)
Nausea	63 (11.6)	14 (2.8)
Pyrexia	48 (8.8)	22 (4.3)
Nasopharyngitis	57 (10.5)	38 (7.5)
Fatigue	46 (8.5)	14 (2.8)
Oropharyngeal pain	36 (6.6)	26 (5.1)
Abdominal pain	45 (8.3)	18 (3.5)
Upper respiratory tract infection	49 (9.0)	27 (5.3)
Nasal congestion	37 (6.8)	23 (4.5)
Viral upper respiratory tract infection	28 (5.1)	10 (2.0)
Rhinitis	25 (4.6)	5 (1.0)
Blood creatinine phosphokinase increased	34 (6.3)	19 (3.7)
Sinusitis	21 (3.9)	22 (4.3)
Flatulence	29 (5.3)	2 (0.4)
Rash	28 (5.1)	11 (2.2)
Vomiting	24 (4.4)	14 (2.8)
Abdominal pain upper	19 (3.5)	11 (2.2)
Rhinorrhoea	25 (4.6)	7 (1.4)
Productive cough	19 (3.5)	7 (1.4)
Constipation	20 (3.7)	10 (2.0)
Bacterial test positive	21 (3.9)	11 (2.2)
Pulmonary function test decreased	9 (1.7)	11 (2.2)

Abbreviations: CF, cystic fibrosis; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400mg every 12 hours; SoC, standard of care.
Source: Vertex Pharmaceuticals, data on file (23).

4.12.2.2 Serious adverse events

LUM-IVA + SoC was generally well tolerated for up to 48 weeks of treatment. Overall, the incidence of SAEs during the active treatment period of PROGRESS (24 to 48 weeks of treatment) generally did not exceed that reported in the preceding studies (TRAFFIC/TRANSPORT: weeks 0 to 24). The most commonly reported SAEs are outlined in Table 30.

In ongoing safety reporting, one death has been reported from respiratory failure following a pulmonary exacerbation at day 344 (>48 weeks). The report is considered unrelated to study drug.

Table 30: Serious adverse events occurring in ≥4 patients, active treatment period, Part A, Safety Set

Active treatment period	**0–24 weeks of treatment**	**24–48 weeks of treatment**
Serious adverse event	**LUM-IVA + SoC N=544 n (%)**	**LUM-IVA + SoC N=508 n (%)**
Infective pulmonary exacerbation of CF	60 (11.0)	64 (12.6)
Haemoptysis	8 (1.5)	5 (1.0)
Distal intestinal obstruction syndrome	4 (0.7)	2 (0.4)

Abbreviations: CF, cystic fibrosis; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.
Source: Vertex Pharmaceuticals, data on file (23).

4.12.2.3 Adverse events of special interest

Elevations in levels of ALT and AST were observed in LUM-IVA + SoC group (

Table 31). The incidence of elevated liver enzymes in PROGRESS was similar to that seen in TRAFFIC and TRANSPORT.

Table 31: Summary of liver function test elevations, active treatment period, Part A, Safety Set

Active treatment period	0–24 weeks of treatment	24–48 weeks of treatment
Parameter	**LUM-IVA + SoC N=544 n (%)**	**LUM-IVA + SoC N=508 n (%)**
ALT (U/L) >3x to ≤5xULN >5x to ≤8xULN >8xULN	 14/543 (2.6) 3/543 (0.6) 4/543 (0.7)	 6/506 (1.2) 3/506 (0.6) 2/506 (0.4)
AST (U/L) >3x to ≤5xULN >5x to ≤8xULN >8xULN	 11/543 (2.0) 3/543 (0.6) 5/543 (0.9)	 10/506 (2.0) 2/506 (0.4) 1/506 (0.2)
Total Bilirubin (µmol/L) >1.5xULN to ≤2xULN >2xULN	 0/543 (0.0) 0/543 (0.0)	 0/506 (0.0) 0/506 (0.0)
ALT or AST and Total Bilirubin ALT or AST >3xULN and Total Bilirubin >2xULN	0/543 (0.0)	0/506 (0.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care; ULN, upper limits of normal.
Source: Vertex Pharmaceuticals, data on file (23).

4.13 Interpretation of clinical effectiveness and safety evidence

A pooled analysis of the results from TRAFFIC and TRANSPORT, the largest interventional RCTs conducted to date in CF (with 1,108 patients enrolled) (see Appendix 3), is the basis of the integrated summary of efficacy, intended to evaluate the totality of the data. Based on the pooled analysis, at 24 weeks, LUM 400 mg-IVA 250 mg (every 12 hours) treatment resulted in consistent improvements in several clinically significant treatment measures agreed in previous appraisals by NICE of medicines for CF (TA266 and TA276) (17-21).

The pivotal Phase 3 studies included the oral FDC, containing 200 mg of LUM and 125 mg of IVA as two tablets, taken orally every 12 hours (4 tablets per day, total daily dose LUM 800 mg-IVA 500 mg) with fat-containing food. This is the licensed dose of LUM-IVA FDC, for which the results are presented in this submission. The RCTs also included a LUM 600 mg once daily-IVA 250 mg every 12 hours arm, the results of which are not reported within this submission as this dose of LUM-IVA is not included in the licensed indication.

As demonstrated by these studies and supportive data from PROGRESS, LUM-IVA addresses the primary goals of CF treatment, improving $ppFEV_1$, reducing pulmonary exacerbations and improving nutritional status as reflected by an improvement in BMI (absolute change), all of which are independent key drivers of mortality in CF (6, 7). The multi-factorial effects of the LUM-IVA systemic therapy reflect the benefits to the patient of treating, and potentially modifying, the underlying cause of CF.

In the LUM-IVA and placebo arms, the study protocols specified that patients should continue with their usual CF management, e.g. dornase alfa, pancreatin, inhaled hypertonic

saline, bronchodilators and antibiotics, as clinically indicated. Therefore, the improvements seen in key clinical outcomes with LUM-IVA treatment are in addition to those that can be achieved at present with SoC alone. The adjunct use of LUM-IVA with SoC in the Phase 3 studies appropriately reflects the intended use of LUM-IVA in real-world clinical practice. Patients eligible for treatment with LUM-IVA will be identified through molecular testing for *F508del*, currently recommended for those in whom a clinical diagnosis of CF has been made (54).

Clinical benefits were seen across a variety of subgroups, defined according to various baseline characteristics and concomitant medications, suggesting that all eligible patients will benefit from treatment with LUM-IVA (17, 20, 21).

There are no inherent limitations imposed by the design of the pivotal Phase 3 clinical studies, with positive results achieved against the pre-specified primary endpoint (absolute change from baseline in ppFEV$_1$). The study duration, 24 weeks, did not allow demonstration of long term survival benefit associated with the improvements in the key drivers of CF mortality. However, it is expected that the ongoing PROGRESS study (planned duration 96 weeks) will confirm the improvements in the key drivers of CF mortality achieved with LUM-IVA + SoC up to 48 weeks.

LUM-IVA has the potential to restore lung function and slow the rate of lung function decline, which may lead to a reduction in disease progression, and an improvement in CF patients' life expectancy, which is currently only 28 years (UK median age of death).

The safety assessments conducted in the pivotal trials are standard parameters for clinical studies in drug development, especially in this population. Also, the scope of the assessments are considered appropriate for safety monitoring in the context of these studies. Therefore the safety results from TRAFFIC and TRANSPORT, and the interim analysis of PROGRESS, showing that LUM- IVA is generally well tolerated, demonstrate that it addresses the treatment needs in patients with CF while maintaining an acceptable benefit/risk profile (17, 22).

The patient population included in the pivotal Phase 3 studies, are also directly relevant to the population considered in this submission; patients with CF age 12 years and older who are homozygous for the *F508del-CFTR* mutation. The demographics of both studies were similar in terms of age, sex and disease severity, TRAFFIC and TRANSPORT included 5 sites in the UK and the population studied appropriately reflect the characteristics of the patient population,

The UK Cystic Fibrosis Registry reports 8,076 actively treated patients with CF in England. Of these, 5,430 are aged 12 years and over, of whom 50.6% are homozygous for the *F508del* mutation (see Section 6). Therefore 2,748 patients in England are eligible for treatment with LUM-IVA.

By targeting, and potentially modifying, the underlying cause of disease and thereby improving survival, LUM-IVA improves and sustains outcomes across multiple clinical parameters and represents a step-change targeted treatment for CF patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. This treatment thus addresses an unmet medical need in a population with a short life expectancy and high morbidity and unmet medical need.

LUM-IVA does not meet all of the end-of-life criteria (Table 32).

Table 32: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	N/A
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Clinical evidence is not available for this to date.
The treatment is licensed or otherwise indicated for small patient populations	Yes, only 2,748 patients in England are expected to be eligible for LUM-IVA

4.14 Ongoing Studies

The ongoing extension study, PROGRESS will conduct an interim analysis on 72 week data for selected endpoints in February 2016 (producing a total of 96 weeks of data for patients initially randomised to LUM-IVA in TRAFFIC and TRANSPORT) and then a total of 120 weeks in Q3 2015.

5. Cost effectiveness

5.1 Published cost effectiveness studies

5.1.1 Identification of studies

A systematic review was conducted to obtain all relevant CF cost-effectiveness studies. The outcomes from this review identified studies to validate and inform the cost-effectiveness model. The full search methodology is provided in the Appendix (separate document). This section provides a summary of the methodology.

The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review question:

- "What modelling techniques have been used to conduct economic evaluations for the treatment of CF?"

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 33, with no restrictions on date or language of publication. Searches were conducted using the following interfaces:

- Embase.com (which also covers Medline and Medline (R) In-Process)
- The Cochrane Library (which covers Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (covers EconLit with Full Text, Health Economic Evaluations Database).

Table 33: Databases searched and interfaces used in the cost-effectiveness systematic review

Database	Interface
Embase 1966 to 2015	Embase
Medline 1966 to 2015	Embase
Medline (R) In-Process 1966 to 2015	Embase
Cochrane Database of Systematic Reviews 1996 to 2015	The Cochrane Library
Database of Abstracts of Reviews of Effects 1994 to 2015	The Cochrane Library
Health Technology Assessment 1989 to 2015	The Cochrane Library
NHS Economic Evaluation Database 1968 to 2015	The Cochrane Library
EconLIT with Full Text 1961 to 2015	EBSCO host
Health Economic Evaluations Database 1990 to 2015	EBSCO host

The Embase interface was searched using terms for the population and an economic studies filter adapted from the Scottish Intercollegiate Guidelines Network (55). Similar filters for economic studies have previously been used in NICE Health Technology Assessment submissions and were deemed appropriate by the evidence review groups responsible for the technology appraisal.

Searches were not restricted by study intervention or comparator to ensure all relevant structures are identified. The Cochrane Library and EBSCO host interfaces were searched using terms for the population only to broaden the results.

The searches include terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) through the use of Boolean combination techniques. A grey literature search was performed to include additional studies that had not been identified by the search strategies. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table 34.

The searches were conducted on 22nd September 2015, the search strategy is provided in the Appendix (separate document).

Table 34: Eligibility criteria used in the cost-effectiveness systematic review

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	New born screening
Outcomes	• Cost per QALY • Cost per life year • Other cost-effectiveness outcomes	-
Study type	Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews‡ • Letters • Comment articles • Individual case study reports

‡ To be retained for cross checking purposes

A grey literature search was performed to include any additional studies that were not identified by the search strategy. This included the following websites:

- Cystic Fibrosis Foundation http://www.cff.org/
- American Lung Association http://www.lung.org/lung-disease/cystic-fibrosis/
- European Cystic Fibrosis Society (ECFS) https://www.ecfs.eu/
- CF Europe http://www.cf-europe.eu/
- CF Network http://cf.eqascheme.org/
- European Lung Foundation (ELF) http://www.europeanlung.org/en/lung-disease-and-information/lung-diseases/cystic-fibrosis
- Cystic Fibrosis Trust http://www.cysticfibrosis.org.uk/
- The British Library: http://www.bl.uk/
- National Institute for Health Research: http://www.hta.ac.uk/
- National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk/

- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/Home
- National Centre for Pharmacoeconomics NCPE Ireland: http://www.ncpe.ie/submission-process/hta-guidelines/
- All Wales Medicines Strategy Group: http://www.wales.nhs.uk/sites3/home.cfm?orgid=371
- Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/en/home.2724.html
- Haute Autorité de Santé (HAS): http://www.has-sante.fr/portail/jcms/j_5/home
- Italian Medicines Agency (AIFA): http://www.agenziafarmaco.gov.it/en
- Agencia de Evaluación de Tecnologías Sanitarias (AETS): http://www.isciii.es/
- Canadian Agency for Drugs and Technologies in Health (CADTH): http://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): http://www.pbs.gov.au/info/industry/listing/participants/pbac
- Search Engine (Google): http://www.google.co.uk/

The bibliographies of review papers were checked to identify studies that may have been missed in the electronic searches.

Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts was undertaken using the inclusion/exclusion criteria to identify papers to be included at this stage (also known as the first pass). The first pass was performed by two independent reviewers with discrepancies between included papers resolved by a third independent reviewer. Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria (also known as the second pass).

5.1.2 Search results

The PRISMA diagram shown in Figure 10 illustrates the numbers of studies included and excluded at each stage of the systematic review. Database searching identified 1062 references. Following title and abstract screening 922 references were excluded. 48 references were included for full-text evaluation. A total of 12 references met the inclusion/exclusion criteria following full-text evaluation. Of these 12 references, all studies were deemed relevant to the review and key elements were extracted and put through a critical appraisal checklist (See Appendix 7 and Appendix 8 – separate document).

Figure 10: Cost-effectiveness - PRISMA diagram

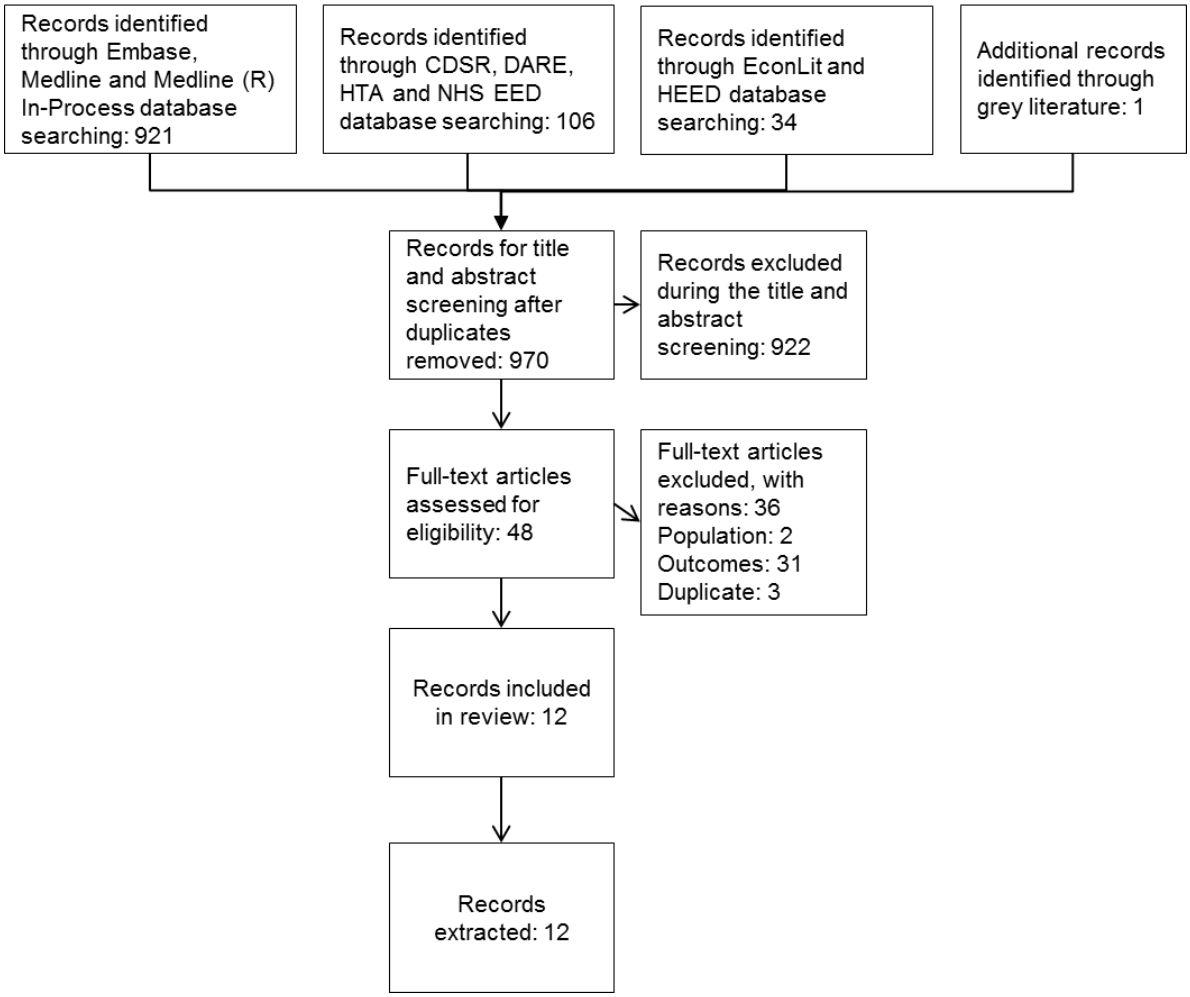


Table 35: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
Christopher et al.(56)	1999	A mean change model where patients were assigned an acute change in ppFEV1 that represented the treatment effect. After this acute change, patients declined at an age dependent rat of $pPFEV_1$. The cost per life year of rhDNase was compared to no rhDNase treatment.	CF patients aged 11 with mild to moderate lung disease	rhDNase was associated with 2 discounted incremental life years. A discount rate of 6% was used.	Calculating back from the ICER, the incremental cost of rhDNase was £26,275	Cost per life year was £52,550
Suri et al. (57)	2002	A cost consequence model was developed to analyse rhDNase compared to hypertonic saline and alternate day rhDNase. The cost consequence model outputted a cost per ppFEV1, this was chosen over using utility values to calculate QALYs as it was thought they would be insensitive to change in treatment regime over a 12 week period.	Children with a confirmed diagnosis of CF were recruited from two large CF centres in London, the Great Ormond Street Hospital for Children NHS Trust and the Royal Brompton and Harefield NHS Trust. Patients has to be between ages 5 to 18 years and have capacity to perform spirometry.	Incremental effectiveness in $ppFEV_1$ Daily rhDNase vs. HS - 14 Daily rhDNase vs. alternate-day rhDNase - 2 Alternate-day rhDNase vs. HS - 89	Incremental cost Daily rhDNase vs. HS - £1409 Daily rhDNase vs. alternate-day rhDNase - £464 Alternate-day rhDNase vs. HS - £945	Daily rhDNase vs. HS - £110 Daily rhDNase vs. alternate-day rhDNase - £214 Alternate-day rhDNase vs. HS £89
Iles et al. (58)	2002	Iles et al. conducted a study assessing the cost effectiveness of tobramycin nebuliser solution. The cost effectiveness model considered two 1 year periods, one before	Cystic fibrosis patients aged 6 years or older	Tobramycin nebuliser solution change between year 1 and year 2 – -1.26	Year 1 £22,102 Year 2 £28,394	Not reported

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
		TNS treatment and one during TNS treatment. The model was developed alongside a clinical study where 71 patients were studied, 41 with TNS and 30 usual therapy.				
Groen et al. (59)	2004	Groen at al. conducted a cost effectiveness analysis utilising data from the Dutch lung transplantation program collected between 1991 and 1999. The Dutch lung transplant program captured data for lung transplants associated with several disease areas, including cystic fibrosis.	Cystic fibrosis patients referred for lung transplant	Without transplant 652 With transplant 1177	Without transplant $37m With transplant $81m	$83,200
Thornton et al.(60)	2005	Thornton et al. assessed the cost effectiveness of home based i.v. antibiotics with hospital i.v. antibiotics for respiratory exacerbations in adults with CF. The cost effectiveness analysis was under taken alongside a clinical trial.	The study was conducted in a UK adult CF centre from a health service perspective.	Hospital was associated with 8.8% increase in proportion of patients with a decline >0% compared to mixed treatment Home was associated with -7.4% increase in proportion of patients with a decline >0% compared to mixed treatment	Hospital was associated with £3,000 increase in cost compared to mixed treatment Home was associated with £6,000 decrease in cost compared to mixed treatment	Hospital vs. both = £10,923 Home vs. both = £71,710
Veenstra et al. (61)	2007	Decision analytic model to evaluate the incremental clinical, patient, and economic outcomes associated with the use of the A1555G test	A hypothetical cohort of patients with CF	A1555G test - 17.16467 No A1555G test - 17.16467	A1555G test - $1603 No A1555G test - $1265	The ICER of a A1555G test $79,300
TA266 (18)	2011	The impact of bronchitol treatment on costs	Taken to match	Control - 9.75	Control - 180,188	Bronchitol

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
		and outcomes in the adult CF population. The chosen structure of the model was a patient-level simulation model. Bronchitol was compared to best supportive care either as mono-therapy or as add-on therapy to rhDNase.	DMP-CF-301 and DMP-CF-302. Mean age – 28.5 BMI – 22.4 ppFEV$_1$ – 59.3 Male – 58%	Bronchitol - 10.52 Control +rhDNase - 9.75 Bronchitol + rhDNase - 10.52	Bronchitol - 211,923 Control +rhDNase - 249,472 Bronchitol + rhDNase - 285,858	compared to control resulted in an ICER of £41,074 Bronchitol + rhDNase compared to control + rhDNase resulted in an ICER of £47,095
Yeola et al.	2012	Cost-effectiveness analysis was conducted using efficacy data and costs associated with adverse events. A decision tree was used response and non-response definitions, recurrence within one year.	CF patients with pneumothorax	Response rate Thoracoscopic pleural abrasion – 91.9% Thoracoscopic talcage – 95%	Thoracoscopic pleural abrasion – $2535 Thoracoscopic talcage - $3614	Cost per responder Thoracoscopic pleural abrasion – $2758 Thoracoscopic talcage - $3804
Schechter et al. (62)	2012	Schechter et al. conducted an economic evaluation of aztreonam lysine for inhalation and tobramycin for inhalation in patients with CF and chronic pulmonary pseudomonas. The analysis was conducted from the perspective of a third party payer in the US. Costs and	Cystic fibrosis patients with chronic pulmonary pseudomonas aeruginosa	Aztreonam lysine 2.263 Tobramycin 2.240	Aztreonam lysine $152,977 Tobramycin $157,187	Aztreonam lysine is dominant

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
		outcomes were considered over a 3 year time horizon. A Markov model was used to consider transitions between health states, which were defined by ppFEV$_1$.	infection			
Tappenden et al. (63)	2013	The cost effectiveness model compared treatment with colistimethate sodium DPI with Tobramycin nebulised as patient level data was available for these treatments. The model was a state transition model with three health states defined by ppFEV$_1$. Whilst in a health state patients can transition of any of the ppFEV$_1$ health states. Transitions between health states were calculated from trial data for the duration of the trial and then extrapolated. The health state with the lowest ppFEV$_1$ health state (<40%) is associated with a risk of lung transplant.	People aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary colonisation.	Colistimethate sodium DPI 9.48 Tobramycin Nebulised 9.61	Colistimethate sodium DPI Price £10.60 - £107,391 Price £15.98 - £156,045 Tobramycin Nebulised £110,519	Price £10.60 - £23,788 Price £15.98 - Dominated
Whiting et al.(64)	2014	Whiting et al. published a cost effectiveness analysis based on a cost effectiveness model developed by Vertex Pharmaceuticals assessing ivacaftor. Whiting et al. made modifications and updates where necessary. The key change made by Whiting et al. was to include the lung transplants in the model. Patients were assumed to be eligible for lung transplant if they had a ppFEV$_1$ < 30%, with only 17% of patient eligible receiving a lung transplant.	For the treatment of CF patients aged >6 with at least G551D	Standard care - 8.60 Ivacaftor + Standard care - 9.87 (Conservative) 13.86 (Optimistic)	Standard care - £267,393 Ivacaftor + Standard care - £1,882,254 (Conservative) £2,029,969 (Optimistic)	Conservative scenario £1,273,805 Optimistic scenario £334,775

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
Schwenkglenks et al. (65)	2015	A decision-analytic microsimulation framework assessed the incremental cost-effectiveness ratio of best supportive care plus mannitol versus best supportive care alone	Taken to match two Phase III randomised control trial	Compared to best supportive care, mannitol plus best supportive care was associated with an incremental QALY of 0.54	Compared to best supportive care, mannitol plus best supportive care was associated with an incremental €18,370	The ICER associated with best supportive care was €33,772

Abbreviations; ICER, incremental cost effectiveness analysis; HS, hypertonic saline; NHS, national health service; CF, cystic fibrosis; I.V., intravenous; rhDNase, recombinant human deoxyribonuclease; $ppFEV_1$, Percent predicted forced expiratory volume in 1 second; QALYs, quality adjusted life years.

5.2 De novo analysis

5.2.1 Patient population

The model considers a patient population in line with the licensed indication. LUM-IVA fixed dose combination is indicated for the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

5.2.2 Model structure

An individual patient level micro-simulation model was constructed to estimate incremental clinical outcomes, health outcomes, and costs of LUM-IVA + SoC versus SoC alone from an NHS and PSSRU perspective. This model is similar in structure to a previous economic model used to evaluate another CFTR modulator (i.e. Kalydeco) in other HTA submissions, it has been updated to reflect the recommendations of a recent assessment by Whiting et al. 2014. As in the prior submission, model results were estimated over a lifetime horizon.

To estimate the incremental impact of LUM-IVA on health outcomes and costs versus SoC alone, each patient is run through the model twice: once assuming the patient receives SoC alone and once assuming the patient receives LUM-IVA + SoC. Baseline patient characteristics for the base case are drawn from the patients included in the TRAFFIC and TRANSPORT studies.

The cost-effectiveness model simulates several clinical parameters over time to model a patient's disease progression, clinical outcomes and associated health outcomes and costs. In each cycle the model follows a patient's: $ppFEV_1$, weight-for-age z-score, risk of pulmonary exacerbations, age, probability of lung transplantation, probability of adverse events (AEs), diabetes status and probability of treatment discontinuation. These factors influence;

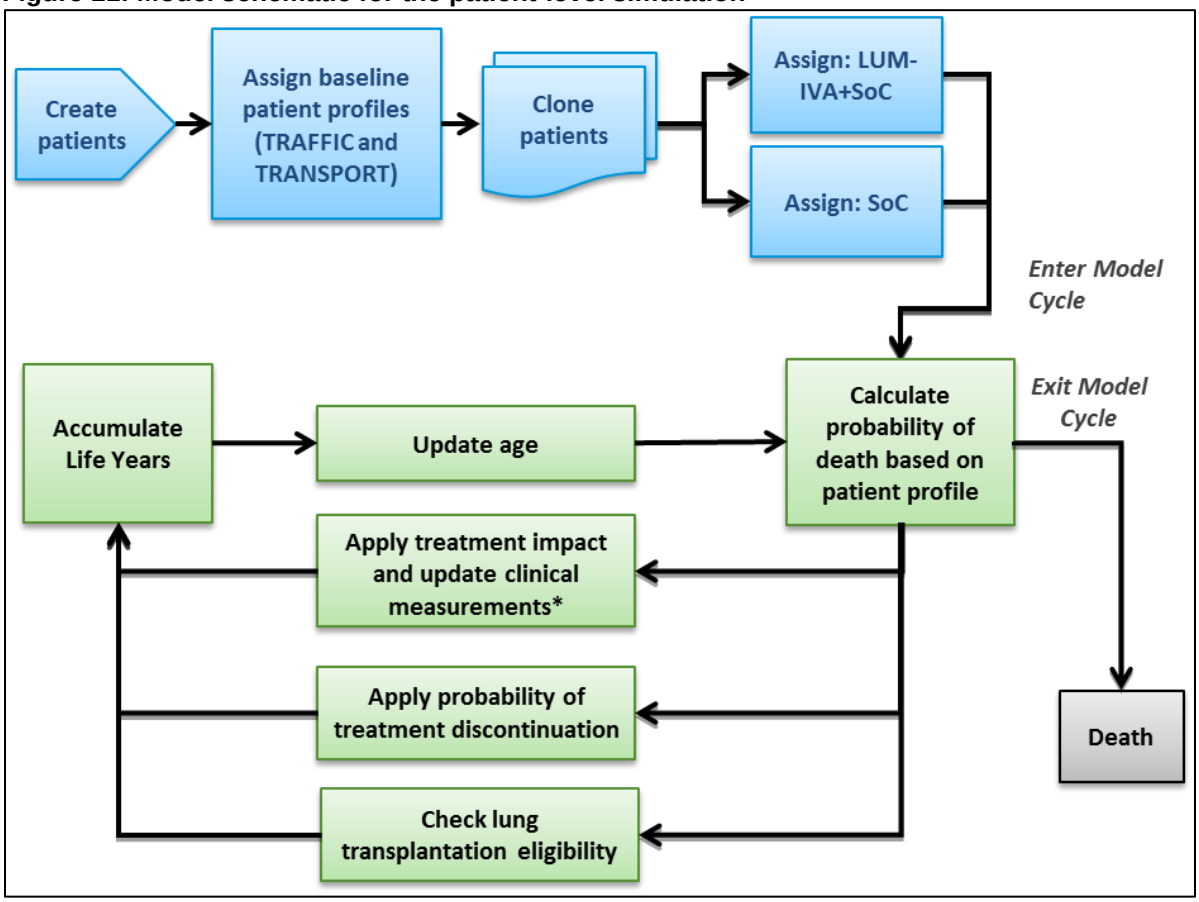
- Survival projections (described in section 5.3.7) – Survival is modelled by combining a survival function with a cox proportional hazards model (Liou et al., 2001) (6) to account for a number of clinical parameters known to be relevant to CF.
- Utility (described in section 5.4.6) – Utility is based on $ppFEV_1$, pulmonary exacerbation status and lung transplant status
- Disease management costs (described in section 5.5) – Costs are dependent on treatment received, $ppFEV_1$ and lung transplant status

Variables are estimated at every 4 week cycle for the first two years and annually thereafter. A 4 week cycle length is used at the start of the model to allow TRAFFIC and TRANSPORT study outcomes to be synchronised at the relevant time point.

The model structure is illustrated in Figure 11. The underlying disease progression model tracks nine risk factors known to predict survival in CF based on a 2001 paper published by Liou et al. (6): $ppFEV_1$, pulmonary exacerbations, weight-for-age z-score, pancreatic sufficiency, diabetes, *B. cepacia*, *S. aureus*, age and gender. A cohort for the purpose of the simulation is built by drawing patients from the pool of patients who participated in the TRAFFIC or TRANSPORT studies. Each simulated patient's baseline characteristics are defined based on the measured baseline characteristics of the corresponding patient from TRAFFIC or TRANSPORT. Each patient is duplicated and run through each treatment arm

(see section 5.2.3). At the start of each cycle patients are at risk of death; the risk of death is based on patient characteristics known to predict survival in CF (section 5.3.7). While a patient remains alive, their clinical characteristics, including $ppFEV_1$ and age, are updated. Based on clinical characteristics patients are at risk of subsequent pulmonary exacerbations, diabetes, discontinuation of LUM-IVA, AEs and lung transplant. The events experienced by a patient and the patient's clinical disposition determine the cost and QALY calculations. This is repeated until the patient dies, at which time the patient exits the model.

Figure 11: Model schematic for the patient-level simulation



Abbreviations: QALYs, Quality-adjusted life-years; SoC, standard of care.
*Clinical measurements include $ppFEV_1$, the occurence of pulmonary exacerbations, diabetes, infections and weight-for-age z-score.

The model is in line with previously published CF cost-effectiveness analysis, as shown by the cost effectiveness systematic literature review. $ppFEV_1$ has been used to model disease progression in several cost effectiveness models. The model is similar in structure to the model published by Whiting et al. (64)

Table 36: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	Chronic progressive disease
Were health effects measured in QALYs; if not, what was used?	The health effects were measured using QALYs	NICE reference case

Discount of 3.5% for utilities and costs	3.5%	NICE reference case
Perspective (NHS/PSS)	NHS and PSS	NICE reference case
Cycle length	4 Weeks for the first 2 years and then annual	To allow the model to match the outcomes of the trials at 24 weeks.
Half cycle correction	Yes	To account for the annual cycle length

Abbreviations: PSS, personal social services; QALYs, quality-adjusted life years

5.2.3 Intervention technology and comparators

The relevant group of patients are currently managed with SoC treatment which is focused on controlling symptoms, maintaining lung function, and attempting to avoid complications of the disease such as infection. SoC treatments are individualised and generally include daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, and daily physiotherapy. Other than SoC there are no active comparator treatments in patients with CF age 12 years and older who are homozygous for the *F508del* mutation.

LUM-IVA is the only treatment which addresses the underlying cause of the disease (the defective CFTR protein) in this patient population and it is intended for use as adjunct to SoC and therefore is not a direct comparator to any existing CF medication. In the TRAFFIC and TRANSPORT studies, patients in all treatment groups remained on their stable CF medication regimens e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated, for the duration of the studies. Thus, patients being simulated through the model arm receiving LUM-IVA were assumed to continue using SoC treatments in addition.

5.3 Clinical parameters and variables

The model tracks CF disease progression over time and considers the following patient characteristics known to predict survival in CF: $ppFEV_1$, pulmonary exacerbations, weight-for-age z-score, as well as diabetes, certain respiratory infections, pancreatic sufficiency, patient age, and gender. The model also tracks additional events such as lung transplantation, occurrence of adverse events and treatment discontinuation. Of these clinical parameters LUM-IVA has been shown to have a clinically and statistically significant impact on $ppFEV_1$, the risk of pulmonary exacerbations and weight-for-age z-score (17).

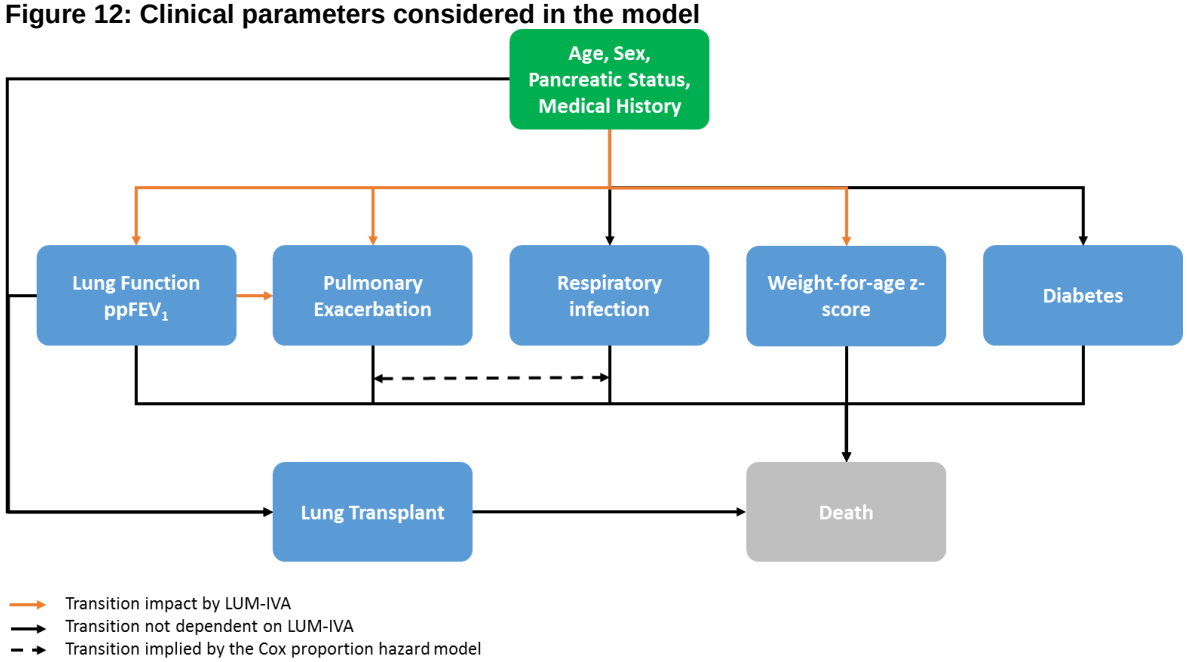
To track disease progression, each patient's characteristics and medical history are updated at each four-week cycle for the first two years and annually thereafter. These characteristics feed into a Cox proportional hazards model which is used to adjust the underlying population survival function for each individual patient in each model cycle:

- Sex, *S.aureus* infection status, and *B.cepacia* infection status are assumed to remain unchanged from baseline over time and are the same in both the patient receiving SoC and his/her LUM-IVA treated "clone" over time; all patients are assumed to be pancreatic insufficient in both arms given the age and genotype of this population

- Age and diabetes status are updated each cycle and are also assumed to be equivalent for both the patient receiving SoC and his/her LUM-IVA treated "clone" over time
- $ppFEV_1$ and annual number of acute pulmonary exacerbations change over time and differ between treatments
- Weight-for-age z-score is updated during the first 24 weeks (the TRAFFIC and TRANSPORT study duration) then assumed to remain constant over time with the difference between treatments also remaining constant.

Figure 12 shows the dependencies in the model, how each of the clinical parameters relate and which dependencies are treatment specific. A summary of the base case settings is shown in Table 59.

Figure 12: Clinical parameters considered in the model



5.3.1 Patient characteristics

The baseline patient characteristics (age, gender, weight-for-age z-score and baseline $ppFEV_1$), drawn at the start of the model, are derived directly from the baseline characteristics for the 1,097 patients included in the TRAFFIC and TRANSPORT trials who had $ppFEV_1$ data available at baseline. Baseline diabetes and infection status were derived from published prevalence data and all patients were assumed to be pancreatic insufficient. Patients are randomly drawn from this pool of trial participants using bootstrapping methods to create a cohort of 1,000 patients to be simulated though the model. A summary of the characteristics of this 1,000 patient cohort is shown in Table 37. The model is then run for 6 replications on the 1,000 patient cohort using different random numbers for each replication. The use of 1,000 patients and 6 replications ensures the base case results are stable and consistent in that they are not unduly influenced by the specific random numbers used in sampling.

Table 37: Baseline characteristics for 1,097 patients in TRAFFIC and TRANSPORT

Characteristic	Mean Value – Total Population
Age (years)	25.5

Male	50.6%
Mean BMI	21.2
$ppFEV_1$	60.6%

Abbreviations: $ppFEV_1$: Forced expiratory volume in one second, BMI: Body mass index

The age and $ppFEV_1$ of the study population were compared with those of the UK CF Registry population (all genotypes) to assess the generalisability of the study population. Reported baseline $ppFEV_1$ is higher and age is lower in patients in the general UK CF Registry than in the TRAFFIC and TRANSPORT study populations; however this is likely due to the age (12+ years), severity of the genotype (with the trial population being restricted to patients who were homozygous for the *F508del* mutation) and $ppFEV_1$ (40%-90%) criteria applied for inclusion in the studies. This comparison is shown in Table 38.

Table 38: Comparison between TRAFFIC and TRANSPORT and the UK CF Registry annual report (18)

Characteristic	TRAFFIC and TRANSPORT	UK CF
Mean Age (years)	25.5	19.6
Median $ppFEV_1$	60.5%	75%

Abbreviations: $ppFEV_1$: Forced expiratory volume in one second

In order to provide an accurate comparison of the TRAFFIC and TRANSPORT population to the population of interest in the UK, it would be best to compare the study population to the UK CF *F508del* homozygous population (12 years and older). In the absence of these data, a validation exercise is included in section 5.10 to compare survival of patients with the same baseline patient characteristics as the UK CF registry and the estimated survival.

5.3.2 Change in $ppFEV_1$

LUM-IVA significantly increased $ppFEV_1$ compared to SoC in the 24-week phase 3 studies, TRAFFIC and TRANSPORT. The change in $ppFEV_1$ was maintained through an additional 24 weeks in the open label study, PROGRESS (96 weeks planned duration extension study, giving 120 weeks data in total). Based on these data, the model assumes that LUM-IVA continues to impact $ppFEV_1$ after the study period and considers the 24 week placebo-controlled study period separately from the time beyond the study period. This allows the model to make the most of the TRAFFIC and TRANSPORT studies, which is the best source of evidence for LUM-IVA.

The progression of $ppFEV_1$ is split into two stages:

- Changes observed in the TRAFFIC + TRANSPORT studies – up to 24-weeks
- Extrapolated change in $ppFEV_1$ post 24-weeks

Changes observed in the TRAFFIC + TRANSPORT studies – up to 24-weeks

For the first 24 weeks, the $ppFEV_1$ of patients on LUM-IVA + SoC increases by 2.8 percentage points by week 16 compared to their starting $ppFEV_1$ and remains constant until week 24. This is based on the pooled placebo-adjusted mean change from baseline in $ppFEV_1$ (treatment effect) measured as the average of weeks 16 and 24 from TRAFFIC and TRANSPORT (17). The $ppFEV_1$ of patients on SoC alone is assumed to remain unchanged from baseline, as the aforementioned treatment effect for LUM-IVA is measured relative to SoC.

As discussed in section 4.7.1, the 2.8 increase in percentage points associated with LUM-IVA + SoC is an absolute increase in $ppFEV_1$, LUM-IVA is associated with a 4.8 relative increase in $ppFEV_1$.

Extrapolated change in $ppFEV_1$ post 24-weeks - SoC

It is well-documented that lung function declines over time in patients with CF, with several papers reporting on large observational studies representing real world data (10, 66). Thus after week 24, the $ppFEV_1$ of patients on SoC is assumed to decline from its value at week 24. The assumed rate of decline for SoC is age dependent and was derived from a large, prospective, multicentre, encounter-based, observational study of US and Canadian CF patients (N=4,161 adults 1994-2005; N=1,359 children 1997) reported in two separate studies (children vs. adults) (10, 66). The rates of decline used in the model are reported in Table 39.

These prospective, multicentre observational studies represent the best sources of evidence for rate of $ppFEV_1$ decline associated with SoC as the studies report long-term longitudinal data across a large sample of CF patients. There was no placebo control group during the PROGRESS extension study, prohibiting the determination of 48-week change in $ppFEV_1$ for the placebo (i.e., SoC) treatment group from the clinical study data; the data from the 24-week study period was of an insufficient duration to calculate an annual rate of decline with the accuracy required for inclusion within the model. In the absence of these data, to inform the annual rate of $ppFEV_1$ decline for the SoC arm of the model beyond the 24-week study period, data from the most robust studies in the published literature were used. Moreover, although $ppFEV_1$ by age is reported in the UK CF registry report, this is only cross-sectional aggregate median data based on one $ppFEV_1$ measurement per patient. It is most appropriate to calculate rate of decline using patient-level longitudinal data with all recorded $ppFEV_1$ measurements. The registry is an inferior source for rate of decline relative to the long-term observational studies published by Konstan et al (10) .

Extrapolated change in $ppFEV_1$ post 24-weeks – LUM-IVA

The TRAFFIC, TRANSPORT, and PROGRESS studies were used to estimate the annual rate of $ppFEV_1$ decline for the LUM-IVA arm of the model beyond the 24 week study period. The 24-week interim readout of the open-label study (PROGRESS) provides a total of 48 weeks of efficacy and safety data for the LUM-IVA + SoC treatment group. The baseline to 48-week pattern of changes in $ppFEV_1$ observed in the TRAFFIC, TRANSPORT, and PROGRESS studies is shown in section 3.2.

Utilising a total of 48 weeks of data directly from the clinical studies to calculate the annual rate of $ppFEV_1$ decline represented the only available option for determining the annual lung function decline in these patients treated with LUM-IVA. There are distinct advantages to utilising this data, as it is based on the population of interest; patients with CF age 12 years and over who are homozygous for the *F508del-CFTR* mutation, and represents actual $ppFEV_1$ changes observed in patients who were treated with LUM-IVA.

The methods used to calculate the rate of decline followed an approach that has previously been used in CF (67). Using mixed model analysis, the mean annual rate of change in $ppFEV_1$ was calculated using the available data from the TRAFFIC, TRANSPORT, and PROGRESS studies for patients randomised to LUM-IVA in TRAFFIC and TRANSPORT (allowing for 48 week follow-up). To avoid including the initial acute change observed with LUM-IVA treatment (changes in $ppFEV_1$ assumed to be the treatment effect), the analysis

included all $ppFEV_1$ measurements at, or post, the Week 4 visit from the TRAFFIC and TRANSPORT studies, and all measurements from the PROGRESS study. The analyses included all patients (n = 339) who were randomised to LUM-IVA and had at least one spirometry reading while on treatment; the number of visits ranged from 2 to 16 (readings did not need to be associated with a study visit, to ensure that readings during acute episodes were considered). A mixed model with random intercepts and slopes for each patient was developed to estimate the slope of $ppFEV_1$. The unadjusted slope was annualised, and the analyses determined that patients declined at an average of 0.68 (95% CI -1.58% to 0.16%) percentage points per year while on LUM-IVA treatment. This observed rate of decline was applied to all simulated patients receiving LUM-IVA therapy through the residual life span of the patient.

Summary

Based on the analyses described above, Table 39 summarises the inputs used in the model.

Table 39: Age-dependent annual change in $ppFEV_1$ by treatment

Age	SoC	LUM-IVA
<18 years	-2.34%	-0.68%
18-24 years	-1.92%	-0.68%
25+ years	-1.45%	-0.68%

Abbreviations: $ppFEV_1$: Forced expiratory volume in one second, SoC: Standard of Care

To avoid unrealistically low $ppFEV_1$ values, a lower bound of 15% is set based on the opinion of clinical experts (68).

5.3.3 Pulmonary exacerbations

To calculate the frequency of pulmonary exacerbations for patients treated with SoC, an age-dependent equation relating $ppFEV_1$ to the annual expected rate of pulmonary exacerbation is used. Using this expected rate and a Poisson distribution, the model calculates an integer number of pulmonary exacerbations per patient per cycle. This relationship was taken from Whiting et al. (64) based on data from the 2004 US CFF Registry data and reported in Goss et al. (69). It should be noted that the study by Goss et al. defined exacerbations as those requiring IV antibiotics and/or inpatient stays and as such the model only tracks these types of exacerbations.

$$Annual\ rate\ of\ exacerbation \geq 18\ years = 3.7885e^{-0.026 \times ppFEV_1}$$

$$Annual\ rate\ of\ exacerbation\ < 18\ years = 8.5938e^{-0.035 \times ppFEV_1}$$

A similar method is applied for patients receiving LUM-IVA but the rate is multiplied by a rate ratio of 0.442 to reflect the durable treatment benefit observed in the study. LUM-IVA demonstrated a significant reduction in the annualised rate of any protocol-defined pulmonary exacerbation (39%), those requiring IV antibiotics (56%), and those requiring hospitalisation (61%) in the TRAFFIC and TRANSPORT studies. The rate ratio for pulmonary exacerbations requiring IV antibiotics and/or hospitalisation for LUM-IVA + SoC versus SoC (0.442) derived from the TRAFFIC and TRANSPORT studies is applied for LUM-IVA, since the model only tracks these types of events.

The clinical experts who were consulted consistently agreed that the impact of LUM-IVA on $ppFEV_1$ and pulmonary exacerbation are independent and that the treatment effect of LUM-IVA on pulmonary exacerbations is not fully mediated through changes in $ppFEV_1$, as these are separate benefits of treating the underlying cause of disease in patients with this genotype. Thus, even though LUM-IVA improves $ppFEV_1$ over time, (thereby conferring some indirect reduction in the rate of pulmonary exacerbations), the treatment effect of LUM-IVA on $ppFEV_1$ and pulmonary exacerbation are assumed to be independent in the model, and thus the treatment effect on pulmonary exacerbation is applied for the duration of the model. Clinical experts agreed that this assumption was clinically plausible (68). Alternative scenarios were tested in scenario analyses.

To test this assumption and isolate the impact of LUM-IVA on the rate of pulmonary exacerbations requiring IV antibiotics or hospitalization from $ppFEV_1$ changes, a repeated measures binomial regression model was conducted estimating the rate of exacerbations based on a number of variables, predominantly previous $ppFEV_1$ and a dummy variable to represent the treatment effect of LUM-IVA. This analysis estimated LUM-IVA to be associated with a rate ratio of 0.2941 (confidence interval 0.2054 – 0.4211), implying that treatment with LUM-IVA confers a large benefit on exacerbations even when accounting for $ppFEV_1$ changes and in fact the base case assumption may be conservative.

5.3.4 Weight-for-age z-score

Weight-for-age z-score is assumed to remain unchanged for SoC-treated patients for the entire model time horizon. For patients treated with LUM-IVA, an absolute increase from baseline of 0.068 is applied by week 24, based on the placebo-adjusted improvement observed in the TRAFFIC and TRANSPORT studies. This treatment effect is assumed to be a one-time increase that is maintained (43, 44). While BMI was a secondary endpoint in the LUM-IVA clinical studies, weight-for-age z-score is included in the Cox proportional hazards model used in the model to project survival; thus weight-for-age z-score has been included based on the observed changes in the studies, allowing the Cox proportional hazards model to capture the treatment effect of LUM-IVA on nutritional status.

Table 40: Summary of $ppFEV_1$, pulmonary exacerbation and weight-for-age z-score inputs

Parameter		SoC	LUM-IVA + SoC
$ppFEV_1$	First 16 weeks through week 24	Baseline	Baseline + 2.8%
	Annual change after 24 weeks	Age < 18: -2.34% Age 18-24: -1.92% Age ≥ 25: -1.45%	Age < 18: -0.68% Age 18-24: -0.68% Age ≥ 25: -0.68%
Annual rate of pulmonary exacerbation		Predicted conditional on $ppFEV_1$ and age	Predicted conditional on $ppFEV_1$ and age, and multiplied by 0.442
Weight-for-age z-score	First 24 weeks	Baseline	Baseline + 0.068
	After 24 weeks	Remains unchanged	Remains at baseline + 0.068

Abbreviations: $ppFEV_1$, percent predicted forced expiratory volume in one second; SoC, standard of care.

5.3.5 Diabetes

Each patient who does not have diabetes is at risk of developing this condition in each model cycle. Annual incidence stratified by age range and gender were obtained from a study by Adler et al., (2008) on patients in the UK CF Registry (70); the results are shown in Table 41. During the first phase of the model where the model uses a 4-week cycle length, the annual incidence is converted to a 4-week probability. Diabetes risk is assumed to be the same for those on LUM-IVA + SoC and SoC alone.

Table 41: Annual incidence of diabetes

Age Range (years)	Males	Females
12–19	3.9%	6.0%
20–29	4.9%	7.1%
30–39	6.5%	7.2%
40–100	5.1%	2.9%

5.3.6 Lung transplant

The UK clinical guideline for transplantation suggests referral for a lung transplantation for patients with $ppFEV_1$ <30% (27), and a previous study has shown that the benefit from transplantation was statistically significant only in patients with $ppFEV_1$ less than 30% (71). The $ppFEV_1$ threshold of 30% was also accepted by the National Health Service health technology assessment for ivacaftor in treatment of patients with CF with the *G551D* mutation (64). The model assumes that once a patient's $ppFEV_1$ drops below 30%, the patient becomes eligible to receive a lung transplant. Among all patients who are eligible, only a proportion of patients actually receive a lung transplant. In clinical practice, whether an eligible patient can receive a lung transplant is influenced by various factors, including: whether the patient meets the requirements for the waiting list, whether they are an eligible recipient for a transplant, the availability of matching donor organ and patients' health status. However, as data on annual incidence of lung transplant were not available, the model relies on data regarding prevalence of lung transplantation among patients with $ppFEV_1$ below 30%. In the model, these patients are assumed to have a one-time probability of receiving a transplant in the cycle in which $ppFEV_1$ falls below 30%. Based on data from the UK CF registry report that, among 247 patients with annual review data evaluated for transplant, 61 received lung transplant (5), the proportion of eligible patients who receive a lung transplant is estimated at 24.7%. This risk is applied equally to all patients who reach the $ppFEV_1$ threshold.

The modelled consequences of receiving a lung transplant are additional costs, changes in health-related quality of life and in the risk of mortality. The post-lung transplantation mortality assumes constant annual mortality in the first year after transplantation (15.2%) and for each subsequent year (6.1%). These estimates are derived from data collected from 6,766 adult CF patients (all genotypes) who received a lung transplant between 1990 and 2012 in the UK, with median follow up of 8.3 years (72).

5.3.7 Mortality

For patients who haven't received a lung transplant the model estimates individual patient risk of death in each cycle using a two-part calculation: first the age-specific background

mortality hazard derived from UK CF Registry data is calculated; second, the hazard is adjusted in each cycle to account for individual patient characteristics that predict survival in CF based on the cox proportional hazards model published by Liou et al. (6). Mortality is calculated from the following elements:

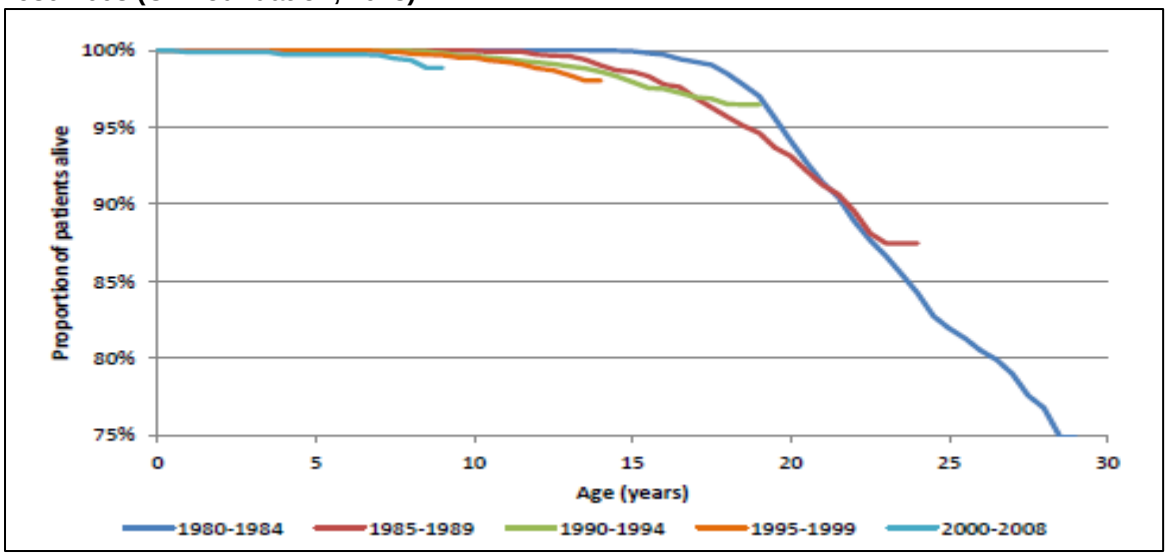
- CF survival estimates (section 5.3.7.1)
- Incorporation of patient level characteristics

5.3.7.1 Derivation of a function to estimate survival probabilities

There are no publications of complete survival curves for CF patients in England. In the absence of complete curves, partial curves based on data from the UK CF Trust Registry are used to derive background mortality hazard for CF patients in the UK. Due to complete survival data not being available in the UK CF Registry annual report (as data collection is ongoing) parametric survival analysis is used to fit a parametric function to the observed curves from the registry, in order to extrapolate the survival over the entire lifespan of all members of the population. The parametric survival analysis was conducted in accordance with NICE guidance on survival analysis in economic evaluations (73).

The analyses are based on the most recent published Kaplan-Meier curves of CF survival in the UK, which reported survival for 6,082 patients grouped into birth cohorts ranging from 1980 to 2008 (Figure 13). The published curves were digitised. Simulated patient-level data were generated based on the digitised curve and the number of patients in each birth cohort using methods described by Ishak et al. (2013) (74) and Tierney et al. (2007) (75). Various parametric functions were tested to arrive at the best parametric fit that is visually and statistically credible, as well as clinically plausible (74, 76).

Figure 13: **Kaplan-Meier curves of survival in the UK CF Registry birth cohorts (all genotypes) 1980-2008 (CF Foundation, 2013)**



Analyses of the UK data presented the following challenges:

- Long flat periods in older birth cohorts, potentially due to the lack of information earlier in the samples' lifetime, causing potential selection bias and representing artificial 100% survival, which can distort fits and projections
- Survival observed in the more recent birth cohorts is relatively short, making long-term extrapolation potentially unreliable

For instance, in separate parametric analyses of each birth cohort, median projected survival estimates for the most recent birth cohorts were either unrealistically high (e.g., over 100 years) or implausibly low (around 25 years), which is inconsistent with findings from similar analyses of other registry data (CF Foundation US patient registry; CF Ireland registry; French cystic fibrosis registry). Thus, pooling data from birth cohorts was undertaken. Two possible groupings were considered: 1990-2008 and 1985-2008. Parametric curves were fitted to these two datasets. The parametric curves were compared to assess which provides the most valid output. Projections from the 1990-2008 grouping were not reasonable. The median estimate using a Gompertz distribution was around 31 years, but the projection declined so rapidly that no patients would be predicted to survive beyond 40 years of age. In contrast, the projection using a Gamma distribution is more realistic, but implies a median projected survival of 55.5 years, which is considerably higher than estimates in analyses of other cohorts. Thus, final analyses were based on the 1985-2008 birth cohorts. Table 42 summarises estimates of median projected survival and goodness of fit statistics for each distribution, in addition to goodness of fit statistics diagnostic plots were considered. These suggest the Weibull, Gompertz, and Gamma distributions offer comparable fit to the observed data, with Akaike Information Criterion (AIC) statistics within one point of each other. Median estimates from these three distributions, while plausible, do imply a fairly broad range in projected median survival from 31 years with a Gompertz fit to 41 years with Weibull. Thus, a clear decision is difficult to make based on these criteria alone.

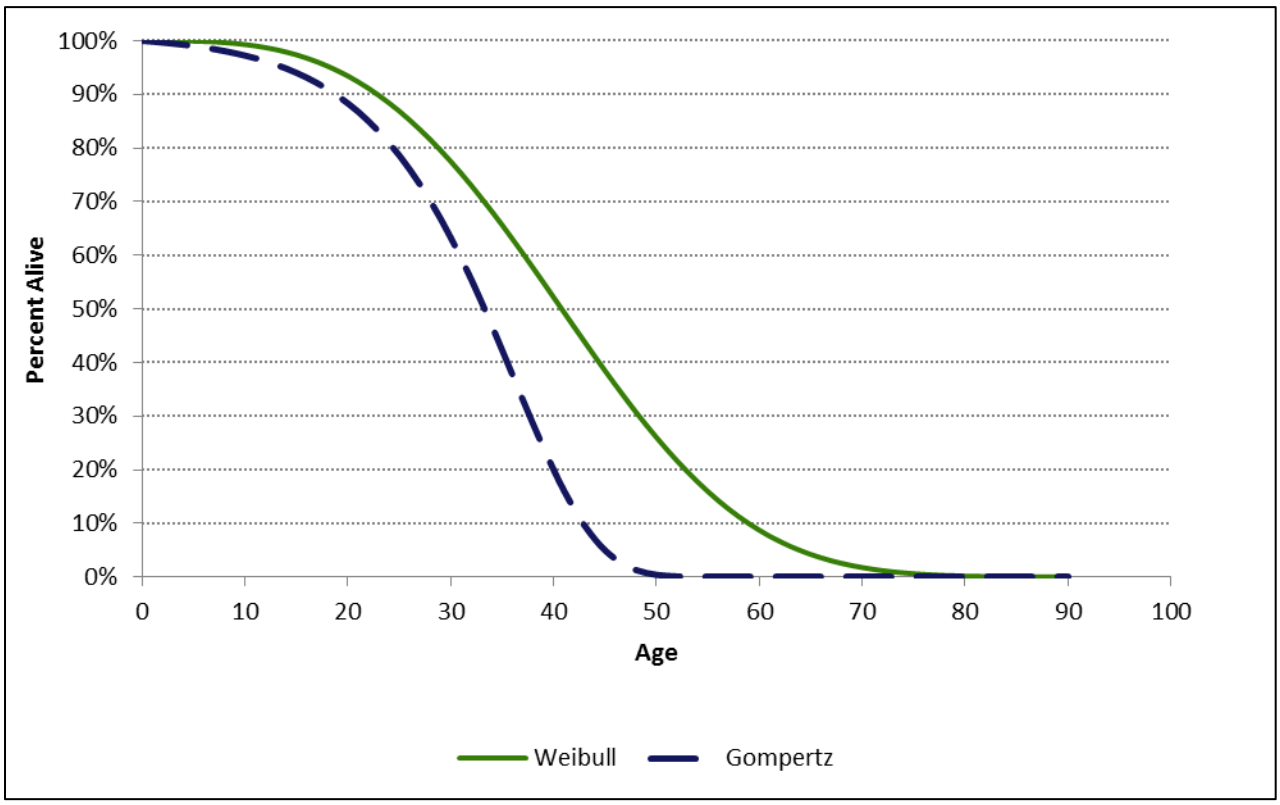
Table 42: Projected median survival estimates and fit statistics for fits to UK CF registry population (all genotypes) birth cohort 1985-2008

Distribution	Predicted Median	AIC	BIC
Weibull	40.8	702.626	715.589
Log-normal	83.3	740.975	753.938
Log-logistic	44.6	703.470	716.433
Exponential	372.7	850.475	856.956
Generalized gamma	37.7	703.811	723.256
Gompertz	30.6	702.588	715.551

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

The face validity of long-term projections was considered in the selection of the optimal fit. Long-term projections suggest an unrealistically rapid decline in the Gompertz and Gamma fits with all patients predicted to have died by age 50. The Weibull fit produces more plausible projections with the curve reaching 0% alive near 80 years of age, and a predicted median of 40.8 years (Figure 14). These assumptions were tested with clinicians at an advisory board and it was agreed that the Weibull projections for this UK population are the most clinically plausible (68).

Figure 14: Survival projections using Weibull and Gompertz distribution – derived from UK CF registry population (all genotypes) birth cohort 1985-2008



The coefficients of the Weibull function selected to conduct the base-case analyses are summarised in Table 43.

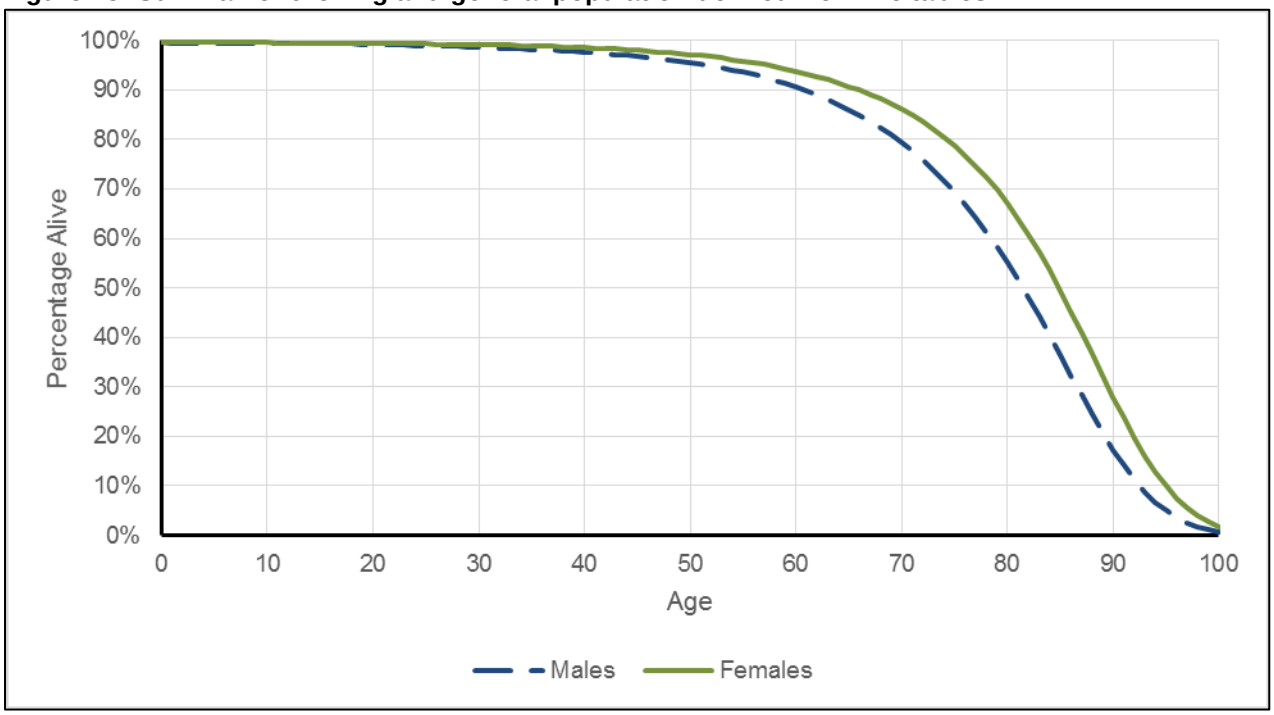
Table 43: Parameters for Weibull distribution used to derive CF survival projections based on UK CF registry population (all genotypes) birth cohort 1985-2008

Parameter *	Value
λ	3.938E-6
γ	3.2577

*Weibull Survival Function: $(t)=e^{-\lambda t\gamma}$; Weibull Hazard Function: $h(t)= \lambda\gamma t\gamma-1$

The gender- and age-specific mortality hazard for simulated patients is not allowed to go below that of the UK general population for any patient in any model cycle. Life table data were retrieved for the UK population to impose this limit (77) i.e. the maximum of the general population and CF specific mortality is applied. Figure 15 shows the survival derived from the mortality life table data of the England general population.

Figure 15: Survival for the England general population derived from life tables



5.3.7.2 Relating individual patient characteristics to survival

To assess instantaneous hazard for an individual patient, age-specific hazard is derived from the survival function that was fitted to the UK CF Registry population. This age-specific hazard is then adjusted to allow for the incorporation of patient-level characteristics using a cox proportional hazard model developed by Liou et al. (2001) (6). Liou et al. developed the model using registry data collected from 1993 to 1998 by the United States (US) Cystic Fibrosis Foundation on 11,630 individuals and found that the following nine characteristics of patients with CF predict survival: age, ppFEV$_1$, gender, weight-for-age z-score, pancreatic insufficiency, diabetes, *S aureus* infection, *B cepacia* infection, and number of acute pulmonary exacerbations per year.

Specifically, the Cox proportional hazards equation (as described below Table 44) is used to adjust the age-specific hazard derived from the Weibull parametric curve. Reference values for each of the eight characteristics besides age are used to make the adjustment from the UK CF Registry to an individual patient in the model at baseline through the Cox proportional hazards model. Because the underlying hazard function was based on UK CF Registry data available in 2008, the reference values used in the Cox proportional hazards equation were derived from the 2008 UK CF registry report, where available (78). For those values which were not available from the UK CF Registry report (weight-for-age z-score, pancreatic status and diabetes status), values from alternative sources were used. The covariates included in the Liou model and the corresponding coefficients as well as the reference values used in the Cox proportional hazards equation and corresponding sources are shown in Table 44.

Table 44: Cox proportional hazards model coefficients and reference values

Covariate	Coefficient*	SE	Reference Value (Mean)	Reference
Age (per year)	0.011	0.0049	19.6	UK CF Registry 2008 (79)

ppFEV$_1$ (per percentage point)	-0.042	0.0025	73.2	UK CF Registry 2008 (79)
Sex (female = 1)	0.15	0.074	0.467	UK CF Registry 2008 (79)
Weight-for-age z-score	-0.28	0.041	-0.85	Liou et al. 2001 (6)
Pancreatic sufficiency (yes = 1)	-0.14	0.23	0.126‡	2011 US CFF Registry Estimated based on the % of patients NOT requiring a pancreatic supplement (80)
Diabetes mellitus (yes = 1)	0.44	0.098	0.187†	2012 UK CF Registry (81)
S. aureus (yes = 1)	-0.25	0.09	0.179	UK CF Registry 2008 (79)
B cepacia (yes = 1)	1.41	0.19	0.034	UK CF Registry 2008 (79)
Annual number of acute exacerbations (max 5)	0.35	0.024	1.1	Liou et al. 2001 (6)
Exacerbations × *B. cepacia*	-0.28	0.06	Calculated	Assumed equal to mean *B. cepacia* multiplied by mean annual exacerbations

Abbreviations: *B.cepacia*, Burkholderia cepacia; ppFEV$_1$, percent predicted forced expiratory volume in one second; *S.aureus,* Staphylococcus aureus; SE, standard error

The risk factors included in the Cox proportional hazards model described above were measured only at baseline in Liou's study and their changes over time were not taken into account. Thus, the model requires that the reference values update over time in order to generate valid results, as described below.

The initial hazard of death for a particular patient is computed as the initial hazard corresponding to the mean profile of the reference population at the individual patient's baseline age ($h_{\bar{x}0}$) times the hazard ratio for that patient (HR_i) at baseline:

$$h_{i0} = h_{0\bar{x}} HR_i$$

With the hazard ratio computed as:

$$HR_i = e^{\beta_1 (x_1 - \bar{x}_1) + \beta_2 (x_2 - \bar{x}_2) + \ldots + \beta_9 (x_9 - \bar{x}_9)}$$

where $\beta_{1\text{-}9}$ are the cox proportional hazards model coefficients from Liou et al. for each risk factor, the x_{1-9} are the values of the individual patient's risk factors at baseline, and $\bar{x}_{1-9}$ are the reference values, most of which are mean values in the UK Registry. Age is not included in the baseline calculation of this hazard ratio, as the hazard derived from the reference population's mortality function is age-specific and thus needs no further adjustment for the simulated patient's age. The hazard corresponding to the mean profile of the reference population is calculated as:

$$h_{0\bar{x}} = \lambda \gamma t^{y-1}$$

where λ and γ are the parameters of the Weibull distribution in Table 43 (82)and t is the patient's age at baseline.

This h_{i0} provides a starting point for the projection of the simulated patient's mortality (i.e., their hazard of death at baseline). To continue the projection requires adjusting the hazard to reflect progression in any of the risk factor values (e.g., deterioration of respiratory function reflected in a lower ppFEV$_1$) for that particular patient. This adjustment is achieved by calculating the HR with respect to that patient's own hazard at the beginning of the just

concluded time step. In other words, the equation for HR_i in the current cycle replaces the $\overline{xj}$ mean values from the Registry with the patient's own risk factor values from the previous cycle. This HR is then applied to the hazard in the previous cycle to derive the hazard in the current cycle. This methodology is applied both to simulated patients receiving LUM-IVA and those receiving SoC. Thus, as the clinical characteristics of a patient on LUM-IVA differ from his/her "clone" on SoC, so do these two patients' hazards diverge over time.

The per-cycle probability of death is computed from the instantaneous hazard in each cycle using the formula:

$$p = 1 - e^{-h/t}$$

where *h* is the instantaneous mortality hazard calculated at that cycle and *t* is the cycle length (in years) (83). Random numbers are used in conjunction with this calculation to determine in which cycle an individual patient dies. After death, the patient exits the model and the next patient runs through the model calculation.

While the Cox proportional hazards model used in this model was based on analyses published in 2001, Liou et al. (84) presented an updated analysis of the logistic regression that was originally published in 2001 along with the Cox proportional hazards model. The updated logistic regression used data from 1993 – 2010. The updated analysis concluded that while there were some slight changes to the coefficients, the factors predicting mortality in CF have remained stable. Liou et al. also concluded that the dramatic reduction in mortality observed among patients with CF over the past several decades is due to improvements in clinical outcomes, disease management and reduced disease progression and that the survivorship from patients with similar health profiles has not changed. This validation exercise suggests that the original Cox proportional hazards model from the published peer-reviewed paper is appropriate to use in our model.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D-3L questionnaire was administered at each study visit in the TRAFFIC and TRANSPORT clinical studies. To convert trial participants' EQ-5D assessments into EQ-5D utility index values, UK-specific valuation weights were applied to each of the subjects' response levels for each EQ-5D dimension.

In the TRAFFIC and TRANSPORT studies, many EQ-5D observations led to EQ-5D index values at the ceiling (a value of one), and the median EQ-5D index values across all measurements was one. Considering the impact CF has on patients' lifestyles and the burden of disease, these scores may be considered high. This is a common phenomenon in CF and the HRQoL data (EQ-5D) collected in the TRAFFIC and TRANSPORT trials may demonstrate that patients with CF have adapted to life with a chronic condition, and accordingly rate their HRQoL higher with less regard to the impact of the disease. This is consistent with other studies which have generally found that adults with CF had similar or better HRQoL than healthy controls (82) despite having a serious illness with almost constant symptoms and regular medical intervention. Abbott et al. suggests that in CF there may be "a phenomenon known as response shift: a re-evaluation of the meaning of life and subsequently adapting to changing conditions." It has been reported elsewhere that other patients with serious chronic diseases exhibit response shift or adaptation to their imperfect

health state (53, 85). When patients have high baseline health state utility values, it is difficult to detect a treatment effect as there is little room for improvement. As such, there were no statistically significant differences in the mean change from baseline in EQ-5D measures between the LUM-IVA treatment group and placebo in the TRAFFIC and TRANSPORT studies.

The following two tables summarize the EQ-5D utility index values derived from all participants in TRAFFIC and TRANSPORT irrespective of treatment assignment, stratified by study visit (Table 45) and by $ppFEV_1$ at the time of the assessment (Table 46). Using the observed data, the derived values for the EQ-5D index were generally high across all study visits, and across all levels of disease severity as measured by $ppFEV_1$.

Table 45: EQ-5D Index Values* by Study Visit

Study Visit	Sample size	Mean (SD)
Day 1	1104	0.91 (0.131)
Day 15	1089	0.912 (0.139)
Week 4	1095	0.914 (0.144)
Week 8	1093	0.913 (0.136)
Week 16	1084	0.912 (0.137)
Week 24	1065	0.914 (0.136)

Abbreviation: SD, standard deviation
* EQ-5D index values derived using UK-specific valuation weights

Table 46: EQ-5D Index Values† by $ppFEV_1$ Category

		$ppFEV_1$ Category				
Statistic	**All Patients**	**<40%**	**40% - <70%**	**70% - <90%**	**≥90%**	**p-value***
N	6,569	428	3,891	1,897	108	<0.001
Mean (SD)	0.912 (0.137)	0.878 (0.14)	0.906 (0.141)	0.933 (0.124)	0.951 (0.096)	-
Median (IQR)	1 (0.812-1)	0.883 (0.779-1)	1 (0.796-1)	1 (0.848-1)	1 (1-1)	-
Range	(-0.003-1)	(0.193-1)	(-0.003-1)	(0.055-1)	(0.62-1)	-

Abbreviations: SD, standard deviation; IQR, Interquartile range; $ppFEV_{1,}$ percent predicted forced expiratory volume in one second.
* p-value from Spearman rank test (for trend); $ppFEV_1$ was missing for 245 study visits where EQ-5D was collected
†EQ-5D index values derived using UK-specific valuation weights

5.4.2 Mapping

As EQ-5D was collected in the trials no utility mapping has been used.

5.4.3 Health-related quality-of-life studies

A systematic review was conducted to obtain all relevant health-related quality of life studies in cystic fibrosis.

The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review questions:

- "What is the utility of patients and carers with CF?"
- "What are the disutilities associated with patients and carers with CF?"

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 47, restricted from the year 2000 to May 2015. Searches were conducted using the following interfaces:

- Embase (which also covers Medline and Medline (R) In-Process)
- The Cochrane Library (which covers Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (covers EconLit with Full Text, Health Economic Evaluations Database)

Table 47: Databases searched and interfaces used in the utility systematic review

Database	Interface
Embase 2000 to 2015	Embase
Medline 2000 to 2015	Embase
Medline (R) In-Process 2000 to 2015	Embase
Cochrane Database of Systematic Reviews 2000 to 2015	The Cochrane Library
Database of Abstracts of Reviews of Effects 2000 to 2015	The Cochrane Library
Health Technology Assessment 2000 to 2015	The Cochrane Library
NHS Economic Evaluation Database 2000 to 2015	The Cochrane Library
EconLIT with Full Text 2000 to 2015	EBSCO host
Health Economic Evaluations Database 2000 to 2015	EBSCO host

The searches include terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) through the use of Boolean combination techniques. Searches were not restricted by study intervention or comparator to ensure studies reporting utilities in this population are identified. The EBSCO host interface was searched using terms for the population only to broaden the results. The searches were conducted on 26th May 2015, the search strategy is provided in the Appendix (separate document).

A grey literature search was performed to include any additional studies that have not been identified by the search strategy. This included the following websites:

- Cystic Fibrosis Foundation http://www.cff.org/
- American Lung Association http://www.lung.org/lung-disease/cystic-fibrosis/
- European Cystic Fibrosis Society (ECFS) https://www.ecfs.eu/
- CF Europe http://www.cf-europe.eu/
- CF Network http://cf.eqascheme.org/
- European Lung Foundation (ELF) http://www.europeanlung.org/en/lung-disease-and-information/lung-diseases/cystic-fibrosis
- Cystic Fibrosis Trust http://www.cysticfibrosis.org.uk/
- The British Library: http://www.bl.uk/
- National Institute for Health Research: http://www.hta.ac.uk/

- National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/Home
- National Centre for Pharmacoeconomics NCPE Ireland: http://www.ncpe.ie/submission-process/hta-guidelines/
- All Wales Medicines Strategy Group: http://www.wales.nhs.uk/sites3/home.cfm?orgid=371
- Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/en/home.2724.html
- Haute Autorité de Santé (HAS): http://www.has-sante.fr/portail/jcms/j_5/home
- Italian Medicines Agency (AIFA): http://www.agenziafarmaco.gov.it/en
- Agencia de Evaluación de Tecnologías Sanitarias (AETS): http://www.isciii.es/
- Canadian Agency for Drugs and Technologies in Health (CADTH): http://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): http://www.pbs.gov.au/info/industry/listing/participants/pbac
- Search Engine (Google): http://www.google.co.uk/

References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table 48.

Table 48: Eligibility criteria used in the utility systematic review

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	Diagnostics New born screening
Outcomes	• Utility scores in CF • Disutilities	Utility data reported before the year 2000
Study type	• Observational studies • QoL elicitation studies • QoL validation studies • Randomised controlled studies • Economic evaluations: • Cost-utility analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews‡ • Letters • Comment articles • Individual case study reports

‡ To be retained for cross checking purposes

The bibliographies of review papers were checked to identify studies that may have been missed in the electronic searches.

Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts were undertaken using the inclusion/exclusion criteria to identify papers to be included at this stage (also known as the first pass). The first pass was performed by two independent reviewers with discrepancies between included papers resolved by a third independent reviewer. Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria (also known as the second pass).

5.4.4 Search results

The PRISMA diagram shown in Figure 16 illustrates the numbers of studies included and excluded at each stage of the systematic review. Database searching identified 753 references from which duplicates were removed resulting in 707 references. Following title and abstract screening 647 references were excluded. Sixty references were included for full-text evaluation. No further studies were identified from the review of grey literature. A total of 18 references met the inclusion/exclusion criteria following full-text evaluation. Of these 18 references, all studies were deemed relevant to the review and key elements were extracted (See Appendix – separate document).

Figure 16: Quality of life – PRISMA diagram

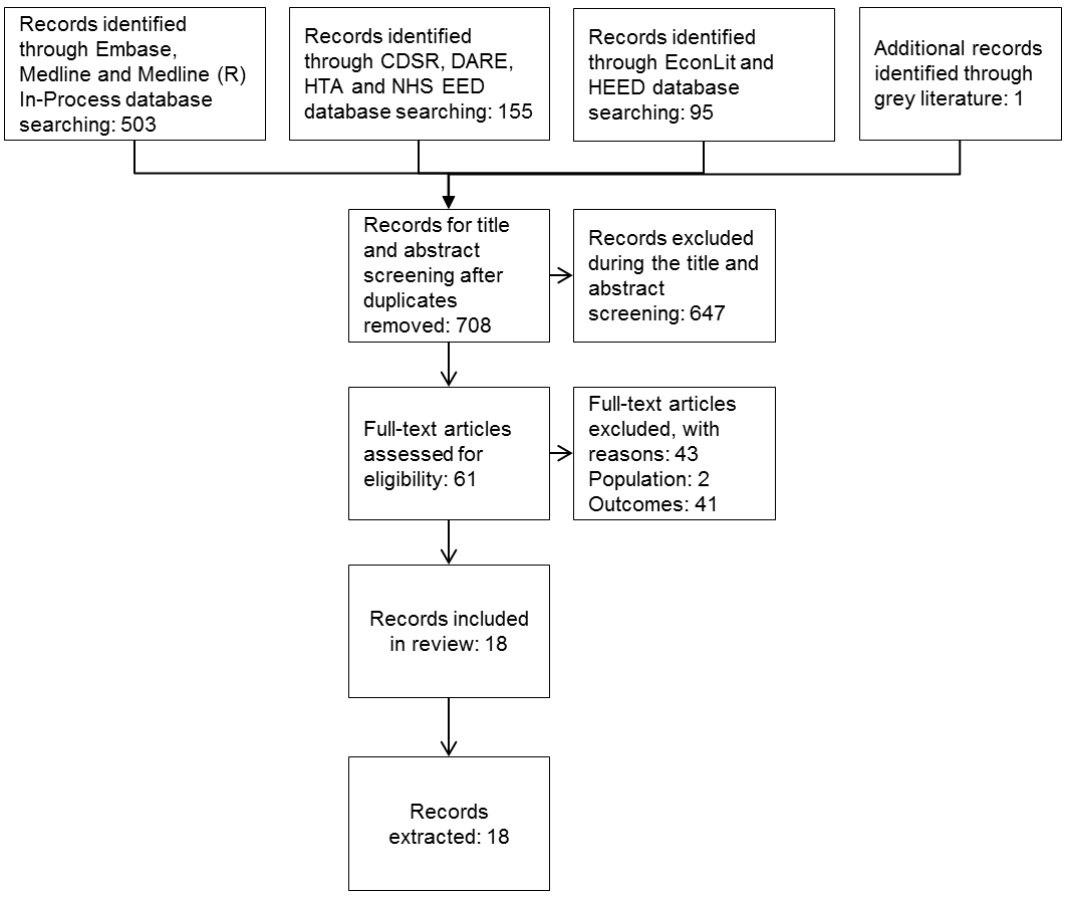


Table 49: Relevant Utility Search Results

Study	Population	Recruitment	Sample	Method of elicitation	Results
Johnson et al.(86)	Adults with CF receiving rhDNase	registered at the CF clinic at the University of Alberta Hospital	59 Patients	Patients received the SF-36 and EQ-5D questionnaires via the post with a follow-up survey one year later.	No change in EQ-5D over 1 year of treatment
Kotwicki et al.(87)	CF patients aged 5 - 12	Patients were recruited from the Paediatric Pulmonary/Cystic Fibrosis Centre at the University of Wisconsin and had been enrolled in the Newborn CF Screening Project.	45 patients were invited, 26 accepted	The QWB survey was administered by a clinic pharmacist to their parents with	A mean of 0.77. It was observed that lower quality of life was associated with increasing number of respiratory infections ($p<0.02$), increasing concurrent medical conditions ($p<0.001$) and increasing number of different medications per day ($p<0.05$).
Selvadurai et al. (88)	CF patients aged 8 to 16	Admitted to the Royal Alexandra Hospital for Children for the treatment of an infectious pulmonary exacerbation.	66 children that participated in the study	Aerobic training, resistance training and the control group.	The QWB scale was used to assess QoL by being administered on the day of admission and 1 month following hospital discharge. Aerobic training - 0.62 (0.09 change over the trial) Resistance training – 0.60 (0.02 change over the trial) Control – 0.62 (-0.01 change over the trial)
Suri et al.(57)	5-18 years	12 weeks in two UK hospitals (Great Ormond Street Hospital and Royal Brompton Hospital)	48 patients	Patients were randomised to one of 6 treatments, 8 patients were assigned to each treatment. Data were collected in a prospective, open, randomised crossover trial.	The mean QWB Scale recorded was 0.61 (SD = 0.12) ranging from 0.35-0.84.

Study	Population	Recruitment	Sample	Method of elicitation	Results
Yi et al.(89)	Adolescents with CF aged 12 - 18	Recruited from Cincinnati Children's Hospital Medical Centre in Cincinnati, Ohio, and The Children's Medical Centre in Dayton, Ohio.	65 patients	Cross sectional study	Quality of life questionnaires were administered to the patients in a single interview session. The mean scores for the following questionnaires were VAS - 0.76 TTO - 0.96 SG - 0.92 HUI2 – 0.83
Fitzgerald et al.(90)	patients who had CF with mild to moderate supportive lung disease	These patients were recruited through attendance at the CF outpatient clinics at the Children's Hospital at Westmead, Sydney, and the John Hunter Children's Hospital, Newcastle, in New South Wales, Australia.	52 patients	To determine if dornase alfa is more efficacious when administered 30 minutes before or 30 minutes after physiotherapy/positive expiratory pressure therapy in clinically stable children. The quality of well-being score was completed by each participant at each visit (every 2 weeks from week 0 to week 6).	The mean quality of well-being score was 0.76
Simpson et al.(91)	The setting considered was a hypothetical UK health region without an existing neonatal screening program for CF.	Utilities taken from existing literature	Utilities taken from existing literature	Utilities taken from existing literature	Symptoms ($ppFEV_1$ – 60%, range 40%–80%) – 0.75 Severe irreversible symptoms ($ppFEV_1$ – 30%, range 20–40%) – 0.68
Veenstra et al.(61)	patients with mitochondrial mutation A1555G	Utilities taken from existing literature	Utilities taken from existing literature	Utilities taken from existing literature	CF patient without hearing loss – 0.80 Patient with cochlear implant – 0.80 CF patient with mild hearing loss – 0.91

Study	Population	Recruitment	Sample	Method of elicitation	Results
Dewitt et al.(92)	CF patients aged 5 years and older with mild impairment in lung function ppFEV$_1$ of 75% or more	Trial enrolled in 61 sites in the United States and 1 site in Canada	352 participants	Patients completed the Health Utilities Index Mark 2/3 (HUI2/3) questionnaire every 12 weeks during the trial.	The HUI2/3 mean utility and median utility at baseline was 0.90 (SD 0.14) and 0.95 (interquartile range 0.88-1.00), respectively.
NICE TA266 (18)	People aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary colonisation.	As per the DPM-CF-301 trial	151 patients	Within the cost effectiveness model, an equation is used to calculate patient utilities. Baseline utility was taken to match the baseline HUI2 score of the total population in the trial.	Baseline utility – 0.899 Utility patient with improvement in respiratory symptoms – 0.918 Utility no improvement in respiratory symptoms – 0.877 Utility decrement for exacerbation - -0.23 Utility for patients with FEV$_1$ < 30 – 0.31
Simonova et al.(93)	Children with CF in Russia and commonwealth of independent states countries	Not reported	70 children aged 5 to 16 years	Questionnaires completed either by themselves (those aged over 12 years) or via their parents (those aged below 12 years).	HUI mark 2 5 years old – 0.85 6 years old – 0.80 12 years old – 0.85 16 years old – 0.95 HUI mark 3 6 years old – 0.75 12 years old – 0.75 16 years old – 0.77
Bradley et al. (51)	UK adult CF patients with chronic Pseudomonas aeruginosa infections	Five UK centres contributed data	94 patients attending two visits	At both visits, patients were required to answer the following two questionnaires: CFQ-R and EQ-5D and a clinical form. In addition, forced expiratory volume in 1	EQ-5D value No pulmonary exacerbation – 0.85 Mild pulmonary exacerbation – 0.79 Severe pulmonary exacerbation – 0.60

Study	Population	Recruitment	Sample	Method of elicitation	Results
				second was measured.	
Tappenden et al. (63)	People aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary colonisation.	Taken from Bradley et al., presented as a poster at the European respiratory society conference in 2010	Taken from Bradley et al., presented as a poster at the European respiratory society conference in 2010	Taken from Bradley et al., presented as a poster at the European respiratory society conference in 2010	Mild ($ppFEV_1$ 70% – 90%) – 0.864 Moderate ($ppFEV_1$ 40% – 70%) – 0.81 Severe ($ppFEV_1$ < 40%) – 0.641 Disutility major exacerbation – 0.17 Disutility minor exacerbation – 0.02
Solem et al.(52)	Patients in the trial were aged 12 years and above and 146 pulmonary exacerbations were experienced by 72 patients with G551D-CFTR mutation	As per ivacaftor phase 3 trials	72 patients	During the trial EQ-5D was measured directly from patients at the following time points: baseline, 15 days, 8 weeks and every 8 weeks thereafter.	pulmonary exacerbations requiring hospitalisation, score within 1-8 weeks before pulmonary exacerbation start – 0.91 pulmonary exacerbations requiring hospitalisation, score within 1 week of pulmonary exacerbation start – 0.76 pulmonary exacerbations not requiring hospitalisation, score within 1-8 weeks before pulmonary exacerbation start – 0.89 pulmonary exacerbations not requiring hospitalisation, score within 1 week of pulmonary exacerbation start – 0.90
Solem et al.(94)	Solem et al. undertook a post-hoc analysis to assess the relationship between the EQ-5D index and VAS with FEV1 severity in CF patients in the STRIVE clinical trial.	G551D-CFTR mutation aged at least 12	121 patients participated resulting in 1,214 observations	During the trial EQ-5D and FEV1 were measured directly from patients at the following time points: baseline, 15 days, 8 weeks and every 8 weeks thereafter. Utilities were derived using the US preference-based algorithm	No lung dysfunction (FEV1 ≥ 90%) – 0.967 Mild (FEV1 70 – 90%) – 0.949 Moderate (FEV1 40 – 70%) – 0.918 Severe (FEV1 < 40%) – 0.881

Study	Population	Recruitment	Sample	Method of elicitation	Results
Whiting et al. (64)	For the treatment of CF patients aged >6 with at least G551D	As per a paper by Gee et al.	As per a paper by Gee et al.	223 Patients	Mild ppFEV$_1$ (>70%) – 0.803 Moderate ppFEV$_1$ (41-70%) – 0.749 Severe ppFEV$_1$ (<41%) - 0.688
Acaster et al.(95)	Survey of adults (18 years or above) with CF in the UK	Data were obtained from a cross-sectional survey of adults (18 years or above) with CF in the UK following recruitment by the Cystic Fibrosis Trust. The survey was conducted from January to March 2012.	401 Patients	The survey consisted of three questionnaires: CFQ-R, EQ-5D, and a demographic/clinical background questionnaire. In addition, participants were required to rate their CF severity as either mild, moderate or severe.	Mild ppFEV$_1$ (>70%) - 0.741 Moderate ppFEV$_1$ (41-70%) – 0.695 Severe ppFEV$_1$ (<41%) - 0.552 Total sample – 0.67
Chevreul et al.(96)	75 adults and 91 children	Patients were recruited for a retrospective cross-sectional study from the CF reference centre of Nantes–Roscoff, the French CF Society and the patient association Vaincre la Mucoviscidose	166 patients	Of the children, 10 completed the EQ-5D-5L questionnaire themselves while parents responded on behalf of the others. Forty carers also completed the questionnaire (6 adults and 34 children). Since a value set does not currently exist to obtain utilities from the EQ-5D-5L questionnaire, a mapping was undertaken from a French EQ-5D-3L value set instead.	All patients – 0.730 Adult patients – 0.667 Child patients – 0.783 Disease duration: 0–9 years – 0.783 Disease duration: 10–19 years – 0.712 Disease duration: 20–29 years – 0.702 Disease duration: after 30 years – 0.589

Abbreviations: CF, cystic fibrosis; QWB, quality of well being; QoL, quality of life; VAS, visual analogue scale; TTO, time trade off; SG, standard gamble; HUI, health utility index; FEV, forced expiratory volume; SD, standard deviation; CFTR, Cystic fibrosis transmembrane conductance regulator.

5.4.5 Adverse reactions

The systematic literature search identified several studies that considered the impact on HRQoL from pulmonary exacerbations (18, 51, 52, 63). The impact of other adverse reactions in CF patients were not identified.

Tappenden et al., (2014) (97) considered disutilities associated with PEs, the disutility of a major PE and minor PE being 0.17 and 0.02, respectively. These disutilities were lower than the disutility considered in NICE Technology Appraisal 266 (TA266), which used a disutility of 0.23. Solem et al., (2014) (94) found that, after taking a patient's $ppFEV_1$ into account, experiencing a pulmonary exacerbation that required hospitalisation was associated with a utility reduction of 0.0695; pulmonary exacerbations that did not require hospitalisation were associated with a negligible difference in utility (+0.0007). It should be noted that Solem et al. uses an equation to determine utility that also takes the patient's $ppFEV_1$ into account, and therefore cannot be compared with the utility decrements reported elsewhere as the latter likely include both the impact of the pulmonary exacerbation itself and the concomitant decrease in $ppFEV_1$.

Table 50: Utilities by pulmonary exacerbation status

Reference	Pulmonary exacerbation status (mean ± SD)
Solem et al., (2014) (52)	EQ-5D index values derived from clinical trial data Pulmonary exacerbations requiring hospitalisation, score within 1-8 weeks before pulmonary exacerbation start 0.91 (±0.13) Pulmonary exacerbations requiring hospitalisation, score within 1 week of pulmonary exacerbation start 0.76 (±0.33) Pulmonary exacerbations not requiring hospitalisation, score within 1-8 weeks before pulmonary exacerbation start 0.89 (±0.16) Pulmonary exacerbations not requiring hospitalisation, score within 1 week of pulmonary exacerbation start 0.90 (±0.13).
	Regression Utility equation includes a coefficient of -0.0256 for experiencing a pulmonary exacerbation, after accounting for $ppFEV_1$ When stratified by not requiring hospitalisation versus requiring hospitalisation the coefficients were +0.0007 and -0.0695 respectively
NICE TA266 (2012) (18)	A utility decrement of 0.23
Tappenden et al., (2014) (63) (original source Bradley et al.)	Major pulmonary exacerbation 0.174 decrement Minor pulmonary exacerbation 0.015 decrement

Abbreviations: SD, standard deviation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

5.4.6 Health-related quality-of-life data used in cost-effectiveness analysis

5.4.6.1 Health-related quality-of-life related to $ppFEV_1$ and experience of pulmonary exacerbation

Pulmonary exacerbations, particularly those that are severe, have been reported to impact HRQoL (49, 51, 89, 98). Lung function as measured by $ppFEV_1$ has been shown to be

related to patients' HRQoL in cross-sectional and longitudinal studies (49, 99). In order to understand these associations in CF patients for whom LUM-IVA is indicated (*F508del* homozygous 12+ years of age), the EQ-5D, $ppFEV_1$ and pulmonary exacerbation data collected in the TRAFFIC and TRANSPORT studies were analysed.

The results of this analysis were used to derive an equation that includes ppFEV1 and the occurrence of pulmonary exacerbation as predictors of the EQ-5D index. Data collected from patients in the TRAFFIC and TRANSPORT trials were pooled across studies, study visits and treatments. Patients contributed 6,580 EQ-5D measurements of which 6,569 were analysable. Of these 6,569 assessments, 245 (4%) were missing a concurrent $ppFEV_1$ assessment. For the 245 visits that had missing $ppFEV_1$, a last observation carried forward approach was used for the purposes of the multivariate analyses described below.

UK-specific valuation weights were applied to each of the subjects' response levels for each EQ-5D dimension to derive EQ-5D index values.

A multivariate mixed-model repeated measures regression analysis was conducted on the trial data to model the relationship between experiencing a pulmonary exacerbation, $ppFEV_1$ and EQ-5D index. While a series of model specifications were explored, for the purpose of economic modelling the selected statistical model included the EQ-5D index as the dependent variable and $ppFEV_1$ (linear and quadratic terms) and whether the patient was experiencing a pulmonary exacerbation as covariates. The variables $ppFEV_1$ and experiencing a pulmonary exacerbation were identified as statistically significant predictors of the EQ-5D index; squared $ppFEV_1$ was marginally significant.

The following relationship was derived between $ppFEV_1$ levels, occurrence of pulmonary exacerbation and EQ-5D scores:

$$U = \beta_0 + \beta_1 \, x \, ppFEV_1 + \beta_2 \, x \, ppFEV_1{}^2 + \beta_3 \, x \, experiencing \, a \, pulmonary \, exacerbation$$

Where U is the EQ-5D utility score, experiencing a pulmonary exacerbation is a binary variable that equals 1 if the patient is experiencing a pulmonary exacerbation and equals 0 if the patient is not experiencing a pulmonary exacerbation and β_0, β_1, β_2 and β_3 are model coefficients.

Table 51 shows the parameter estimates from the utility equation and their standard errors.

Table 51: Parameter Estimates for the Utility Equation

Parameter	Coefficient	Standard Error	p-value
β_0	[redacted]	[redacted]	[redacted]
β_1	[redacted]	[redacted]	[redacted]
β_2	[redacted]	[redacted]	[redacted]
β_3	[redacted]	[redacted]	[redacted]

The economic model applies the utility equation with the variable for experiencing a pulmonary exacerbation equal to 1 for the proportion of any cycle during which the patient is experiencing a pulmonary exacerbation, and a value equal to 0 for the remainder of the cycle. Each pulmonary exacerbation event was assumed to last for 21.7 days, based on data from the TRAFFIC and TRANSPORT trials.

One limitation of the utility equation is the ceiling effect observed in the EQ-5D data used to derive it, leaving little room to demonstrate potential health gains of new treatments. The EQ-5D is not a disease-specific preference measure; ceiling effects have been reported in other analyses (100). Furthermore, in the case of CF and other lifelong and chronic conditions, observed ceiling effects may also be the result of response shift, as discussed in section 5.4.1. Another limitation is that due to study design, the EQ-5D questionnaire was not administered at the time of pulmonary exacerbation start and therefore the impact of a pulmonary exacerbation may not have been fully captured. Nonetheless, EQ-5D data from the TRAFFIC and TRANSPORT studies remains the best available data source for health-state utilities for patients with CF age 12 years and older who are homozygous for the *F508del* mutation. Other utility sets are tested in sensitivity analyses.

Utilities for a simulated patient in the economic model vary as a function of $ppFEV_1$ and whether the patient is experiencing a pulmonary exacerbation. Thus, for a given patient, utilities vary over time insofar as these clinical parameters vary over time.

No utility decrements were assigned for adverse events other than pulmonary exacerbations.

5.4.6.2 Health-related quality-of-life related to lung transplant

Utility post-lung transplantation is taken from Whiting et. al. (64) who calculated weighted EQ-5D post-lung transplant utility measurements for lung-transplant recipients regardless of previous treatment and clinical status prior to transplantation based on a cross-sectional survey by Anyanwu et. al (101). Anyanwu et. al measured HRQoL of 255 patients post single or bilateral lung or heart-lung transplant from four of seven UK lung transplant centres. Whiting et. al. weighted the measurements from patients who received bilateral lung transplant in the study conducted by Anyanwu et. al. because these patients are the ones who were most likely to have CF (64). The number of months since the transplantation was used as weights for mean utility values measured at different time windows after bilateral lung transplantation. The resulting EQ-5D utility value is 0.81, as shown in Table 52.

Table 52: Derivation of Post-transplant Utility

Time Post Transplant, Months	Mean Utility	Number of Months	Month Weighted Utility	Weighted Average Post-Transplant Utility for use in model
0-6	0.75	6	0.08	0.81
7-18	0.83	12	0.17	
19-36	0.81	18	0.24	
>36*	0.82	24	0.33	

Source: Whiting et. al. (64)
*Whiting et. al. assumed that >36 category contributes 24 months.

5.5 Cost and healthcare resource use identification, measurement and valuation

A systematic review was conducted to obtain all relevant cystic fibrosis (CF) unit costs and resource use studies in accordance with NICE requirements

The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review question:

- "What are the costs and resource use associated with the management of CF?"

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 53 restricted from the year 2000 to May 2015. Searches were conducted using the following interfaces:

- Embase (which also covers Medline and Medline (R) In-Process)
- The Cochrane Library (which covers Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (covers EconLit with Full Text, Health Economic Evaluations Database)

Table 53: Databases searched and interfaces used in the cost and resource use systematic review

Database	Interface
Embase 2000 to 2015	Embase
Medline 2000 to 2015	Embase
Medline (R) In-Process 2000 to 2015	Embase
Cochrane Database of Systematic Reviews 2000 to 2015	The Cochrane Library
Database of Abstracts of Reviews of Effects 2000 to 2015	The Cochrane Library
Health Technology Assessment 2000 to 2015	The Cochrane Library
NHS Economic Evaluation Database 2000 to 2015	The Cochrane Library
EconLIT with Full Text 2000 to 2015	EBSCO host
Health Economic Evaluations Database 2000 to 2015	EBSCO host

The Embase interface was searched using terms for the population and an economic studies filter adapted from the Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network, 2014). Similar economic studies filters have previously been used in numerous NICE Health Technology Assessment (HTA) submissions and were deemed appropriate by the evidence review groups responsible for the technology. In the absence of reported resource use search filters, a resource use filter was constructed using Emtree terms in the Embase.com website. Finally, a filter for the UK was constructed and applied.

Searches were not restricted by study intervention or comparator in order to identify studies reporting cost and resource use in CF regardless of the intervention studied. The Cochrane Library interface was searched using terms for the population, adapted economic studies and resource use filters, and the EBSCO host interface was searched using terms for the population only to broaden the results.

The searches include terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) through the use of Boolean combination techniques. A grey literature search was performed to include additional studies that have not been identified by the search strategies.

The searches were conducted on the 18th May 2015, the search strategy is provided in the Appendix (separate document).

References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table 54.

Table 54: **Eligibility criteria used in the cost and resource use systematic review**

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	Diagnostics New born screening
Outcomes	• Unit or episode costs (direct and indirect) • Resource use (direct and indirect) • End of life costs • Health state costs	Non-UK costs and resource use Cost and resource use reported before the year 2000
Study type	• Costing analysis • Budget impact analysis • Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews‡ • Letters • Comment articles • Individual case study reports

‡ To be retained for cross checking purposes

A grey literature search was performed to include any additional studies that have not been identified by the search strategy. This included the following websites:

- Cystic Fibrosis Foundation http://www.cff.org/
- American Lung Association http://www.lung.org/lung-disease/cystic-fibrosis/
- European Cystic Fibrosis Society (ECFS) https://www.ecfs.eu/
- CF Europe http://www.cf-europe.eu/
- CF Network http://cf.eqascheme.org/
- European Lung Foundation (ELF) http://www.europeanlung.org/en/lung-disease-and-information/lung-diseases/cystic-fibrosis
- Cystic Fibrosis Trust http://www.cysticfibrosis.org.uk/
- The British Library: http://www.bl.uk/
- National Institute for Health Research: http://www.hta.ac.uk/

- National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/Home
- National Centre for Pharmacoeconomics NCPE Ireland: http://www.ncpe.ie/submission-process/hta-guidelines/
- All Wales Medicines Strategy Group: http://www.wales.nhs.uk/sites3/home.cfm?orgid=371
- Pharmaceutical Benefits Advisory Committee (PBAC): http://www.pbs.gov.au/info/industry/listing/participants/pbac
- Search Engine (Google): http://www.google.co.uk/

The bibliographies of review papers were checked to identify studies that may have been missed in the electronic searches. Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts were undertaken using the inclusion/exclusion criteria to identify papers to be included at this stage (also known as the first pass). The first pass was performed by two independent reviewers with discrepancies between included papers resolved by a third independent reviewer. Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria (also known as the second pass). Data was extracted from eligible publications into a pre-defined spreadsheet (which contained the structure pre-defined by NICE) by the reviewer.

5.5.1 Search Results

The PRISMA diagram shown in Figure 17 illustrates the numbers of studies included and excluded at each stage of the systematic review. Database searching identified 849 references from which duplicates were removed resulting in 776 references. Following title and abstract screening 717 references were excluded. 59 references were included for full-text evaluation. No further studies were identified from the review of grey literature. A total of 24 references met the inclusion/exclusion criteria following full-text evaluation. Of these 24 references, all studies were deemed relevant to the review and key elements were extracted.

Figure 17: Cost and resource use – PRISMA diagram

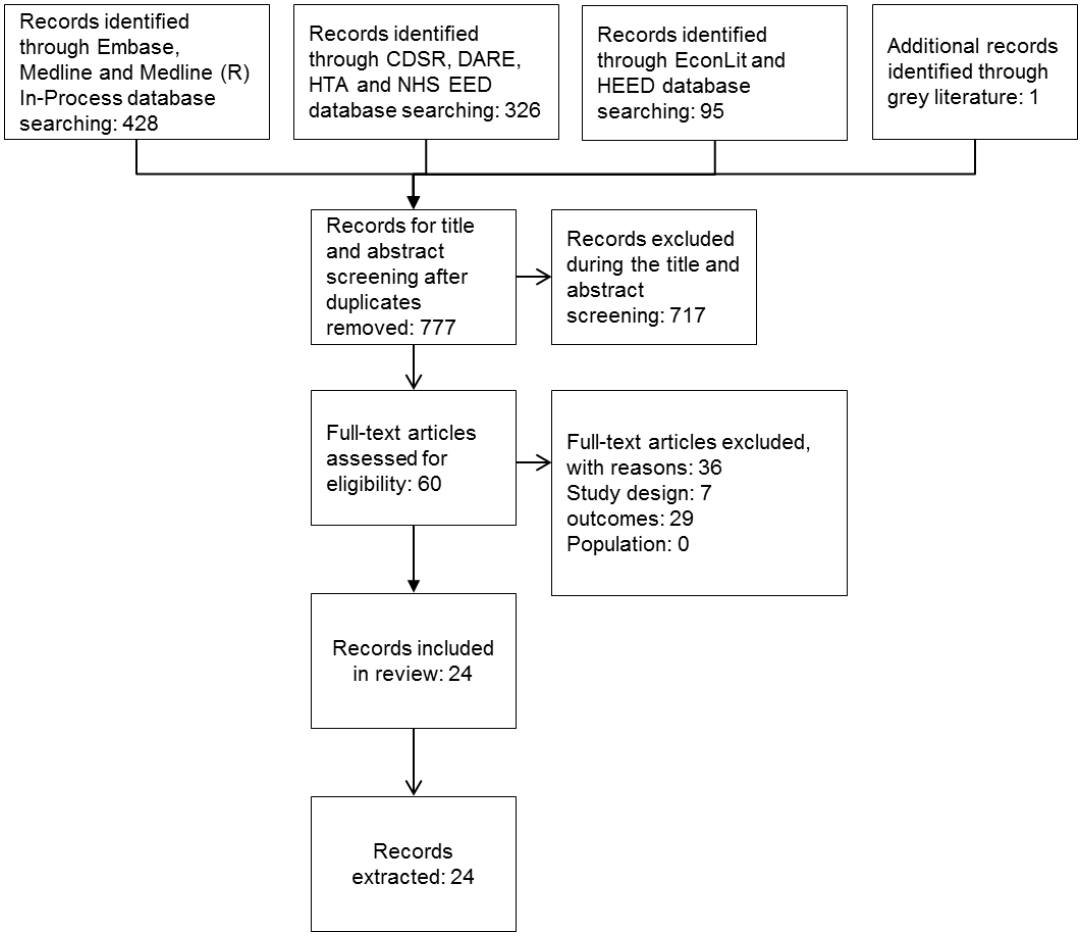


Table 55: Relevant cost and resource use studies

Study	Country	Patient population	Cost valuations	Results
Suri et al.(57)	UK	Data were collected in a prospective, open, randomised crossover trial. Patients received one of the three treatments for 12-weeks.	Hospital contacts Radiological investigations Blood tests Drug use Use of community services	Daily rhDNase Intervention £1,755 Non intervention drugs £2,271 Grand total £5694 Daily HS Intervention £37 Non intervention drugs £2364 Grand total £4285
Grieve et al. (102)	UK	a trial conducted in children in UK hospitals. The trial enrolled 47 patients.	hospital contacts (inpatient, outpatient, and day case) radiological investigations blood tests drugs the use of community services	Daily rhDNase - 4,285 Hypertonic saline - 5,694 Alternate day rhDNase - 5,230
Iles et al. (58)	UK	An observational study was undertaken capturing both clinical and resource use data. Data was collected 12-months prior to Tobramycin nebuliser solution treatment and 12-months after. A total of eight centres contributing data for 71 patients were included in the study	Days in Hospital Length of IVs Outpatient visits IV courses Ward admissions Intensive care unit admissions	Total cost Before - £22,102 After - £28,394 Intensive care cost Before – £1182 After – £1306 Ward cost Before – £9715 After - £7,246
Elliott et al. and Thornton et al. (60, 103)	UK	The study observed patients over a 1 year time horizon, patients who expected to have more than 60% of total intravenous antibiotic courses at home were classified as being on the home treatment arm.	Antibiotics Home kits Laboratory tests	Total Population- £18,513 Home - £13,528 Hospital - £22,609

Study	Country	Patient population	Cost valuations	Results
		Similarly, patients who expected to have more than 60% of total intravenous antibiotic courses at hospital were classified as being on the hospital treatment arm. The study observed 454 courses of treatment	Clinic visits Days in the hospital Home visits	Both - £19,927
Kerem et al. (104)	UK	Kerem et al. details the requirements of a specialist cystic fibrosis centre, and as part of these requirements adult specialist centres were considered separately to paediatric centres	Consultant 1 Consultant 2 Staff grade Registrar Specialist nurse Physiotherapist Dietitian Social worker Psychologist Secretary Pharmacist	Adult specialist centre Consultant 1 – 0.5 Consultant 2 – 0.25 Staff grade – 0.6 Registrar – 0.5 Specialist nurse - 1.25 Physiotherapist – 1.0 Dietitian - 0.4 Social worker – 0.4 Psychologist – 0.4 Secretary – 1.0 Pharmacist - 0.3
Farrell et al.(105)	Ireland	Farrell et al. undertook a study evaluating the costs of conducting sweat testing in Ireland during 2001 and 2003. All clinical centres undertaking sweat tests were surveyed.	Wescor electrolyte test Wescor conductivity test Filter paper chloride method	Costs were presented for three differing methods of testing: Wescor electrolyte test: : €71.50 Wescor conductivity test: €69.50 Filter paper chloride method: €44.25
Smalarz et al.(106)	UK	Smalarz et al. sought to determine the cost of pseudomonas aeruginosa infections from a UK societal perspective.	health care utilisation other (non-medical) components of care productivity for CF patients	Direct medical £12,945 Direct nonmedical £505 Indirect £8,735 Total £22,186
Ashish et al.(107)	UK	Ashish et al. evaluated the cost associated with pseudomonas aeruginosa strains in the UK. A comparison between the most common UK transmissible pseudomonas aeruginosa strain (Liverpool Epidemic Strain) and unique pseudomonas aeruginosa strains was undertaken to understand differences in costs over a 5-year period.	Inpatient care Outpatient attendances Home and hospital antibiotic therapy Prescription costs	Liverpool Epidemic Strain Inpatient care £13970 Outpatient attendances £2635 Home and hospital antibiotic therapy £806 Prescription costs £847

Study	Country	Patient population	Cost valuations	Results
				Pseudomonas Aeruginosa Strains Inpatient care £4553 Outpatient attendances £1627 Home and hospital antibiotic therapy £181 Prescription costs £732
Bradley et al.(51)	UK	A retrospective chart review was undertaken. Five UK hospitals contributed data, with 12-months of records included. Mean per patient per year event rates were estimated as were proportions of patients requiring specific types of care.	The mean rate of hospital exacerbations The mean rate of home treated exacerbations Mean length of hospital days per exacerbation	The mean rate of hospital exacerbations 1.5 per patient per year The mean rate of home treated exacerbations 2.2 per patient per year Mean length of hospital days per exacerbation 9.2
Lambrelli et al.(108)	UK	A retrospective medical chart review was conducted capturing patient and clinical characteristics, health care resource and drug usage data for patients (≥6 years old) with a diagnosis of CF caused by genotypes G551D or *F508del* homozygous. A total of eight centres contributing data for 200 (50% female) patients were included in the study. N=63 (32%) of participants had *G551D* genotype.	Mean number of visits Mean number of emergency visits Mean number of hospitalisations	Patients requiring >1 clinical visit – 99.5% Mean number of visits – 15.2 per patient Patients requiring an emergency visit – 23% Mean number of emergency visits – 2.4 per patient Patients having a hospitalisation - 71% Mean number of hospitalisations3.5 per patient Mean number of days in hospital - 48
Ledger et al. 2012 (109)and Ledger et al. 2012 (110)	UK	Sixteen children with moderate-to-severe CF who needed more than 40 IV days in the previous year participated in the study. Patients attended 1-2 weekly personal training and physiotherapy sessions as well as nutritional education sessions.	Hospital IV days Home IV days	20% reduction in hospital IV days (488 vs. 608 in previous year) 40% reduction in home IV days (203 vs. 339 in previous year) (p=0.05) Trend of improvement in outcomes
Urquhart et al.(111)	UK	The study was conducted in children with cystic fibrosis at least 10 years old. Patients had to have had at least 4 or more IV antibiotic courses in the year prior to the trial. Patients were also required to have at least an $ppFEV_1$ of 30%. In total 13 patients were recruited in the study.	Hospital and home IV days Total IV cost	Hospital IV days 318 before compared to 224 after. Home IV days 406 before compared to 378 after Total cost of IV £276,009 before compared

Study	Country	Patient population	Cost valuations	Results
				to £209,625
NICE TA266 (18)	UK	NICE submission TA266 considered patients people aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary colonisation..	The economic model considered treatment costs, pulmonary exacerbation costs, lung transplant costs and medical resource costs.	Bronchitol No PDPE in trial period - 4,391 PDPE in trial period - 12,852 Pulmonary exacerbation –10,925 Control No PDPE in trial period - 4,664 PDPE in trial period - 10,354 Pulmonary exacerbation - 10,227
Toward et al.(112)	UK	The aim of this study was to quantify the economic impact of pulmonary exacerbations. This study was conducted alongside clinical trials, DPM-CF-301 and DPM-CF-302. These clinical trials included centres across the globe, the DPM-CF-301 trial had a centre in the UK.	Cost of experiencing no pulmonary exacerbations, 1 pulmonary exacerbation and > 1 pulmonary exacerbation	No Pulmonary exacerbations £2,587 1 Pulmonary exacerbation £9,318 >1 Pulmonary exacerbations £10,385
Wyatt et al.(113)	UK	Wyatt et al. conducted a retrospective chart review to look at the resource implications of specific cystic fibrosis genotypes. The chart review included 200 cystic fibrosis patients age 6 or older. Patients were also required to have either the G551D/other or F508/F508 mutation.	Routine Visits Number of Hospitalisations Hospital IV days Home IV days	G551D/other Routine Visits - 14 Number of Hospitalisations – 3.4 Hospital IV days - 35 Home IV days - 45 DF508/DF508 Routine Visits – 15.7 Number of Hospitalisations – 3.5 Hospital IV days - 39 Home IV days - 33
Barry et al.(114)	UK and Ireland	Barry et al. assessed the outcomes for patients treated with Ivacaftor in the UK and Ireland. This included analysis of all centres enrolled in the UK and Ireland compassionate ivacaftor use program, with optional enrolment in the study. Patient outcomes were retrospectively evaluated pre	Median inpatient antibiotic days per year Total IV antibiotic days per year	Pre-ivacaftor Median inpatient antibiotic days per year - 23 Total IV antibiotic days per year - 74

Study	Country	Patient population	Cost valuations	Results
		introduction of treatment (12-months) and for between 3 to 9 months following initiation of Ivacaftor. A matched CF control population was evaluated to allow comparison against non-Ivacaftor treated patients. Twenty one Ivacaftor subjects were enrolled, with 35 control subjects enrolled.		Post-Ivacaftor Median inpatient antibiotic days per year - 0 Total IV antibiotic days per year - 38
Tappenden et al.(63)	UK	Tappenden et al. published a review of a cost effectiveness model that was submitted to NICE as well as a de novo economic analysis.	Cost minor exacerbation Cost major exacerbation Mean cost exacerbation	Cost minor exacerbation £428 Cost major exacerbation £1500 Mean cost exacerbation £1135
Ledger et al.(115)	UK	Ledger et al. build on the work in their two previously published papers. This publication is the full write up of the two previous publications, which were both published as abstracts.	Hospital IV days Home IV days	Total pre-intervention Hospital IV days - 619 Home IV days – 304 Cost - £963,904 Total post-intervention Hospital IV days - 478 Home IV days – 243 Cost - £850,334
Pocket et al.(116)	UK	Pocket et al. conducted a comparison of the length of stay and cost between healthy and vulnerable patients. Within the study vulnerable patients were defined as children with a primary diagnosis of rotavirus gastroenteritis or respiratory syncytial virus who also had cystic fibrosis, insulin dependent diabetes, cancer or epilepsy.	Average length of stay Average cost	The mean age of patients was 0.2 years old with an average length of stay of 11.1 days and average cost of £4,095, compared to length of stay of 1.9 days and an average cost of £595 for healthy patients. In the sample of patients there were 34 patients with cystic fibrosis.
Rowan et al.(117)	UK	Rowan et al. aimed to consider the financial implications of antibiotic allergy (beta-lactam allergy) in cystic fibrosis patients. The financial implications consisted of the impact of desensitisation, additional hospital stay and the use of more expensive alternative antibiotics. To quantify the financial implications the medical records of 375 patients were reviewed.	Mean drug cost Mean total cost for a course of treatment	Allergic Mean drug cost £924.10 Mean total cost for a course of treatment £4,264 Non-allergic Mean drug cost £517.36

Study	Country	Patient population	Cost valuations	Results
				Mean total cost for a course of treatment £3,442
Whiting et al.(64)	UK	Whiting et al. published a review of the ivacaftor submission reviewed in NIHR HTA journal, and the results of changes made by the authors.	Whiting et al. incorporated standard care costs which hadn't been included by the manufacturer. Standard care costs were included based on a banding system that is used in the UK. The costs cover most treatment costs directly related to cystic fibrosis during a financial year. However the costs do not include the use of expensive inhaled/nebulised drugs, totally implantable venous access devices and primary care costs.	Banding 1 - £5210 Banding 1a - £7707 Banding 2 - £7707 Banding 2a - £12,457 Banding 3 - £19,067 Banding 4 - £34,388 Banding 5 - £41,458
Jackson et al.(118)	Ireland	Jackson et al. conducted a review of Irish CF registry data to understand the health service utilization of Irish CF patients. A cross sectional population analysis based on data abstracted from annual registry records was undertaken.	The analysis considered hospitalisations, respiratory medications and culture samples. The changes over a five year time horizon are reported	2008 Annual frequency of hospitalisations - 0.65 An increase was observed in the use of beta agonists - 47.7% rhDNase - 32.3% H2 receptor antagonists/proton pump inhibitors - 28.5% nebulised hypertonic saline - 3.1% The per-person average of pulmonary exacerbations requiring IV antibiotics - 0.9 2012 Annual frequency of hospitalisations - 1.02 An increase was observed in the use of beta agonists - 65.8% rhDNase - 45.7% H2 receptor antagonists/proton pump inhibitors - 41.2% nebulised hypertonic saline - 44.9% The per-person average of pulmonary exacerbations requiring IV antibiotics - 1.3

Abbreviations: rhDNase, Recombinant human deoxyribonuclease; HS, hypertonic saline; IV, Intravenous; PDPE, protocol defined pulmonary exacerbation; HTA, health technology appraisal; NIHR, National Institute for Health Research.

5.5.2 Intervention and comparators' costs and resource use

The drug price of LUM-IVA is £8,000 per 28-day supply. The annual cost of LUM-IVA (£104,000) was calculated based on a twice-daily dosing schedule assuming a 365-day year. The expected annual cost of the generic medicine is 11% of the net price, this is applied for LUM-IVA treatment after 12 years, when the generic treatments are expected to enter the market. This assumption of future generic pricing has been used in prior submissions and is consistent with the published evaluation of Kalydeco, a CFTR modulator approved to treat patients with class III (specified gating mutations), in England (64).

A rate of discontinuation of 6.8% for LUM-IVA patients during the 24 week trial period is used to match the observed rate from the pooled TRAFFIC and TRANSPORT trial data. For patients who discontinue during the first 24 weeks, treatment efficacy is assumed to be the same for patients who remain on treatment by week 24. No efficacy loss is applied for the initial 24 week period. Beyond 24 weeks, after a patient discontinues LUM-IVA treatment, $ppFEV_1$ decline is assumed to be the same as for patients on SoC. Treatment impact on pulmonary exacerbations is stopped immediately after treatment discontinuation.

Trial-based adherence of 90% was used to estimate the annual cost of the LUM-IVA treated patients over the course of the lifetime projection. An estimate of 96.5% adherence was derived from the 24-week clinical data, intuitively it is an unrealistically high estimate of life-long adherence and most likely reflects the well-accepted "Hawthorne Effect" of unnatural or unsustainable patient behaviours that are observed in clinical trials due to the interventional nature of the trial and reinforced by frequent visits, which were characteristic of the LUM-IVA studies (119, 120).

5.5.3 Health-state costs and resource use

Costs are stratified by $ppFEV_1$ strata in the model, based on a study that demonstrates higher disease management costs for patients with lower lung function. A chart review study was conducted in the UK specifically to collect resource use data in the CF population (121). Data were retrospectively collected from 200 CF patients carrying the *G551D* mutation or homozygous for the *F508del* mutation from eight specialist CF centres in the UK. Full 24-month data were extracted for each patient, including patient characteristics, pharmacotherapy and healthcare resource use. Costs were estimated by multiplying the mean resource use with respective unit costs, reported in 2010 GBP. Direct medical costs stratified by $ppFEV_1$ and inflated to 2014 GBP (122) are shown in Table 56.

Patients treated with LUM-IVA are assumed to incur lower hospital costs due to the observed reductions in hospitalised pulmonary exacerbations. Thus, although it is assumed that routine care recommendations for CF remain unchanged for LUM-IVA treated patients, cost-offsets associated with LUM-IVA are incurred both indirectly via improvements in lung function and directly via a reduction in hospitalizations associated with pulmonary exacerbations. This assumption is supported by a clinical advisory board, where expert clinicians agreed that the significant reduction in pulmonary exacerbation risk associated with LUM-IVA treatment may impact the total disease management cost within $ppFEV_1$ strata. A reduction in hospitalisation costs of 61% for patients on LUM-IVA +

SoC is assumed for the base case. The reduction is estimated based on the rate ratio of 0.39 for pulmonary exacerbation requiring hospitalisation for LUM-IVA + SoC versus SoC in TRAFFIC and TRANSPORT, assuming that the majority of hospitalisations for CF patients are due to pulmonary exacerbation.

Disease management costs are accrued for the patients over a lifetime until death or lung transplantation occurs.

Table 56: Disease management direct medical costs (inflated to 2014 GBP)

$ppFEV_1$	Categories	SoC	LUM-IVA + SoC†
$ppFEV_1$ > 70%*	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ 40-69%	Total cost	[redacted]	[redacted]
	Hospitalization cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ < 40%	Total cost	[redacted]	[redacted]
	Hospitalization cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]

Abbreviations: SoC=standard of care; $ppFEV_1$ = forced expiratory volume in one second
* Weighted average of cost for 70% <= $ppFEV_1$ <90% and $ppFEV_1$ >= 90%
†Assuming 61% reduction in hospitalization cost.
Source: Vertex data on file for SoC, Healthcare resource use and cost burden of cystic fibrosis in the NHS. (121)

In addition, costs associated with lung transplantation are considered in the model base case. The costs of transplantation procedure are estimated based on the 2010 reference costs for elective in-hospital stay, plus the costs of excess elective hospital days in the UK (64, 123). The costs associated with follow-up care are based on a study by Anyanwu et al. (101) which reported costs for up to 15 years post-lung transplant. The average costs per year for all patients receiving lung transplant reported by Anyanwu et al. were used by Whiting et al. and were adjusted to reflect costs for patients still alive in the given year. The costs were inflated to 2014 value and are applied in the model base case (Table 57) (122).

Table 57: Lung transplantation costs (inflated to 2014 GBP)

Parameter	Cost
Procedure	£46,640
Follow-up year 1	£24,014
Follow-up year 2	£14,500
Follow-up year 3	£15,244
Follow-up years 4-10	£9,156
Follow-up years 10+	£5,095

Abbreviations: SoC, standard of care.

5.5.4 Adverse reaction unit costs and resource use

Adverse events that impacted greater than 5% of LUM-IVA patients compared to placebo patients in the TRAFFIC and TRANSPORT clinical studies were included in the model.

Simulated LUM-IVA + SoC patients in the model were assumed to experience each of these adverse events at a rate equal to the annualized rates calculated for the LUM-IVA patients in TRAFFIC and TRANSPORT, while the corresponding rates observed for patients receiving placebo in these trials were applied for patients on SoC. Each of these adverse events was assumed to incur the cost of a GP visit (122, 123). The adverse events costs and event rates are reported in Table 58.

Table 58: Adverse event unit costs and resource use

Adverse Event	Cost per event	SoC	LUM-IVA + SoC
Dyspnea	£ 67.50	16.1%	27.9%
Diarrhea	£ 66.00	17.3%	22.3%
Nausea	£ 66.00	15.7%	20.8%
Respiration abnormal	£ 67.50	12.3%	20.0%
Oropharyngeal pain	£ 66.00	16.7%	18.9%

Abbreviations: SoC, standard of care.

5.5.5 Miscellaneous unit costs and resource use

Treatment with LUM-IVA is associated with an additional liver function test each year. In the first year of treatment, LUM-IVA is associated with an additional GP visit. It is mandated in the draft PI that liver function tests be collected prior to commencement of therapy, every three months for the first year, and annually thereafter. Similarly, one additional GP visit, beyond the normal 3-monthly follow-up of these patients, is assumed to account for potential follow-up visits from abnormal liver function results. The cost of liver function tests (£1.25) and GP visits (£66) resulted in a cost of £87.24 in the first year of LUM-IVA and then £3.64 annually for the subsequent years (122, 123).

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of the base-case de novo analysis inputs

The key parameters included in the base case and the associated uncertainty are shown in Table 59.

Table 59: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Annual Discount Rate	3.5%	Distribution (CI 0 - 0.06)	Section 5.2.2
Adherence	90%	Beta Distribution (CI 0.87- 0.93)	Section 5.5.2
Disease Management Costing, ppFEV$_1$ <40% - LUM-IVA	[redacted]	[redacted]	Section 5.5.3
Disease Management Costing, ppFEV$_1$ between 40% to 69% - LUM-IVA	[redacted]	[redacted]	Section 5.5.3
Disease Management Costing, ppFEV$_1$ > 70% - LUM-IVA	[redacted]	[redacted]	Section 5.5.3
Disease Management Costing, ppFEV$_1$ <40% - SoC	[redacted]	[redacted]	Section 5.5.3
Disease Management Costing, ppFEV$_1$	[redacted]	[redacted]	Section 5.5.3

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
between 40% to 69% - SoC			
Disease Management Costing, ppFEV$_1$ > 70% - SoC	[redacted]	[redacted]	Section 5.5.3
Lung Transplant Procedure	£46,640	Gamma Distribution (CI 30182.95- 66620.76)	Section 5.5.3
Lung Transplant First Year Follow-Up	£24,014	Gamma Distribution (CI 15540.59- 34301.69)	Section 5.5.3
Lung Transplant Second Year Follow-Up	£14,500	Gamma Distribution (CI 9383.64- 20711.86)	Section 5.5.3
Lung Transplant Third Year Follow-Up	£15,244	Gamma Distribution (CI 9865.11- 21774.59)	Section 5.5.3
Lung Transplant Years 4-10 Follow-Up	£9,156	Gamma Distribution (CI 5925.28- 13078.47)	Section 5.5.3
Lung Transplant Years 10+ Follow-Up	£5,095	Gamma Distribution (CI 3297.22- 7277.72)	Section 5.5.3
Dyspnea Cost	£67.5	Gamma Distribution (CI 43.68- 96.42)	Section 5.5.4
Diarrhea Cost	£66	Gamma Distribution (CI 42.71- 94.27)	Section 5.5.4
Nausea Cost	£66	Gamma Distribution (CI 42.71- 94.27)	Section 5.5.4
Respiration abnormal Cost	£67.5	Gamma Distribution (CI 43.68- 96.42)	Section 5.5.4
Oropharyngeal pain Cost	£66	Gamma Distribution (CI 42.71- 94.27)	Section 5.5.4
Liver Function Tests First Year	£87.24	Gamma Distribution (CI 56.46- 124.61)	Section 5.5.5
Liver Function Tests Subsequent Year	£3.86	Gamma Distribution (CI 2.5- 5.51)	Section 5.5.5
Liou equation - Age coefficient	0.011	Normal Distribution (CI 0- 0.02)	Section 5.3.7
Liou equation - ppFEV$_1$ coefficient	-0.042	Normal Distribution (CI -0.05- -0.04)	Section 5.3.7
Liou equation - Sex (male = 0) coefficient	0.15	Normal Distribution (CI 0- 0.3)	Section 5.3.7
Liou equation - Weight-for-age z-score coefficient	-0.28	Normal Distribution (CI -0.36- -0.2)	Section 5.3.7
Liou equation - Pancreatic sufficiency (yes = 1) coefficient	-0.14	Normal Distribution (CI -0.59- 0.31)	Section 5.3.7
Liou equation - Diabetes mellitus (yes = 1) coefficient	0.44	Normal Distribution (CI 0.25- 0.63)	Section 5.3.7
Liou equation - S. aureus (yes = 1) coefficient	-0.25	Normal Distribution (CI -0.43- -0.07)	Section 5.3.7
Liou equation - B. cepacia (yes = 1) coefficient	1.41	Normal Distribution (CI 1.04- 1.78)	Section 5.3.7
Liou equation - Annual number of acute exacerbations (max 5) coefficient	0.35	Normal Distribution (CI 0.3- 0.4)	Section 5.3.7
Liou equation - Exacerbations × B. cepacia coefficient	-0.28	Normal Distribution (CI -0.4- -0.16)	Section 5.3.7
Liou equation reference value - Mean Sex (male = 0)	0.467	Normal Distribution (CI 0.46- 0.48)	Section 5.3.7

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Liou equation reference value - Mean Weight-for-age z-score	-0.85	Normal Distribution (CI -0.88- -0.82)	Section 5.3.7
Liou equation reference value - Mean Pancreatic sufficiency (yes = 1)	0.126	Normal Distribution (CI 0.16- 0.17)	Section 5.3.7
Liou equation reference value - Mean Diabetes mellitus (yes = 1)	0.187	Normal Distribution (CI 0.17- 0.21)	Section 5.3.7
Liou equation reference value - Mean S. aureus (yes = 1)	0.179	Normal Distribution (CI 0.17- 0.19)	Section 5.3.7
Liou equation reference value - Mean B. cepacia (yes = 1)	0.034	Normal Distribution (CI 0.03- 0.04)	Section 5.3.7
Utility equation - Intercept	[redacted]	[redacted]	Section 5.4.6.1
Utility equation - First Order Term	[redacted]	[redacted]	Section 5.4.6.1
Utility equation - Second Order Term	[redacted]	[redacted]	Section 5.4.6.1
Utility equation - Change in Utility for Exacerbation	[redacted]	[redacted]	Section 5.4.6.1
Utility for Lung Transplant (0-6 months)	0.75	Beta Distribution (CI 0.66- 0.83)	Section 5.4.6.2
Utility for Lung Transplant (7-18 months)	0.83	Beta Distribution (CI 0.74- 0.91)	Section 5.4.6.2
Utility for Lung Transplant (18-36 months)	0.81	Beta Distribution (CI 0.72- 0.88)	Section 5.4.6.2
Utility for Lung Transplant (>36 months)	0.82	Beta Distribution (CI 0.74- 0.88)	Section 5.4.6.2
Discontinuation during trial - LUM-IVA	0.142	Beta Distribution (CI 0.11- 0.18)	Section 5.5.2
Dyspnea Incidence - LUM-IVA	27.9%	Beta Distribution (CI 0.23- 0.33)	Section 5.5.4
Diarrhea Incidence - LUM-IVA	22.3%	Beta Distribution (CI 0.18- 0.27)	Section 5.5.4
Nausea Incidence - LUM-IVA	20.8%	Beta Distribution (CI 0.17- 0.25)	Section 5.5.4
Respiration abnormal Incidence - LUM-IVA	20%	Beta Distribution (CI 0.16- 0.24)	Section 5.5.4
Oropharyngeal pain Incidence - LUM-IVA	18.9%	Beta Distribution (CI 0.15- 0.23)	Section 5.5.4
Dyspnea Incidence - SoC	16.1%	Beta Distribution (CI 0.13- 0.2)	Section 5.5.4
Diarrhea Incidence - SoC	17.3%	Beta Distribution (CI 0.14- 0.21)	Section 5.5.4
Nausea Incidence - SoC	15.7%	Beta Distribution (CI 0.12- 0.2)	Section 5.5.4
Respiration abnormal Incidence - SoC	12.3%	Beta Distribution (CI 0.09- 0.16)	Section 5.5.4
Oropharyngeal pain Incidence - SoC	16.7%	Beta Distribution (CI 0.13- 0.21)	Section 5.5.4
Lung Transplant - Percent of Eligible Patients who Receive Lung Transplant	24.7%	Beta Distribution (CI 0.2- 0.3)	Section 5.3.6
Lung Transplant - Annual Death Probability First Year	15.2%	Beta Distribution (CI 0.15- 0.16)	Section 5.3.6
Lung Transplant - Annual Death Probability Subsequent Years	6.1%	Beta Distribution (CI 0.06- 0.06)	Section 5.3.6
Mean Change in ppFEV1 During Trial - LUM-IVA	2.8	Normal Distribution (CI 1.8- 3.8)	Section 5.3.2

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Pulmonary Exacerbations Rate Ratio - LUM-IVA	0.442	Beta Distribution (CI 0.38- 0.5)	Section 5.3.3
Mean Weight-for-Age Z-Score Change At 24 week - LUM-IVA	0.068	Normal Distribution (CI 0.02- 0.11)	Section 5.3.4
Mean BMI Change At 24 week - LUM-IVA	0.24	Normal Distribution (CI 0.11- 0.37)	Section 5.3.4
$ppFEV_1$ Decline Age 0-17	-2.34	Normal Distribution (CI -2.53- -2.17)	Section 5.3.2
$ppFEV_1$ Decline Age 18-24	-1.92	Normal Distribution (CI -2.04- -1.81)	Section 5.3.2
$ppFEV_1$ Decline Age 25+	-1.45	Normal Distribution (CI -1.62- -1.27)	Section 5.3.2
Pulmonary Exacerbation Rate Ratio - LUM-IVA Treatment Effect	0.442	Beta Distribution (CI 0.38- 0.5)	Section 5.3.3
Diabetes Prevalence, Age 12 - 15	4.1%	Beta Distribution (CI 0.04- 0.05)	Section 5.3.5
Diabetes Prevalence, Age 16+	29.4%	Beta Distribution (CI 0.28- 0.31)	Section 5.3.5
Diabetes Incidence, Age 12 - 19, Males	3.9%	Beta Distribution (CI 0.03- 0.05)	Section 5.3.5
Diabetes Incidence, Age 20 - 29, Males	4.9%	Beta Distribution (CI 0.04- 0.06)	Section 5.3.5
Diabetes Incidence, Age 30 - 39, Males	6.5%	Beta Distribution (CI 0.04- 0.09)	Section 5.3.5
Diabetes Incidence, Age 40+, Males	5.1%	Beta Distribution (CI 0.02- 0.09)	Section 5.3.5
Diabetes Incidence, Age 12 - 19, Females	6.0%	Beta Distribution (CI 0.05- 0.07)	Section 5.3.5
Diabetes Incidence, Age 20 - 29, Females	7.1%	Beta Distribution (CI 0.05- 0.09)	Section 5.3.5
Diabetes Incidence, Age 30 - 39, Females	7.2%	Beta Distribution (CI 0.05- 0.1)	Section 5.3.5
Diabetes Incidence, Age 40+, Females	2.9%	Beta Distribution (CI 0.01- 0.06)	Section 5.3.5
S. Aureus Prevalence, Age 12 - 15	17.9%	Beta Distribution (CI 0.15- 0.2)	Section 5.3.1
S. Aureus Prevalence, Age 16 - 23	24.9%	Beta Distribution (CI 0.23- 0.27)	Section 5.3.1
S. Aureus Prevalence, Age 24 - 31	26.5%	Beta Distribution (CI 0.24- 0.29)	Section 5.3.1
S. Aureus Prevalence, Age 32 - 39	21.0%	Beta Distribution (CI 0.18- 0.24)	Section 5.3.1
S. Aureus Prevalence, Age 40 - 49	21.6%	Beta Distribution (CI 0.18- 0.25)	Section 5.3.1
S. Aureus Prevalence, Age 50+	22.4%	Beta Distribution (CI 0.18- 0.27)	Section 5.3.1
B. Cepacia Prevalence, Age 12 - 15	2.2%	Beta Distribution (CI 0.01- 0.03)	Section 5.3.1
B. Cepacia Prevalence, Age 16 - 23	4.6%	Beta Distribution (CI 0.04- 0.06)	Section 5.3.1
B. Cepacia Prevalence, Age 24 - 31	5.4%	Beta Distribution (CI 0.04- 0.07)	Section 5.3.1
B. Cepacia Prevalence, Age 32 - 39	5.8%	Beta Distribution (CI 0.04- 0.07)	Section 5.3.1
B. Cepacia Prevalence, Age 40 - 49	5.8%	Beta Distribution (CI 0.04- 0.08)	Section 5.3.1
B. Cepacia Prevalence, Age 50+	2.8%	Beta Distribution (CI 0.01- 0.05)	Section 5.3.1
LUM-IVA rate of decline in $ppFEV_1$	-0.68	Normal Distribution (CI -1.52- 0.16)	Section 5.3.2

Abbreviations: $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SoC, standard of care

5.7 Base-case results

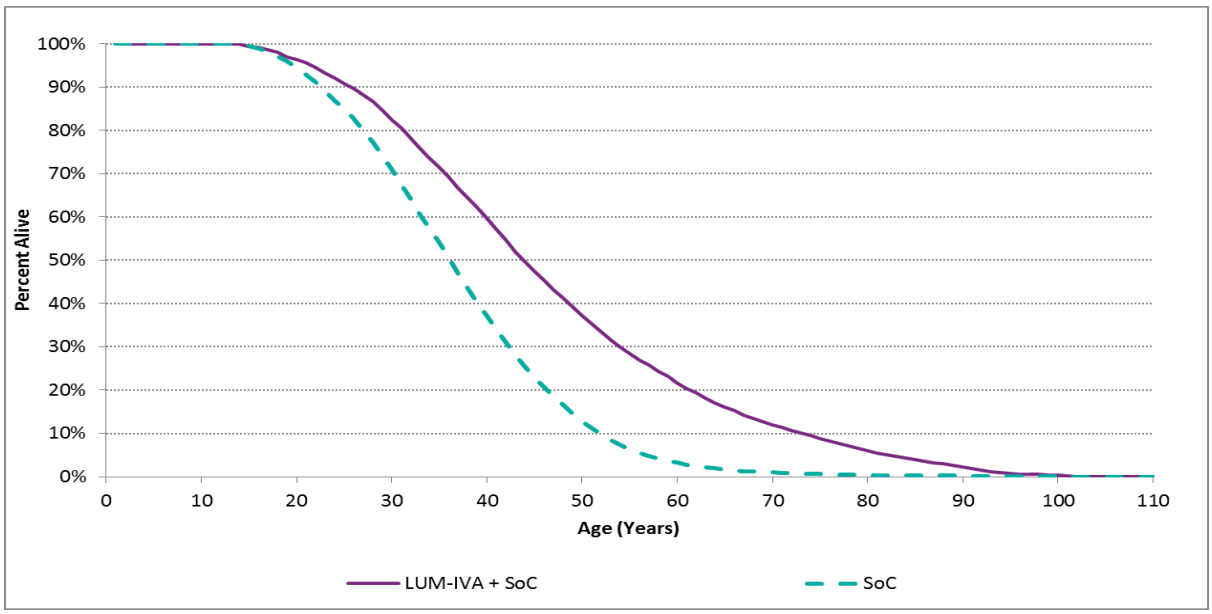
5.7.1 Base-case incremental cost effectiveness analysis results

Using base-case assumptions the model projects that LUM-IVA + SoC will lead to an improvement in projected median survival of 7.69 years and increase mean residual life expectancy (undiscounted life-years gained) by 9.42 years. The median survival with SoC

is projected to be 36.15 years, which is consistent with the projected median survival of 40.1 years reported in the UK CF Trust Registry (5), when considering patients who are homozygous for the *F508del* mutation and alive at age 12 years of age (See Table 38 for a comparison of characteristics of the study patients with the whole of the UK CF registry). The projected 8-year increase in projected survival for patients treated with LUM-IVA represents a significant advancement in the care of patients with CF age 12 years and older who are homozygous for the *F508del* mutation.

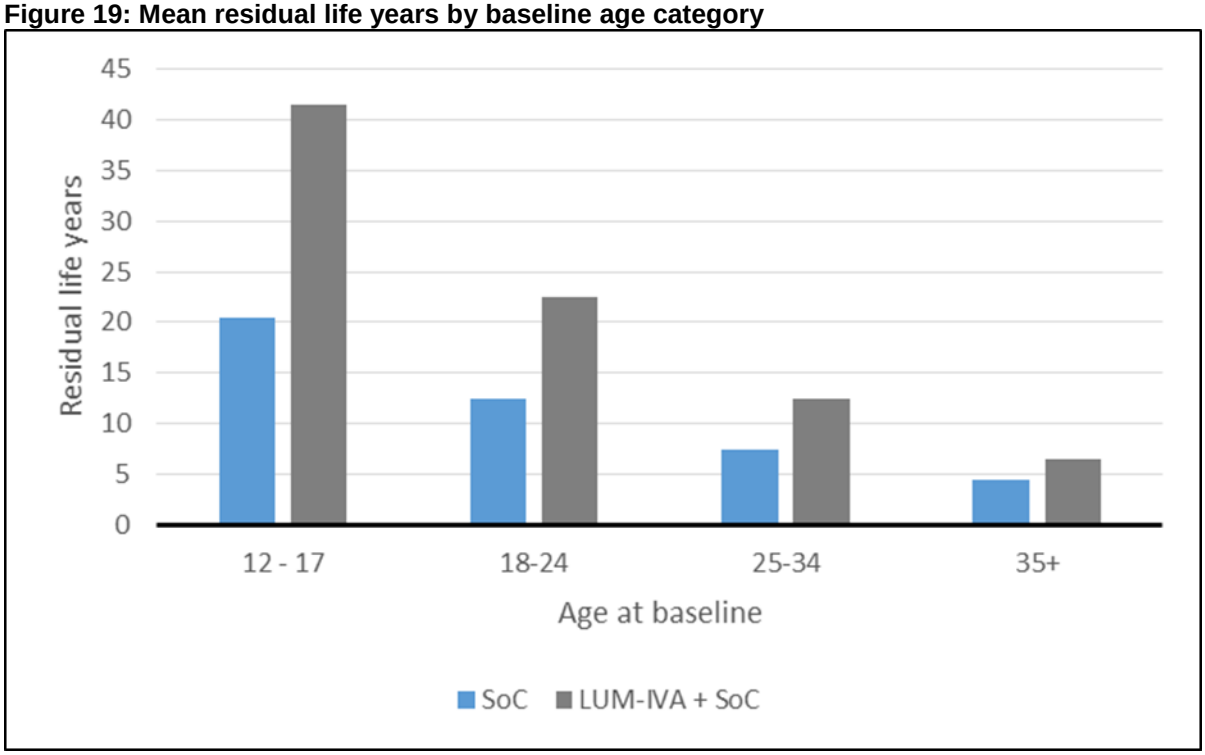
The base case survival predicted from the model is shown in Figure 18.

Figure 18: Base case survival



Model results suggest that treatment with LUM-IVA will provide a survival benefit across all patient age groups, with LUM-IVA improving mean life years by at least 44%. This projected survival benefit is larger in younger cohorts, highlighting the importance of treating early. The mean residual life years for the different age groups is shown in Figure 19.

Figure 19: Mean residual life years by baseline age category



Abbreviations: SoC, standard of care.

The base case cost-effectiveness results are presented in Table 60. The results show that LUM-IVA + SoC is associated with improved health outcomes. LUM-IVA + SoC is associated with 12.38 discounted QALYs compared to 8.92 QALYs in the SoC arm. Costs are higher in the LUM-IVA + SoC arm than the SoC arm, with incremental costs equal to £707,091. The incremental cost in combination with the incremental QALYs result in an ICER equal to £204,787. The results based on a cost per life year gained are also shown in Table 60, these results show the discounted incremental life years to be 3.46 and an ICER of £204,204 per life-year gained.

Table 60: Base-case results

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92					
LUM-IVA	£1,084,725	13.78	12.38	£707,091	3.46	3.45	£204,204	£204,787

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost effectiveness analysis

5.7.2 Clinical outcomes from the model

Results suggest that patients on LUM-IVA preserve 8.37 percentage points of $ppFEV_1$ over their lifetimes, losing an average of 13.51 percentage points compared to 21.89 percentage points for patients on SoC. The model projects that LUM-IVA increases the amount of time spent with $ppFEV_1$ in the normal/mild range ($ppFEV_1 \geq 70\%$) and reduces the time spent with $ppFEV_1 < 30\%$, a common $ppFEV_1$ threshold for recommendation of lung transplantation. The annual exacerbation rate is reduced by 63% representing the combined impact of LUM-IVA on $ppFEV_1$ and pulmonary exacerbations. The model

predicts that the percentage of patients undergoing lung transplantation is reduced by 73% with LUM-IVA + SoC compared to SoC and more than doubles the time to transplant among those who receive a lung transplant (Table 61).

Table 61: Health outcomes

Comparator	LUM-IVA + SoC	SoC	Incremental
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 $ppFEV_1 \geq 70\%$	4.08	1.14	2.94
Mean Years with $ppFEV_1$ between 70% and 40%	17.10	8.84	8.26
Mean Years with $ppFEV_1$ between 40% and 30%	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 Undergoing Lung Transplant	1.82%	6.80%	-4.98%
Mean Years Until Lung Transplant	46.49	19.34	27.14

Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second.

The detailed cost result table (Table 62) shows that the majority of increased costs are due to LUM-IVA. The incremental drug cost was £757,776, in comparison to the total incremental cost of £707,091. Over the lifetime, LUM-IVA + SoC will reduce disease management cost and transplantation costs by £41,959 and £9,442 respectively. Lower disease management costs are estimated for patients treated with LUM-IVA + SoC vs. SoC despite the projected increase in survival. Liver function testing and AE related costs are marginal.

Table 62: Summary of predicted resource use by category of cost

Item	Cost LUM-IVA + SoC	Cost SoC	Increment	Absolute increment	% absolute increment
Drug Cost	£757,731	£0	£757,731	£757,731	93.6%
Disease Management Cost	£324,598	£366,558	-£41,959	£41,959	5.2%
Lung Transplant Cost	£1,097	£10,539	-£9,442	£9,442	1.2%
Adverse Event	£994	£537	£458	£458	0.1%
Liver Function Test	£131	£0	£131	£131	0.0%
Total	£1,084,552	£377,633	£706,918	Total absolute increment	100%

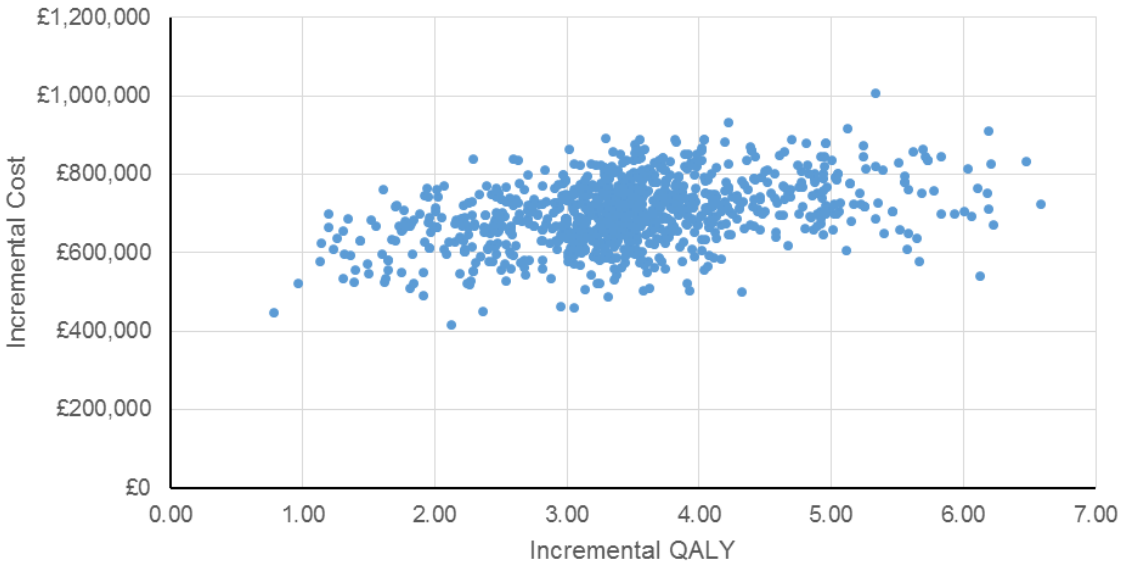
Abbreviations: SoC, standard of care

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analyses

A scatter plot of the output from the probabilistic sensitivity analysis is shown in Figure 20. This shows 1,000 iterations and the associated uncertainty. Of the 1,000 iterations most of the data points fall between 1 and 7 QALYs gained and £400,000 and £1,000,000 incremental costs, with simulations leading to higher QALYs also leading to higher costs, reflecting the survival benefit of LUM-IVA. In every simulation, SoC is associated with less cost and fewer QALYs than the LUM-IVA treatment arms.

Figure 20: Cost Effectiveness Scatter Plot



Abbreviations: QALY, quality adjusted life years

To determine the probability of LUM-IVA + SoC being cost-effective at different cost-effectiveness thresholds, a cost effectiveness acceptability curve (CEAC) is reported in Figure 21. The CEAC shows that for a threshold above £205,000, LUM-IVA + SoC is likely to be a cost effective treatment (at a threshold of £205,000 there is a 50.8% probability that LUM-IVA + SoC is cost effective) and at a threshold of £290,000, LUM-IVA + SoC has a >90% probability of being cost-effective.

Figure 21: Cost Effectiveness Acceptability Curve

The mean results of the probabilistic analysis are comparable to the base case results (Table 63). This demonstrates the results of the probabilistic analysis are robust.

Table 63: Mean Results from the Probabilistic Sensitivity Analysis

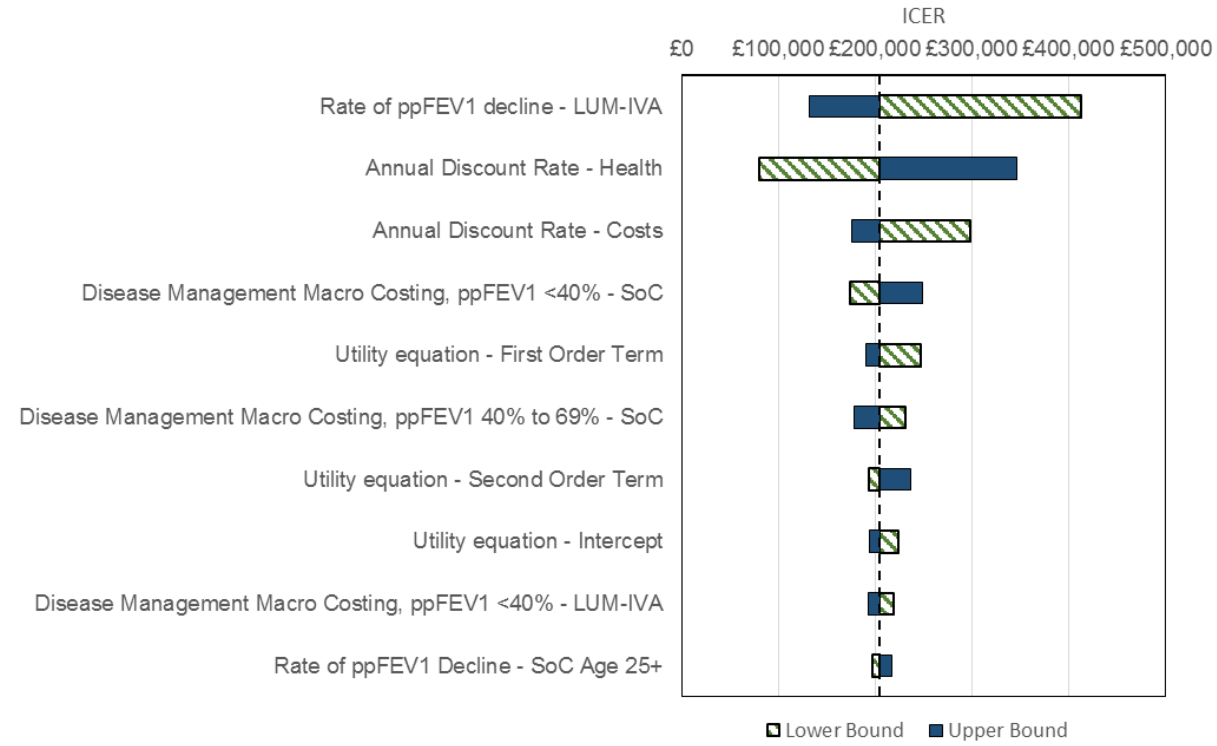
Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,775	10.30	8.92				
LUM-IVA + SoC	£1,079,456	13.78	12.39	£701,681	3.48	3.47	£202,047

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care.

5.8.2 Deterministic sensitivity analysis

Tornado diagrams have been presented in Figure 22 for the comparison between LUM-IVA + SoC vs SOC alone. The tornado diagrams are presented in order of impact on the ICER.

Figure 22: One-way sensitivity analysis



Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second; ICER, incremental cost effectiveness analysis.

The one-way sensitivity analysis shows that the model is most sensitive to the rate of decline for LUM-IVA, discount rates and disease management costs.

5.8.3 Scenario analysis

A series of scenario analyses are included to test for uncertainties around assumptions and data limitations.

5.8.3.1 Discount rates

The model sensitivity to discount rates is due to the sustained health impacts of LUM-IVA for CF patients homozygous for the *F508del* mutation over a long time horizon, and the projected survival benefit, part of which occurs far in the future. Thus in accordance with the NICE decision support unit for products that meet these criteria a discount rate of 1.5% was tested (124).

The model has been shown to be sensitive to the discount rate, see Figure 22. Using a discount rate of 1.5% across both health outcomes and costs reduces the ICER by over £50,000 compared to the base case.

Table 64: Scenario Analysis – annual discount rate of 1.5%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£467,148	12.60	10.83				
LUM-IVA +	£1,314,914	18.50	16.56	£847,766	5.90	5.72	£148,107

SoC							

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.2 Rate of ppFEV$_1$ decline

To test the long term extrapolation of ppFEV$_1$ (see section 5.3.2) two alternative scenarios have been considered, one that that uses an alternative rate of decline for LUM-IVA and second that alters rate of decline for SoC.

The first scenario uses the only available data beyond one year for a CFTR modulator therapy. The data is based on treatment with ivacaftor in a population of patients with a *G551D CFTR* mutation (67). Sawicki et al. conducted an analysis where *G551D* patients receiving ivacaftor in the PERSIST clinical trial were compared with an aged-matched and propensity score matched control group of homozygous *F508del* patients who were not receiving any CFTR modulator therapy. Patients were followed up over a three-year period. The analysis found that the mean rate of ppFEV$_1$ decline in the ivacaftor-treated group was 53% lower than that of the control group. 48 week data from the LUM-IVA PROGRESS clinical trial saw a ppFEV$_1$ rate of decline very similar to that seen in the first year of PERSIST, which suggests that LUM-IVA could also have a similar ppFEV$_1$ trend for subsequent years. As such, assuming the same relative impact of rate of decline for LUM-IVA (53% reduction in rate of decline compared to standard of care) was tested in a scenario analysis.

The results show that when using the data from ivacaftor, the results are in a similar range as the base case. The comparability in results is expected due to the comparability of rates of ppFEV$_1$ decline estimated by the two approaches. The results are shown in Table 65.

Table 65: Scenario Analysis – Sawicki et al. Rate of ppFEV$_1$ decline

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,079,094	13.50	12.10	£701,461	3.19	3.17	£221,213

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

An alternative scenario was tested using a different reference to inform the SoC rate of decline for patients 18+ years of age (annual rate of decline of -2.47). In this scenario the rate of decline for SoC was derived from an analysis by de Boer et al. This study assessed exacerbations and rate of decline in 446 patients over a 3 year time horizon. The patients were from Ontario, Canada. A mean ppFEV$_1$ was calculated from the publication using a weighted average of the estimates reported. The results from using the rate of decline calculated from de Boer et al. are shown in Table 66.

Table 66: Scenario Analysis – de Boer et al. Rate of ppFEV$_1$ decline

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£347,252	9.24	7.91				

LUM-IVA + SoC	£1,084,725	13.78	12.38	£737,473	4.54	4.47	£165,105

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Two alternative scenarios have been conducted to test a plausible range around the rate of decline. The current rate of decline is associated with a large confidence interval, it is likely that as PROGRESS reports more observations the confidence interval will be reduced. A range of ±20% around the mean has been tested.

Table 67: Scenario Analysis – +20% Rate of ppFEV$_1$ decline for LUM-IVA

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,073,831	13.45	12.04	£696,198	3.13	3.11	£223,534

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 68: Scenario Analysis – -20% Rate of ppFEV$_1$ decline for LUM-IVA

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,095,418	14.16	12.76	£717,785	3.84	3.83	£187,346

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

The results show that increasing the rate of decline by 20% increases the ICER by £19,000 whereas decreasing the rate of decline by 20% reduces the ICER by £17,000.

5.8.3.3 Pulmonary exacerbations

Pulmonary exacerbations are a composite of patient signs and symptoms that often result in the need for aggressive treatment, including the use of IV antibiotics that may or may not require hospitalisation. To date, there is no generally accepted objective definition of a pulmonary exacerbation.

A rate ratio of 0.61 for the rate of pulmonary exacerbation in patients treated with LUM-IVA +SoC vs. SoC was calculated from the pooled results of the TRAFFIC and TRANSPORT trials where exacerbations were defined using the modified Fuchs criteria (see section 4.7.1.7). The model uses an equation published by Goss et al. to predict the rate of pulmonary exacerbation for each patient in each cycle. However, the definition of pulmonary exacerbations used in the TRAFFIC and TRANSPORT trials is different from that used in the study conducted by Goss et al. The latter defined a pulmonary exacerbation as a CF-related pulmonary condition requiring admission to hospital or use of home IV antibiotics. Therefore, the base case adopted the pulmonary exacerbation rate ratio (0.442) of LUM-IVA +SoC vs. SoC derived from post-hoc analyses of the TRAFFIC and TRANSPORT trial data based a pulmonary exacerbation definition that closely mirrored that used in the study conducted by Goss et al. (69).

As a more conservative assumption than the base case, the rate ratio of 0.61 in the risk of pulmonary exacerbation (any type) calculated from the pooled results of all exacerbations recorded in TRAFFIC and TRANSPORT is applied to the predicted pulmonary exacerbation rate for patients on LUM-IVA + SoC for the entire model time horizon until treatment discontinuation. The results are shown in Table 69.

Table 69: Scenario Analysis – Pulmonary exacerbation rate ratio from TRAFFIC and TRANSPORT results using all protocol-defined pulmonary exacerbations

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,069,663	13.50	12.09	£692,030	3.19	3.16	£218,813

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.4 Utility

The utility equation described has been used in the base case as this represents the data from the LUM-IVA studies and provides the best source of evidence for utilities in this patient population. However, a paper by Tappenden et al., (2014) was identified in the quality of life literature reviews. The paper by Tappenden et al. (97) reported utilities by ppFEV$_1$ strata, which have been tested as an alternative. The utility values tested are reported in Table 49. The results of this scenario are reported in Table 70.

The results show the ICER to be slightly higher that the base case, this is due to the utilities being lower but having a wider range between health states.

Table 70: Scenario Analysis – Utility Values Tappenden et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	7.97				
LUM-IVA + SoC	£1,084,725	13.78	11.09	£707,091	3.46	3.13	£226,238

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

As well as the paper by Tappenden et al. (97) a paper by Acaster et al., (95) which reported health state utilities for patients with CF was identified. These utility values have been tested in a scenario analysis, and results are shown in Table 71. The results show the ICER to be approximately £60,000 higher than the base case.

Table 71: Scenario Analysis – Utility Values Acaster et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	6.86				

LUM-IVA + SoC	£1,084,725	13.78	9.52	£707,091	3.46	2.66	£265,975

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

The utility values used by Whiting et al. have been tested in the model. These values were derived from a study by Gee et al (125). The methodology used to calculate these utilities is unclear and there is little discrimination between higher and lower $ppFEV_1$ categories. Therefore the results from this analysis should be considered with caution, these results are shown in Table 72.

Table 72: Scenario Analysis – Utility Values Whiting et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	7.61				
LUM-IVA + SoC	£1,084,725	13.78	10.39	£707,091	3.46	2.78	£254,163

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

As an alternative to the base case assumption, an additional scenario was tested using EQ-5D data from the TRAFFIC and TRANSPORT trials. This additional scenario uses the EQ-5D index values by $ppFEV_1$ strata (see Table 46). The results are shown in Table 73.

Table 73: Scenario Analysis – EQ-5D index values by $ppFEV_1$ strata from TRAFFIC and TRANSPORT

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	9.25				
LUM-IVA + SoC	£1,084,725	13.78	12.52	£707,091	3.46	3.27	£216,536

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.5 Rate of discontinuation

In reality, patients may discontinue LUM-IVA treatment for various reasons. Although deriving appropriate discontinuation rates over long periods of time is difficult, a scenario is tested that includes discontinuation beyond the trial period. This scenario makes the assumption that cumulatively 30% of patients discontinue LUM-IVA treatment within 15 years of treatment initiation, with no further discontinuation beyond that point. An annualised discontinuation rate of 1.9% is applied to each year following the 24 week trial period until the end of year 15.

For patients who discontinue LUM-IVA during the first 24 weeks, treatment efficacy is assumed to be the same for patients who remain on treatment by week 24. No efficacy loss is applied for the initial 24 week period. Beyond 24 weeks, after a patient discontinues LUM-IVA treatment, $ppFEV_1$ decline is assumed to be the same as for patients on SoC. Treatment impact on pulmonary exacerbation rate is stopped immediately after LUM-IVA treatment discontinuation.

The results are shown in Table 74. The results show increasing the discontinuation in the model improves the cost effectiveness results, this is due to removing patients from treatment and subsequently reducing the drug cost.

Table 74: Scenario Analysis – Rate of discontinuation

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,046,429	13.68	12.27	£668,796	3.36	3.34	£200,170

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.6 Survival curves

To test the uncertainty in the underlying survival function for the UK CF Registry population, the Gompertz parametric curve (described in section 5.3.7.1) has been tested. The results are shown in Table 75. Using this Gompertz parametric curve reduces incremental projected median survival by about two years (5.7 years when using Gompertz compared to 7.7 when using the base case), and subsequently reduces the incremental QALYs and incremental cost. Despite the reduction in survival estimates, costs and QALYs are reduced by similar proportions and therefore the ICER calculated in this scenario is comparable to the ICER obtained when using the Weibull curve in the base case.

Table 75: Scenario Analysis – Gompertz Curve

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£292,406	8.23	7.18				
LUM-IVA + SoC	£904,913	11.08	10.00	£612,507	2.85	2.83	£216,747

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.7 Excluding disease management costs incurred during additional survival

Based on the base case modelling results, treatment with LUM-IVA + SoC increased the projected median survival by 7.7 years, during which time patients receiving LUM-IVA also incurred disease management costs. This scenario omits any additional disease management costs that would be incurred as a consequence of extending life for patients treated with LUM-IVA. Any of those disease management costs which are accrued for each individual patient on LUM-IVA, past the time at which the patient's "clone" on SoC dies, are omitted. The purpose of this scenario is to remove possible penalties for extension of life. Drug costs of LUM-IVA continue to be included over the patient's lifetime.

The results are shown in Table 76. This analysis shows that when excluding the disease management costs incurred during the incremental survival reduces the ICER to £177,884.

Table 76: Scenario Analysis – Omission of disease management costs incurred during additional survival

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.93				
LUM-IVA + SoC	£ 991,835	13.78	12.38	£ 614,202	3.46	3.45	£ 177,884

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.8.3.8 Adherence

A scenario has been included testing the TRAFFIC and TRANSPORT level of adherence, observed at 96.5%. The base case uses a level of 90% adherence, based on observed adherence levels for Kalydeco.

Table 77: Scenario Analysis – Adherence 96.5 %

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,139,116	13.78	12.38	£761,483	3.46	3.45	£220,539

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.9 Subgroup analysis

The TRAFFIC and TRANSPORT trials analysed pre-specified subgroups, as shown in Wainwright et al. it is expected that all patients will benefit from treatment. The cost effectiveness model tests the same subgroups, with the exception of pseudomonas aeruginosa infection status as the model does not differentiate between positive and negative patients.

For each subgroup, the treatment effect for $ppFEV_1$, BMI, weight-for-age z-score and rate ratio for pulmonary exacerbations were analysed. In addition to this, the patients sampled from the patient cohort is restricted to reflect the subgroup, e.g. for the subgroup of Male patients the cohort was restricted to male patients only. The inputs used for the subgroups are shown in Table 78.

Table 78: Subgroup Analysis Inputs

Subgroup	LUM-IVA Sample size	Mean Absolute Change in FEV_1 Percentage Points From Baseline by 16 Weeks	Pulmonary Exacerbations Rate Ratio	Mean Weight-for-age z-score Change From Baseline by 24 Weeks	Mean BMI Change From Baseline by 24 Weeks
Overall	357	2.81	0.44	0.068	0.24
Age ≥ 12 to <18	93	2.98	0.29	0.06	0.33
Age ≥ 18	259	2.79	0.47	0.07	0.21
$ppFEV_1$ <70%	239	3.26	0.48	0.06	0.17
$ppFEV_1$ ≥ 70%	108	1.86	0.09	0.08	0.34
$ppFEV_1$ < 40%	28	3.3	0.67	0.09	0.29
$ppFEV_1$ ≥ 40%	324	2.77	0.36	0.06	0.23
Male	178	3.19	0.38	0.07	0.24
Female	174	2.46	0.47	0.07	0.24

Abbreviations: BMI, body mass index; $ppFEV_1$, Percent predicted forced expiratory volume in 1 second

5.9.1 Gender

Sub-analysis by gender shows the ICER does not vary by more than £6,000 from the base case. The projected life-year gain (discounted) for a male population is slightly higher than for a female population, the results are shown in Table 79 and Table 80.

Table 79: Subgroup Analysis – Male

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£395,494	10.93	9.49				
LUM-IVA + SoC	£1,131,186	14.62	13.17	£735,692	3.68	3.68	£199,942

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 80: Subgroup Analysis – Female

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£374,972	10.18	8.80				
LUM-IVA + SoC	£1,084,047	13.63	12.22	£709,074	3.46	3.43	£206,956

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.9.2 Age

The results for patients stratified by baseline age, show that treating patients earlier results in a lower ICER. The results for the patients aged between 12 and 18 is approximately 20% lower than the base case, the results are shown in Table 81. The results for treating patients with a baseline age greater than 18 is approximately 10% higher than base-case and shown in Table 82.

Table 81: Subgroup Analysis – Age between 12 and 18

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£552,644	14.99	12.87				
LUM-IVA + SoC	£1,396,530	20.10	18.11	£843,885	5.12	5.24	£161,104

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 82: Subgroup Analysis – Age greater than 18

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£314,109	8.63	7.50				
LUM-IVA + SoC	£973,815	11.55	10.36	£659,706	2.92	2.85	£231,283

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

5.9.3 Baseline ppFEV$_1$

The subgroups stratified by baseline ppFEV$_1$ show the highest variance in ICER, however it is important to note that the patient numbers for the baseline ppFEV$_1$ < 40% are very small as these criteria fall outside the inclusion criteria from the TRAFFIC and TRANSPORT trials.

Table 83: Subgroup Analysis – baseline ppFEV$_1$ > 40%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£393,338	10.85	9.41				
LUM-IVA + SoC	£1,129,429	14.53	13.08	£736,091	3.67	3.67	£200,746

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 84: Subgroup Analysis – baseline ppFEV$_1$ < 40%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£231,283	4.92	4.06				
LUM-IVA + SoC	£694,562	6.76	5.77	£463,278	1.84	1.71	£270,985

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 85: Subgroup Analysis – baseline ppFEV$_1$ > 70%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£493,467	15.12	13.35				
LUM-IVA + SoC	£1,329,388	19.35	17.72	£835,921	4.24	4.37	£191,307

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 86: Subgroup Analysis – baseline ppFEV$_1$ < 70%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£334,865	8.55	7.30				
LUM-IVA + SoC	£1,002,926	11.81	10.48	£668,061	3.26	3.18	£210,127

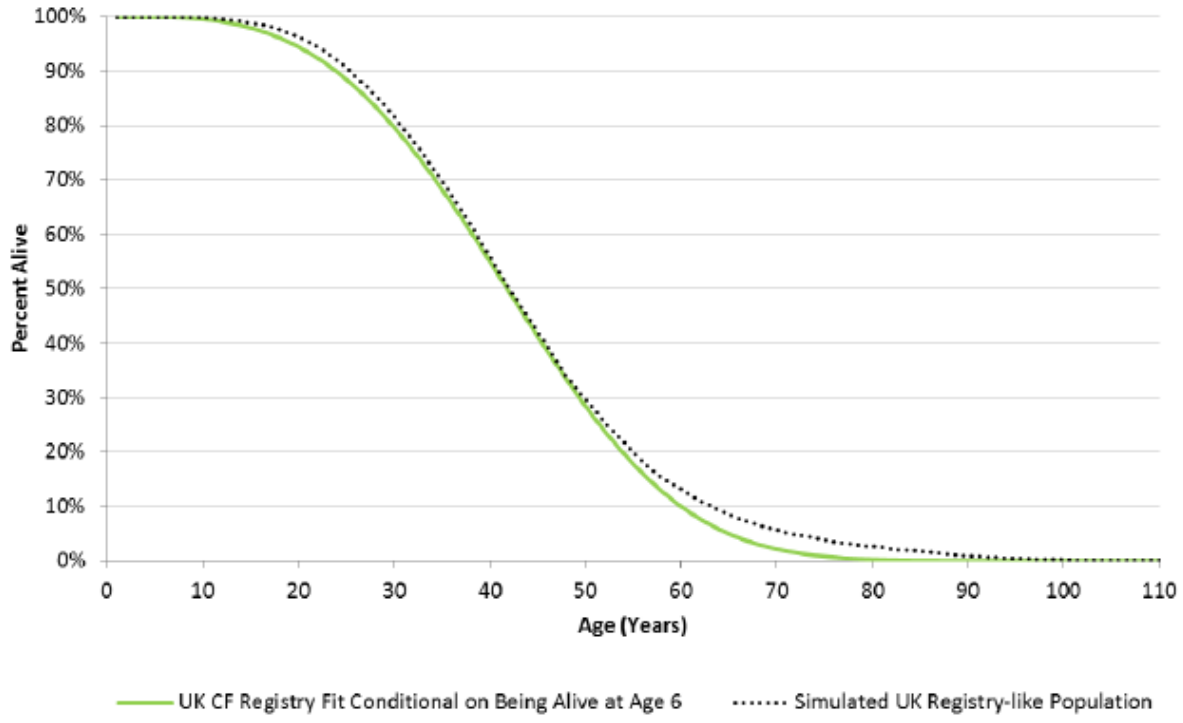
Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Subgroup analyses demonstrate that in all scenarios LUM-IVA leads to incremental improvements in health outcomes. Results by subgroup do not vary considerably, with ICERs varying between £161,000 and £270,000, which is within the general uncertainty of the model (based on one-way, scenario, and probabilistic sensitivity analyses).

5.10 Validation

The methodology to project survival was validated by applying the method to a population with age and ppFEV$_1$ distributions that resemble those of the UK registry population and comparing the simulated survival from the model to the curve fitted to the registry. This comparison is made more difficult because the actual starting risk factor profiles in the registry are not known; thus forcing the analysis to deduce profiles that collectively yield the average profile derived by piecing together information from various sources. Moreover, the changes in values over time in the registry are known only for some risk factors. Thus, a perfect match of the simulation to the registry cannot be expected. Nevertheless, the model output matches the registry curve quite well as shown in Figure 23. This approach validates not only the underlying approach to estimating survival used in the model, but also the inputs used to estimate disease progression in the SoC population.

Figure 23: Validation of the Survival Projection Approach



Abbreviations: CF = cystic fibrosis; UK = United Kingdom

5.11 Interpretation and conclusions of economic evidence

A lifetime individual patient microsimulation model was constructed to estimate the clinical outcomes (disease progression, residual years of life and QALYs) and direct medical costs (including LUM-IVA cost, disease management, lung transplant and adverse events) of a population of patients with CF age 12 years and older who are homozygous for the *F508del* mutation. The clinical outcomes and costs of patients receiving LUM-IVA in addition to SoC were compared with those receiving SoC alone to reflect projected real world use of LUM-IVA as adjunct therapy, and mimic the clinical studies of LUM-IVA which demonstrated the multiple clinically-meaningful benefits of LUM-IVA above and beyond SoC alone. Patients treated with LUM-IVA were assumed to continue to have access to the same level of SoC,

including recommended medications and physical therapy as patients treated with SoC alone.

The individual patient microsimulation found LUM-IVA + SoC to be associated with improved health outcomes, including increased projected median survival, more time spent in higher $ppFEV_1$ states and fewer lung transplants. Specifically LUM-IVA + SoC is projected to increase median survival by 7.7 years (9.4 undiscounted life-years gained) leading to incremental discounted QALYs of 3.45. When considering the incremental cost associated with LUM-IVA + SoC (£707,091) the resulting ICER is £204,787. The results of the model are considered to be generalisable to the CF population indicated for LUM-IVA in England, with UK CF data used where possible. Only in cases where there was a lack of available evidence relevant to England was an alternative reference used. The model was found to validate well when comparing the projected survival produced from the model for a cohort of patients representing the UK CF registry population with the parametric curve fitted to the UK CF registry (see Figure 17).

Sensitivity analysis found the model results to be sensitive to the long term extrapolation of $ppFEV_1$, discount rates and utility values. Several scenario analyses were tested using alternative data sources and the range of ICERs using these alternatives was £260,000 to £149,000. However as described in this section, inputs used in the base-case, and thus corresponding results, utilize the most robust data available. Probabilistic sensitivity analysis showed that the model results were robust, as the mean results were comparable to the base case results.

The utility values generated from the utility equation are based on the EQ-5D values from the TRAFFIC and TRANSPORT studies. Considering the impact CF has on patient's lifestyles and the burden of disease, patients with CF score higher than expected, with a median score of 1. This is a phenomenon that is common in CF and several studies suggest that whilst the utility values from the equation are high, these higher-than-expected values may accurately reflect CF patients' assessments of their own HRQoL. Furthermore, they represent the best available data for the subset of CF patients *F508del* homozygous and 12+ years of age.

As shown in the one way sensitivity analysis, the key assumption in the model is the impact of LUM-IVA on rate of $ppFEV_1$ decline after the study period, which is due to the large amount of uncertainty in this parameter. However, the only and best data available to estimate the effect of LUM-IVA on $ppFEV_1$ rate of decline over time is the calculated rate of decline from the 48 week combined TRAFFIC, TRANSPORT and PROGRESS studies. Rate of decline was tested extensively in scenario and one-way analyses leading to ICERs increasing to £236,000 in the most conservative scenario tested. The model includes several conservative assumptions, one of which is that after the 24-week study period the model does not assume any changes in weight-for-age *z* scores, although continued increases were observed after 24 weeks. Another conservative assumption is using the most robust data source for SoC rate of decline when other studies suggest these rates could be higher (9).

As the only available treatment that targets the underlying cause of disease in CF patients homozygous for the *F508del*-CFTR mutation, LUM-IVA offers meaningful and sustainable clinical and HRQoL benefits to these patients. By targeting the underlying cause of disease and improving multiple clinically meaningful outcomes, the model projects that LUM-IVA will lead to substantial improvements in long-term health outcomes, including increased time in

better health states, significant reduction in pulmonary exacerbations and lung transplants, and ultimately improving the life expectancy for these patients.

6. Assessment of factors relevant to the NHS and other parties

As stated in the UK 2015 CF registry (5), it is anticipated that 2,748 patients will be eligible for treatment with LUM-IVA in England in the first year.

This figure is based on the sum of paediatric and adult patients estimated to be eligible for treatment with LUM-IVA:

- There are 4,455 actively treated adult patients (>16 years old) in England and 50.6% of these patients being homozygous *F508del* patients. This results in 2,254 active adult patients eligible for LUM-IVA.
- It is also estimated that of the paediatric patients (<16 years old), 27% will be aged between 12 and 15, therefore of the 3,621 paediatric patients 975 are assumed to be within this age range. Of these patients 50.6% are assumed to be *F508del* homozygous, resulting 494 paediatric patients eligible for treatment with LUM-IVA.

The distribution of patients by age is shown in Table 87.

Table 87: Distribution of CF patients by age

Age	Patient numbers
2	288
3	276
4	279
5	239
6	278
7	248
8	217
9	238
10	225
11	226
12	201
13	237
14	231
15	258
16	246
Total	3441
Total ≥ 12	927

Source: Annual CF registry report (5)

The calculation of the eligible patient numbers is shown in Table 88.

Table 88: Calculation of prevalent patient number

Population	Active CF Patients in England	Active CF patients in England aged 12+	Active CF patients who are aged 12+ and *F508del* homozygous in England
Adult	4,455	4,455	2,254
Paediatric	3,621	975*	494

*based on 927 patients aged > 12 and <16 out of 3441 paediatric patients. 927/3441 = 27%

Source: Annual CF registry report (5)

From the UK CF registry, it is known how many patients are aged 11, 10, 9 and 8 (5). These patient numbers represent the incidence of patients becoming eligible for LUM-IVA. Table 89 shows how the incidence has been calculated in years 2 to 5.

Table 89: Calculation of incidence

Year	Current age	Active CF Patients in England	Homozygous *F508del*	Incidence
2	11	226	50.6%	114
3	10	225	50.6%	114
4	9	238	50.6%	120
5	8	217	50.6%	110

Market uptake of LUM-IVA has been incorporated into the budget impact model, it is assumed 40% market share in the first year and 60% in the fifth year, with a 5% increment each year. The budget impact model compares two alternate treatment scenarios, one where LUM-IVA is available in the market place and another where there is no LUM-IVA. The patients not on LUM-IVA will receive SoC and patients on LUM-IVA are assumed to continue treatment with SoC.

The budget impact model, considers the same annual costs considered in the cost effectiveness model, except lung transplant. To align with the cost effectiveness model, an adherence rate of 90% has been applied to LUM-IVA patients. The costs per patient per year are shown in Table 90. The costs and resource use are discussed in section 5.5.3. The model accounts for patient survival based on output from the cost effectiveness model.

Table 90: Annual cost per patient per year within the budget impact model

Treatment	LUM-IVA Drug cost	Disease management	Adverse event management	Liver function tests
LUM-IVA + SoC	£104,000	[redacted]	£72	£21
SoC	£0	[redacted]	£52	£0

The treated patient numbers in the two scenarios are shown in Table 91.

Table 91: Treated patient numbers

		LUM-IVA Available		LUM-IVA Not Available	
	Patient population	**Patients treated with LUM-IVA + SoC**	**Patients treated with SoC alone**	**Patients treated with LUM-IVA + SoC**	**Patients treated with SoC alone**
Year 1	2748	1099	1649	0	2748
Year 2	2814	1266	1548	0	2814
Year 3	2832	1416	1416	0	2832
Year 4	2868	1577	1291	0	2868
Year 5	2889	1733	1156	0	2889

The budget impact results are presented in Table 92. The results show the annual budget impact remains within the same region after the first year, when market uptake is stable. The total budget impact over 5 years is £553,328,00.

Table 92: Budget impact results

	After LUM-IVA introduced into the market place	**Without LUM-IVA introduced into the market place**	**Incremental budget impact**
Year 1	£187,953,681	£97,680,243	£90,273,438
Year 2	£197,367,867	£96,763,442	£100,604,425
Year 3	£206,784,441	£95,946,032	£110,838,409
Year 4	£215,962,099	£95,106,577	£120,855,522
Year 5	£225,079,251	£94,323,043	£130,756,207
Total	£1,033,147,338	£479,819,338	£553,328,000

The model is based on simplifying assumptions, the first one being the exclusion of lung transplant from the budget impact model. The exclusion of lung transplant is considered conservative as it is estimated that the SoC arm would incur more lung transplants, providing a cost offset for LUM-IVA. Additionally the expected number of patients receiving a lung transplant has not been factored into the patient numbers, to align with the exclusion in the costs, it is likely that accounting for lung transplant would reduce the budget impact. Another simplifying assumption is the assumption of an equal rate of mortality between the two treatment arms.

7. References

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8. Appendices

Appendix 1: SPC draft

Appendix 2: Search strategy for relevant studies (clinical evidence)

Appendix 3: Excluded studies clinical systematic review (IVA monotherapy, LUM monotherapy and LUM-IVA combination

Appendix 4: Quality assessment of randomised controlled trials (RCTs)

Appendix 5: Subgroup analysis

Appendix 6: Search strategy for cost-effectiveness studies (section 5.1.1)

Appendix 7: Summary of relevant cost effectiveness studies included in the cost effectiveness systematic review

Appendix 8: Quality assessment of cost-effectiveness studies

Appendix 9: Search strategy for measurement and valuation of health effects

Appendix 10: Summary of relevant utility studies included in the health-related quality of life systematic review

Appendix 11: Search strategy for cost and healthcare resource identification, measurement and valuation

Appendix 12: Summary of relevant studies included in the cost and resource use systematic review

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Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Dear [redacted],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th November 2015 by Vertex Pharmaceuticals. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **21st December 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Martyn Burke, Technical Lead (martyn.burke@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Systematic review inclusion/exclusion criteria:

A1. In the eligibility criteria (Table 7, page 27 of company submission), it states that cross-over and pilot studies were excluded. Please explain why these were excluded and how many studies were excluded?

A2. The inclusion criteria (page 28 of company submission) states that 'Observational studies' were eligible. However, Figure 1 shows that 90 full text records were excluded due to study design. What was the design of these excluded studies?

A3. Infections, hospitalisations, adverse events and health related quality of life (HRQoL) are not specified outcomes in the search or eligibility criteria for the systematic review of clinical effectiveness. BMI, weight and Z-score were also not included in the search. Please explain why there were not specified and whether any studies were therefore likely to be missed?

A4. In Table 7 (page 27 of submission) it states that studies of Standard of Care (SoC) not used in current clinical practice were excluded. Were any studies excluded based on this criteria and what SoC treatments were used in these excluded studies?

TRAFFIC and TRANSPORT trials:

A5. **Priority question:** The TRAFFIC and TRANSPORT trials included participants with FEV_1 40-90% of predicted, at screening ('mild to moderate cystic fibrosis'). Please explain why the range of cystic fibrosis patients entered into the studies was limited to mild to moderate?

A6. **Priority question**: Section 4.7.1.13 (page 60 of submission), reports narratively the results of the change from baseline in the EQ-5D-3L but no data are reported. Please provide data for both trials and the pooled results, if possible in a similar format to the presentation of the CFQR data.

A7. Please describe the process for data extraction and quality assessment (for example number of reviewers).

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A8. Page 34 of the submission states that 'a pre-specified pooled analysis of results from TRAFFIC and TRANSPORT was conducted'. Please provide details of the methods used for pooling the two studies.

A9. For each reported outcome (absolute and relative change in ppFEV1, BMI, CFQR), please provide baseline values, change from baseline and a measure of variance for each group.

A10. Pages 37 and 41 of the submission states that response was defined as at least 5% increase in average relative change from baseline in $ppFEV_1$. Please provide the evidence used as the basis for this definition?

Pulmonary exacerbations:

A11. **Priority question**: Please clarify that the number of patients experiencing events and also the number of events in Table 17 (page 51 of submission) are correct. Please also explain how these events were derived; for example, why is the number of events in row 1 of Table 17 different to the number of events in the pooled arm of Table 16 of the submission?

A12. **Priority question**: What is the annualised pulmonary exacerbation event rate in each arm for the TRAFFIC and TRANSPORT studies? Please provide the rate for individual and pooled data?

Adverse events:

A13. Please explain why the adverse events profile of lumacaftor and ivacaftor combination would differ between patients who are homozygous and heterozygous for the F508del-CFTR mutation?

A14. Please provide adverse event data for Part B of study 105.

Other:

A15. **Priority question:** What is the minimum clinically important difference for absolute change and relative change in $ppFEV_1$?

A16. **Priority question**: Please provide details of the safety analysis set and flow of participants for the analysis in question A8. If possible, please also provide separate flow charts for the efficacy and safety sets, including those patients following on into the PROGRESS study.

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A17. **Priority question**: Please provide the 95% confidence intervals for the rate ratios in Tables 16, 18, 19 of the submission.

A18. On page 25 of your submission it states that there are cystic fibrosis consensus documents on best practice. Please outline the current pathway of care for cystic fibrosis and where you anticipate the lumacaftor and ivacaftor combination to fit into this pathway.

A19. Please provide any additional information available on the mechanism of action of lumacaftor and ivacaftor combination, above that currently presented in the submission.

A20. Outcome data for the 4th secondary outcome, 'Response, defined as ≥5% increase in average relative change from baseline in ppFEV1 at week 16 and at week 24' (page 37 of submission) do not appear to be included in the submission. Please provide these data.

A21. The need for hospitalisation and other treatments are included as outcomes in the NICE scope. Please provide any data on hospitalisations (additional to those already presented for pulmonary exacerbations) and other treatments.

A22. An observational study for the lumacaftor and Ivacaftor Combination (Study to Evaluate Lumacaftor and Ivacaftor Combination Therapy in Subjects 12 Years and Older with Advanced Lung Disease (https://clinicaltrials.gov/show/NCT02390219)) is currently in progress, and includes patients with advanced lung disease, therefore potentially more severe than patients recruited to the TRAFFIC and TRANSPORT trials and who are homozygous for the F508del mutation. Are there any interim results available? If not, please could you provide the protocol for this study?

Section B: Clarification on cost-effectiveness data

Health related quality of life:

B1. **Priority question**: Why were utility decrements not assigned to adverse events other than pulmonary exacerbations, either by including decrements directly to events or including treatment arm as a covariate in the regression equation for utility (Section 5.4.6.1 P107 of company submission). Please rerun this model including treatment as a covariate and report whether there are any differences in utility between the arms not explained by ppFEV1 and pulmonary exacerbations.

B2. Please provide a list of excluded studies for the review of health-related quality of life information. There appear to be two excluded studies which have used a condition-specific measure in people with cystic fibrosis.

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Trial adherence and discontinuation:

B3. **Priority question**: The trial adherence rate of 96.5% was assumed to be too high for standard practice, and thus lowered to 90% for the model. Please provide a justification for including such a reduction, but continuing to use the clinical data based on 96.5% adherence in the trial (effectiveness would presumably be lower with 90% adherence, but this has not been taken into account).

B4. **Priority question**: In the company submission it appears that no further patients would discontinue from treatment after the first 24 weeks. Is there any reason to assume people who persist for the first 24 weeks of treatment would then be at no risk of future discontinuations? Please provide any available trial data for discontinuations in weeks 0-24 and 24-48?

Costs:

B5. **Priority question**: Please provide a rationale for assuming the availability of a generic drug in 12 years and an assumed 89% price reduction for lumacaftor and ivacaftor. The cited publication includes these figures, but does not contain any justification for choosing these values. Were any sensitivity analyses undertaken varying these figures?

B6. What elements primarily make up the 'other costs' in table 56 (page 119 of the company submission)? Is there a reason why 'other costs' appear to be lower for people with ppFEV1 < 40% than for the other two groups?

B7. Information on resource use was collected from a UK-based cystic fibrosis population, which included people carrying the G551D mutation or F508del mutation. Please explain why the disease management costs between these two groups are expected to be similar.

Other:

B8. Please explain why all patients in the model are assumed to be pancreatic insufficient. Please provide any data which supports this assumption from the baseline characteristics of the TRAFFIC and TRANSPORT studies?

B9. Table 42 (page 90 of the company submission) suggests that the log-logistic model is also a plausible fit to the data, but only the Weibull, Gamma and Gompertz are considered further. Please explain why the log-logistic model was excluded at this stage.

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B10. Adverse events, other than mortality, as a result of people receiving lung transplantation, were not considered in the model. Please explain why these events have been excluded and provide details of any peri/post-operative events?

B11. For one of the distributions in the probabilistic sensitivity analysis, the mean value appears to lie outside of the credible interval: Liou equation reference value – mean pancreatic sufficiency (yes = 1) -0.126 [normal distribution (CI 0.16 - 0.17)]. Please explain this result?

Section C: Textual clarifications and additional points

C1. **Priority Question**: Please provide the list price for the lumacaftor and ivacaftor combination therapy if available. According to the confidentiality checklist you submitted with the company submission the price would be available in December 2015.

C2. **Priority Question**: Please remove the 'commercial in confidence' confidential marking from the following:

a. Total costs, incremental costs and ICERs for the for the lumacaftor and ivacaftor combination therapy in your submission. Unless NICE is able to make explicit reference to this material in our publicly available documents, it will not be possible for us to provide a complete and transparent account of the Committee's decision-making and be in line with NICE processes.

b. The information included in the EPAR, trial design (e.g. location, methods, outcomes) and statistical analyses. The EPAR is now in the public domain and as such this information cannot be marked as confidential.

C3. **Priority Question:** Please also remove the 'academic in confidence' marking from the following:

a. The description of comparative results of HRQoL data because the EQ-5D data are transparent.

b. Primary outcomes, for example 'relating to pulmonary exacerbations', unless an intended publication date and location can be provided in the checklist. The same applies to any other data marked as AiC in the company submission and appendices (for example Table 10, page 35 of company submission). If these details are not provided the information cannot be marked as AiC.

C4. Please ensure all confidential information is marked appropriately:

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a. Ensure it is underlined as well as highlighted (see instruction on the first page of this letter).

b. Ensure that table and figure titles and row and column titles in tables are not marked as confidential as it must be transparent within your documents what data are being presented even if they are confidential. Ensure that the page numbers in your updated checklist correspond to the confidential information in your submission

c. Ensure that confidential information contained in your appendices (Appendix 1: SmPC, Appendix 2: Subgroup analyses) is included in the checklist.

Please submit any revised documents (submission, model, appendices) with updated highlighting and redacted versions by **5pm on Monday 21st December**. Please ensure your revised documents are consistent with the principles described in sections 3.1.24 and 3.1.25 of the Guide to the processes of technology appraisal and that you mark any confidential data by following the instructions on the first page of this letter.

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Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Section A: Clarification on effectiveness data

Systematic review inclusion/exclusion criteria:

A1. In the eligibility criteria (Table 7, page 27 of company submission), it states that cross-over and pilot studies were excluded. Please explain why these were excluded and how many studies were excluded?

Pilot studies were excluded as they are generally performed in the very earliest stages of drug development to optimise the design of subsequent pivotal studies. A pilot study is not a hypothesis testing study and results may be prone to bias due to small sample sizes. Therefore, for the purposes of this systematic review it was deemed reasonable to exclude pilot studies.

There were 425 records at 1st pass (title and abstract) and 90 records at 2nd pass that were excluded due to study design. Sub-coding was not undertaken. Therefore, in order to determine how many pilot studies were excluded these records would have to be re-reviewed. Due to the timeframe for response to clarification questions, we are unable to provide this information. However, the rationale provided above for the exclusion of pilot studies is justified in the context of this appraisal.

Cross-over studies were not excluded in the systematic review, this is an error in Table 7 of the original submission.

A2. The inclusion criteria (page 28 of company submission) states that 'Observational studies' were eligible. However, Figure 1 shows that 90 full text records were excluded due to study design. What was the design of these excluded studies?

Whilst the 90 full text studies were assigned the exclusion code of study design, this code encompassed other reasons for exclusion i.e. the focus or the purpose of the study was deemed not relevant and therefore they did not satisfy the eligibility criteria (Table 7, page 27 of company submission). Due to the timeframe for response to clarification questions, we are unable to review the 90 studies to determine the design of each study that was excluded.

A3. Infections, hospitalisations, adverse events and health related quality of life (HRQoL) are not specified outcomes in the search or eligibility criteria for the systematic review of clinical effectiveness. BMI, weight and Z-score were also not included in the

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search. Please explain why there were not specified and whether any studies were therefore likely to be missed?

A separate search specifically for HRQoL data was conducted and so HRQoL data beyond the CFQ-R was not sought in this systematic literature review. Adverse events, BMI and weight were considered to be likely reported in tabulations within the paper, rather than in the abstract or indexing, so not incorporating these in the strings was not considered likely to result in papers being missed. Infections and hospitalisations, as AE/SAE data, were thought most likely to be reported with safety data in the main text of the paper. Whilst some of the outcomes were not included in the eligibility criteria (Table 7 of the original submission), Vertex can confirm that none of the outcomes were used to select the studies at 1st and 2nd pass. As such, it was a broad and comprehensive systematic literature review covering any outcomes on the basis of the required population and interventions. Therefore, Vertex believe that there are no relevant studies that have been missed.

A4. In Table 7 (page 27 of submission) it states that studies of Standard of Care (SoC) not used in current clinical practice were excluded. Were any studies excluded based on this criteria and what SoC treatments were used in these excluded studies?

At 1st pass, 26 SoC studies were excluded based upon this criteria. Of these studies aztreonam (AZLI) was the most frequently reported (6 studies). Others included: ceftazidime (3 studies), gene therapy (2 studies), hyaluronic acid (2 studies), ataluren (2 studies), corticosteroids (2 studies), clarithromycin (2 studies), meropenem (2 studies), aminoglycoside (1 study), cysteamine (1 study), lucinactant (1 study), l-arginine (1 study) and glutathione (1 study).

TRAFFIC and TRANSPORT trials:

A5. **Priority question:** The TRAFFIC and TRANSPORT trials included participants with FEV_1 40-90% of predicted, at screening ('mild to moderate cystic fibrosis'). Please explain why the range of cystic fibrosis patients entered into the studies was limited to mild to moderate?

As in virtually all clinical studies in CF, it was necessary to work within upper and lower limits of percent predicted FEV_1 as inclusion criteria in order to standardise the patient population ($ppFEV_1$ ≥40 and ≤90). While CF patients homozygous for F508del demonstrate progression of disease with age and have a decreased life expectancy, the mechanism of action of LUM-IVA would be expected to be of benefit to any patient with this genotype regardless of their current status of lung function or other signs of disease progression.

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Indeed, subpopulation analyses confirmed that in both pivotal studies, and in the pooled analysis, LUM-IVA combination therapy resulted in improvements in ppFEV$_1$ regardless of baseline spirometry measurements. A substantial number of patients had FEV$_1$ values that had fallen to below 40% of predicted at baseline (post screening), offering the opportunity to assess response in this clinically important subgroup that is often neglected in Phase 3 trials due to concerns around increased risk of adverse events (1). A total of 81 patients with ppFEV$_1$ <40 were enrolled in the study and were included in the analyses (1). The clinical benefit and safety profile observed with LUM-IVA in this group of patients with severe lung dysfunction was comparable to the overall patient population.

A6. **Priority question**: Section 4.7.1.13 (page 60 of submission), reports narratively the results of the change from baseline in the EQ-5D-3L but no data are reported. Please provide data for both trials and the pooled results, if possible in a similar format to the presentation of the CFQR data.

Absolute change from baseline in EQ-5D-3L utility score is presented in Figure 1, pooled across TRAFFIC and TRANSPORT. Actual values for the individual studies are presented in Table 1.

Figure 1: Absolute change in EQ-5D utility score: TRAFFIC and TRANSPORT (pooled)

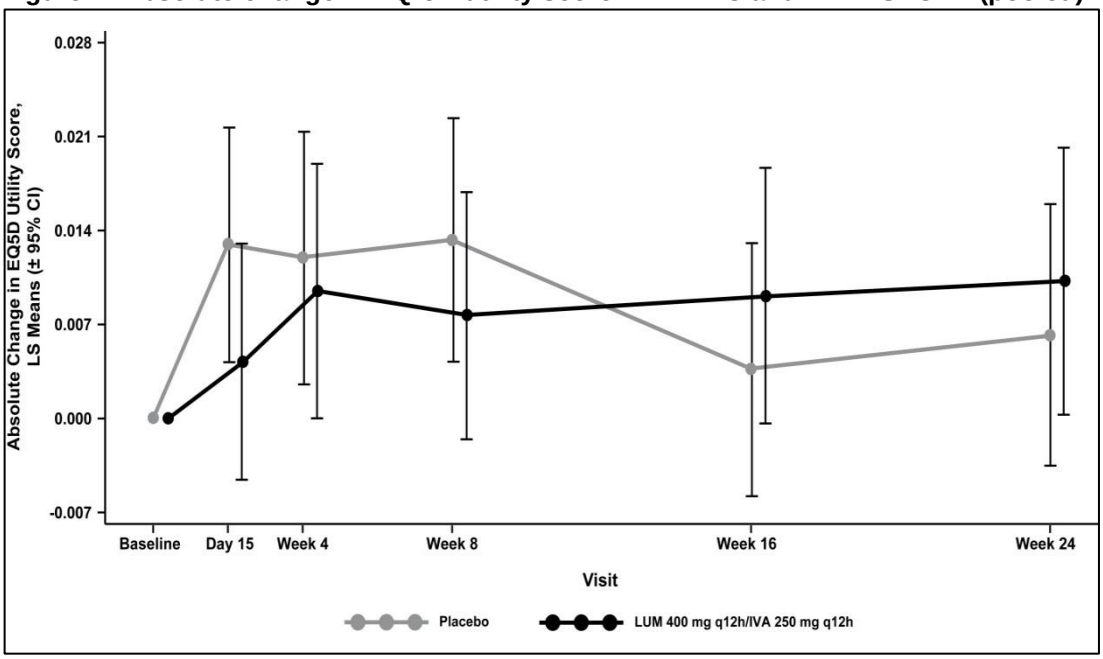

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Table 1: Absolute change from baseline in EQ-5D

	TRAFFIC		TRANSPORT	
	Placebo N=184	LUM 400 mg-IVA 250 mg N=182	Placebo N=187	LUM 400 mg-IVA 250 mg N=187
N	179	170	183	176
Baseline Mean (SD)	0.9237 (0.104)	0.9217 (0.098)	0.9171 (0.10837)	0.9267 (0.10462)
Absolute change at week 24 [LS mean(SE)]	0.0006 (0.0074)	0.01 (0.0076)	0.0117 (0.00673)	0.0108 (0.00683)
LS mean Diff, 95% CI	--	0.0095 (-0.0109, 0.0298)	--	-0.0009 (-0.0192, 0.0174)
p-value vs. placebo	--	0.3613	--	0.9214

As outlined in Table 1, patients in TRAFFIC and TRANSPORT had very high baseline EQ-5D values (mean >0.91 across all groups). As described in our original submission these high baseline values lead to ceiling effects in responses to the EQ-5D.

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A7. Please describe the process for data extraction and quality assessment (for example number of reviewers).

Extraction of included studies and quality assessment was carried out in parallel by two independent reviewers and any discrepancies reconciled by a third reviewer. The systematic review was undertaken in accordance with CRD guidance for undertaking reviews in health care: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf

The quality assessment results for the Phase 2 and Phase 3 studies that are reported in the submission are provided in Appendix 4 of the submission.

A8. Page 34 of the submission states that 'a pre-specified pooled analysis of results from TRAFFIC and TRANSPORT was conducted'. Please provide details of the methods used for pooling the two studies.

As stated on page 34 of the original submission dossier, the study design and methods of analysis for the Phase 3, pivotal studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks) were almost identical, with the exception of inclusion of ambulatory electrocardiography screening (TRAFFIC only) and adolescent PK assessments (TRANSPORT only). Data from TRAFFIC and TRANSPORT were integrated in 2 common databases, one for pooled efficacy in subjects with CF (integrated summary of efficacy [ISE – Phase 3]) and one for pooled safety in subjects with CF (integrated summary of safety [ISS – Phase 3]). The Analysis Data Model (ADaM) was based on Vertex ADaM Guideline and Standard Data Tabulation Model (SDTM) Guideline. The integrated databases were created by using pooled SDTM from each clinical study. For all adverse events, coding was under MedDRA version 17.0 for the Phase 3 ISS. Concomitant medication was pooled for the database containing data for subjects with CF only, coding was based on the WHODDE March 2014 version for concomitant medication for Phase 3 ISE/ISS.

The following analysis sets were defined for ISE and ISS: Full Analysis Set (FAS) for ISE and Safety Set for ISS. Unless otherwise specified, summary tables for the ISE were performed on the FAS; summary tables for the ISS were performed on the Safety Set.

The definitions of the analysis variables and corresponding analyses methods are the same for those that already exist in the original individual study statistical analysis plan.

A9. For each reported outcome (absolute and relative change in ppFEV$_1$, BMI, CFQR), please provide baseline values, change from baseline and a measure of variance for each group.

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In the submission dossier, change from baseline and measure of variance for each group were not provided; however, the data were provided in Table 16 of the Summary of Clinical Efficacy (2) (page 62 and 63; reference 20 of original submission), and are shown in the tables below.

For $ppFEV_1$, baseline values are provided in Table 13 (page 46) of the original submission dossier; Table 14 (page 49) of the original submission dossier provides the treatment difference only. For $ppFEV_1$, data for absolute change from baseline are shown in Table 2; data for relative change from baseline are shown in Table 3.

Table 2: Absolute change from baseline in $ppFEV_1$, FAS population

Absolute change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Within-group change (SE)	**2.16 (0.53) P<0.0001**	-0.44 (0.524) P = 0.4002	**2.85 (0.54) P<0.0001**	-0.15 (0.539) P = 0.7744	**2.49 (0.38) P<0.0001**	-0.32 (0.376) P = 0.3983
Mean treatment difference (95% CI)	**2.6 (1.2, 4.0) p<0.001**	-	**3.0 (1.6, 4.4) p<0.001**	-	**2.8 (1.8, 3.8) p<0.001**	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Bold text indicates statistical significance.

Data in blue were available in the original submission dossier Table 14 (page 49)

Table 3: Relative change from baseline in $ppFEV_1$, FAS population

Relative change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Within-group change (SE)	**3.99 (0.92) P<0.0001**	-0.34 (0.91) P = 0.7113	**5.25 (0.96) P<0.0001**	0.00 (0.96) P = 0.9983	**4.64 (0.67) P<0.0001**	-0.17 (0.66) P = 0.8030
Mean treatment difference (95% CI)	4.3 (1.9, 6.8) P = 0.0006	-	5.2 (2.7, 7.8) P<0.0001	-	4.8 (3.0, 6.6) P<0.0001	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Bold text indicates statistical significance.

Data in blue were available in the original submission dossier Table 15 (page 50)

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For BMI, baseline values are provided in Table 13 (page 46) of the original submission dossier; Table 21 (page 57) of the original submission dossier provides the treatment difference only. For BMI, data for absolute change from baseline are shown in Table 4.

Table 4: Absolute change from baseline in BMI, FAS population

Absolute change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Within-group change (SE)	**0.32 (0.071) P<0.0001**	**0.19 (0.070) P = 0.0065**	**0.43 (0.066) P<0.0001**	0.07 (0.066) P = 0.2892	**0.37 (0.048) P<0.0001**	**0.13 (0.048) P = 0.0066**
Mean treatment difference (95% CI)	0.13 (-0.07, 0.32) P = 0.1938	-	**0.36 (0.17, 0.54) P = 0.0001**	-	**0.24 (0.11, 0.37) P = 0.0004**	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Bold text indicates statistical significance.

Data in blue were available in the original submission dossier Table 21 (page 57)

For CFQ-R, mean baseline values are:

- *69.29 (SD 17.4) for LUM-IVA, and 70.54 (SD 16.03) for placebo in TRAFFIC*
- *67.36 (SD 18.5) for LUM-IVA, and 67.05 (SD 18.4) for placebo in TRANSPORT*
- *68.31 (18.0) for LUM-IVA, and 68.78 (17.3) for placebo pooled TRAFFIC and TRANSPORT*

Table 23 (page 59) of the original submission dossier provides the treatment difference only. The data for absolute change from baseline are shown in Table 5.

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Table 5: Absolute change from baseline in CFQ-R respiratory domain, FAS population

Absolute change (percentage points)	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Within-group change (SE)	**2.60 (1.192) P = 0.0295**	1.10 (1.161) P = 0.3423	**5.66 (1.169) P<0.0001**	**2.81 (1.153) P = 0.0152**	**4.10 (0.834) P<0.0001**	**1.88 (0.818) P = 0.0213**
Mean treatment difference (95% CI)	1.5 (-1.69, 4.69) P = 0.3569	-	2.9 (-0.27, 5.98) P = 0.0736	-	2.2 (-0.01, 4.45) P = 0.0512	-

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Data in blue were available in the original submission dossier Table 23 (page 59)

A10. Pages 37 and 41 of the submission states that response was defined as at least 5% increase in average relative change from baseline in $ppFEV_1$. Please provide the evidence used as the basis for this definition?

There are no agreed explicit response criteria in CF. The 5% difference in $ppFEV_1$ between the LUM-IVA + SoC treatment arms relative to SoC alone was used for power/sample size calculations in TRAFFIC and TRANSPORT to determine statistical significance. As such it is not a measure of clinical response but rather an arbitrary measure of effect size to assess the probability of Type I error and estimate the target number of patients required for these Phase 3 pivotal studies.

Pulmonary exacerbations:

A11. **Priority question**: Please clarify that the number of patients experiencing events and also the number of events in Table 17 (page 51 of submission) are correct. Please also explain how these events were derived; for example, why is the number of events in row 1 of Table 17 different to the number of events in the pooled arm of Table 16 of the submission?

Vertex Pharmaceuticals confirm that the number of patients experiencing events and also the number of events in Table 17 (page 51 of the submission) are correct as are the number of events and rate ratios in Table 16. Annualised (per 48 weeks) event rates in both tables are calculated using binomial regression models [Negative binomial regression model for the active treatment period = study (TRAFFIC vs TRANSPORT), treatment, sex, age (<18 vs >=18 years), percent predicted FEV_1 at screening (<70 vs >=70), with log (time on study) as offset]. However, the pooled TRAFFIC/TRANSPORT placebo + SoC event rate of 1.19 presented in Table 17 of the submission is slightly different to the 1.14 event rate

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presented for TRAFFIC/TRANSPORT pooled in Table 16 as the model used to generate the data in the latter analysis excluded treatment group from the model.

A12. **Priority question**: What is the annualised pulmonary exacerbation event rate in each arm for the TRAFFIC and TRANSPORT studies? Please provide the rate for individual and pooled data?

The number of pulmonary exacerbations was determined using negative binomial regression models that included treatment, study, sex, age group at baseline, and $ppFEV_1$ severity at screening. Hence there is no straightforward method for adjustment of event rates.

Table 6 presents the annualised (per 48 week) event rates in each arm for TRAFFIC and TRANSPORT as well as pooled TRAFFIC/TRANSPORT.

Table 6: Annualised (per 48 week) event rates in TRAFFIC, TRANSPORT and the pooled analysis

	Placebo	LUM-IVA
TRAFFIC		
Event Rate (per 48 weeks)	1.07	0.71
Rate Ratio vs. placebo (95% CI)	--	0.66 (0.47, 0.93), P=0.02
TRANSPORT		
Event Rate (per 48 weeks)	1.18	0.67
Rate Ratio vs. placebo (95% CI)	--	0.57 (0.42, 0.76), P<0.001
TRAFFIC/TRANSPORT Pooled		
Event Rate (per 48 weeks)	1.14	0.70
Rate Ratio vs. placebo (95% CI)	--	0.61 (0.49, 0.76) P<0.0001

The annualised rate of pulmonary exacerbations (0.64) in the PROGRESS study (presented on page 51 of the original submission dossier), is the event rate through 48 weeks of treatment. All annualised rates of events presented in the original submission dossier are calculated per 48 weeks.

Adverse events:

A13. Please explain why the adverse events profile of lumacaftor and ivacaftor combination would differ between patients who are homozygous and heterozygous for the F508del-CFTR mutation?

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The heterozygous population is not included in the licensed indication for LUM-IVA. However, the adverse event profile of LUM-IVA does not differ between patients who are heterozygous for the F508del mutation in the LUM-IVA Phase 2 trial (study 809-102), and in the Phase 3 programme (see presentation by M Boyle at ECFSC 2013). Phase 2 studies were conducted with lumacaftor monotherapy and lumacaftor and ivacaftor combination therapy in CF subjects homozygous or heterozygous for the F508del-CFTR mutation.

A14. Please provide adverse event data for Part B of study 105.

Adverse event data for Part B of the PROGRESS study are provided in Table 12-13 (page 167) and Table 12-15 (page 172) of CSR Study 105 (3) provided as a reference in the original submission.

A15. **Priority question:** What is the minimum clinically important difference for absolute change and relative change in $ppFEV_1$?

There is no empirically, agreed minimum clinically important difference for absolute and relative changes in $ppFEV_1$. This is because CF is a chronic, heterogeneous condition and establishing an MCID would not be clinically appropriate.

The chronic nature of CF means that it is not only the acute (short-term) change in $ppFEV_1$ which is clinically relevant, but also disease progression, i.e. $ppFEV_1$ rate of decline over time, which has been shown to decrease by 1-3 percentage points per annum in CF patients. Liou et al, found that each 1 percentage point reduction in $ppFEV_1$ increases the risk of death over 5 years by 4% (4).

In addition - the heterogeneity of CF means that what is clinically important in terms of $ppFEV_1$ change may vary from patient to patient. For example, for some patients with $ppFEV_1$ above 100 maintaining (i.e. no worsening) of their $ppFEV_1$ is clinically important, while for other patients with very low pulmonary function, increasing $ppFEV_1$ above the threshold for lung transplant could be the most clinically important outcome.

It is important to note that because CF is a multi-organ, systemic disease that the three main goals of CF treatment (i.e. $ppFEV_1$, pulmonary exacerbations and weight gain, which are independent risk factors for mortality), will vary between patients – i.e. $ppFEV_1$ change is not necessarily the most clinically relevant outcome for some patients – e.g. it could be weight gain for children or avoiding pulmonary exacerbations for other patients.

A16. **Priority question**: Please provide details of the safety analysis set and flow of participants for the analysis in question A8. If possible, please also provide separate

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flow charts for the efficacy and safety sets, including those patients following on into the PROGRESS study.

The Full Analysis Set (FAS) is all subjects who received at least one dose of study drug. In efficacy analyses these subjects are summarised in treatment arms based on the randomisation assignment (regardless of what treatment they actually received). This is the set on which the efficacy analyses were performed. The Safety Set is all subjects who received at least one dose of study drug. In safety analysis these subjects are summarised in treatment arms according the treatment they actually received. For those who received more than one treatment, they are summarised in the lowest dose of active drug that they received. The numbers in each of the treatment arms in the safety set, and thus those characterised as LUM 400 mg-IVA 250 mg, are slightly different than the FAS for efficacy analyses. This is because one subject randomised to placebo received at least one dose of LUM 400 mg-IVA 250 mg (and was analysed as part of the latter) and one subject randomised to LUM 400 mg-IVA 250 mg received at least one dose of LUM 600 mg-IVA 250 mg (and was analysed as part of the latter). The patient flow is shown Table 7 (for completeness, the patients assigned to the LUM 600 mg-IVA 250 mg dose are also shown).

Table 7: Patient flow in the full analysis set and safety set

FAS	Placebo	LUM 600 mg-IVA 250 mg	LUM 400 mg-IVA 250 mg	Total
Pooled	371	368	369	1108
TRAFFIC	184	183	182	549
TRANSPORT	187	185	187	559
Safety Set	Placebo	LUM 600 mg-IVA 250 mg	LUM 400 mg-IVA 250 mg	Total
Pooled	370	369	369	1108
TRAFFIC	184	183	182	549
TRANSPORT	186	186	187	559

The disposition of patients assigned to placebo or LUM 400 mg-IVA 250 mg are shown in Table 8.

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Table 8: Disposition of patients assigned to placebo or *LUM 400 mg-IVA 250 mg*

Disposition	Placebo	LUM 400 mg-IVA 250 mg
All Subjects Set (randomised or dosed)	374	376
Randomised but never dosed	3	7
Safety Analysis Set	370	369
Full Analysis Set (FAS)	371	369
Discontinued treatment	9	25
Completed treatment	362	344
Completed study	367	356

Among the FAS (all randomised subjects who received any amount of study drug) during either TRAFFIC or TRANSPORT, 358 patients in the placebo arm (96.5% of FAS, includes 3 patients in the observational cohort) and 349 patients in the LUM-IVA arms (94.6% of FAS, includes 8 patients in the observational cohort) who were enrolled in the PROGRESS study.

A17. **Priority question**: Please provide the 95% confidence intervals for the rate ratios in Tables 16, 18, 19 of the submission.

The 95% confidence intervals for the rate ratios have now been included in Table 9, Table 10 and Table 11 (Table 16, 18 and 19 of the original submission).

Table 9: Number of pulmonary exacerbations through Week 24, TRAFFIC and TRANSPORT, FAS population

Pulmonary exacerbations	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (rate per 48 weeks)	**73 (0.71)**	**112 (1.07)**	**79 (0.67)**	**139 (1.18)**	**152 (0.70)**	**251 (1.14)**
Rate ratio 95% CI P value	**0.66 0.47,0.93 p=0.02†**	**-**	**0.57 0.42,0.76 p<0.001†**	**-**	**0.61 0.49,0.76 p<0.001**	**-**

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

† p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy.

Bold text indicates statistical significance.

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Table 10: Number of pulmonary exacerbations requiring hospitalisation through Week 24, FAS population

Pulmonary exacerbations requiring hospitalisation	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	**17 (0.14)**	46 (0.36)	**23 (0.18)**	59 (0.46)	**40 (0.17)**	105 (0.45)
Rate ratio± 95% CI P value	**0.38 0.22,0.67 p=0.0008**	NA	**0.39 0.24,0.64 p=0.0002**	NA	**0.39 0.26,0.56 p<0.0001**	NA

Abbreviations: CI, confidence interval; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, not applicable; SoC, standard of care.

± Figures are rounded to 2 decimal places

Bold text indicates statistical significance.

Table 11: Number of pulmonary exacerbations requiring IV antibiotics through Week 24, FAS population

Pulmonary exacerbations requiring IV antibiotics	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	**33 (no estimate*)**	62 (no estimate*)	**31 (0.23)**	87 (0.64)	**64 (0.25)**	149 (0.58)
Rate ratio± 95% CI P value	**NA - p=0.0050**	NA -	**0.36 0.24,0.54 p<0.0001**	NA	**0.44 0.32,0.59 p<0.0001**	NA

Abbreviations: CI, confidence interval; IV, intravenous; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, not applicable; SoC, standard of care.

± Figures are rounded to 2 decimal places

Bold text indicates statistical significance.

* The event rate per year could not be estimated because the negative binomial distribution model did not converge.

A18. On page 25 of your submission it states that there are cystic fibrosis consensus documents on best practice. Please outline the current pathway of care for cystic fibrosis and where you anticipate the lumacaftor and ivacaftor combination to fit into this pathway.

There is no standard pathway of care for CF; physicians take an individualised approach to the treatment of CF patients, with treatment tailored according to the current needs of the patient. The UK Cystic Fibrosis Trust has published consensus documents on best practice in the management of CF:

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(http://www.cysticfibrosis.org.uk/media/126838/Publications_List_2013.pdf) *(5); recommendations on the use of chronic medications for maintenance of lung health are provided in the CF pulmonary guidelines:* (http://www.cysticfibrosis.org.uk/media/448939/cd-standards-of-care-dec-2011.pdf) *(6, 7).*

LUM-IVA is intended for chronic use as an adjunct therapy to the medications that are currently used as SoC for CF management; it will not replace SoC treatments in clinical practice. Treatment with LUM-IVA can be initiated at any point in the patient treatment pathway in line with its licensed indication. Early initiation of treatment may benefit patients given the disease progression over time that is characteristic of CF.

The UK Cystic Fibrosis Trust consensus documents on best practice outline the following medications for routine use in CF treatment: aerolised antibiotics, anti-inflammatory agents, macrolide antibiotics, antistaphylococcal antibiotics and bronchodilators, consistent with that outlined in the original submission to NICE (7).

A19. Please provide any additional information available on the mechanism of action of lumacaftor and ivacaftor combination, above that currently presented in the submission.

As previously outlined in the original submission the F508del mutation primarily prevents processing and trafficking of the CFTR protein product to the cell surface, but also impaired activity of the CFTR protein at the apical cell surface, due to low channel open probability.

Lumacaftor is a corrector that increases the delivery of CFTR protein at the cell surface by improving the processing and trafficking of F508del protein to the cell surface through action on the membrane-spanning domain 1 of the protein. In vitro experiments (8, 9) have shown that lumacaftor has the following effects:

- *Protected a subdomain of membrane-spanning domain (MSD1) from proteolytic digestion, suggesting that it alters the protein conformation of MSD1 to result in a more stable folded form*
- *Improved processing in the endoplasmic reticulum, allowing a fraction of the F508del-CFTR in the ER to form a more compact protease-resistant conformation, consistent with improved folding of F508del-CFTR*
- *Improved maturation in human bronchial epithelial cells*
- *Increased the residence time of F508del-CFTR protein to the surface of cultured human bronchial epithelial cells isolated from patients with CF homozygous for* F508del*, which increases F508del-CFTR quantity, and suggests that lumacaftor-corrected F508del-CFTR is not recognised as unfolded by the peripheral protein quality control mechanism.*

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Ivacaftor is an orally administered CFTR potentiator that has been demonstrated to increase the channel open probability (or gating) of CFTR at the cell surface to enhance total ion (chloride) transport in vitro (10).

Thus lumacaftor and ivacaftor have shown additive effects on chloride transport in cultured human bronchial epithelial cells isolated from patients with CF who are homozygous for F508del-CFTR. They have also been shown to increase the airway surface liquid height in cultured human bronchial epithelial cells isolated from patients with CF who are homozygous for F508del-CFTR.

A20. Outcome data for the 4th secondary outcome, 'Response, defined as ≥5% increase in average relative change from baseline in ppFEV$_1$ at week 16 and at week 24' (page 37 of submission) do not appear to be included in the submission. Please provide these data.

The ≥5% increase is an arbitrary threshold, as previously described in responses to question A10 and A15 there is no empirically, agreed minimum clinically important difference for absolute and relative changes in ppFEV$_1$. This is because CF is a chronic, heterogeneous condition and establishing an MCID would not be clinically appropriate.

However, as the data below (Table 12) demonstrates in terms of odds ratios, a patient's probability of reaching/exceeding this arbitrary threshold when treated with LUM-IVA is roughly double the probability of doing so on SoC treatment alone.

Table 12: Patients ≥5% increase in average relative change from baseline in ppFEV$_1$ at Week 16 and Week 24, FAS population

Response	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA N = 182	**Placebo N = 184**	**LUM-IVA N = 187**	**Placebo N = 187**	**LUM-IVA N = 369**	**Placebo N = 371**
Patients with ≥5% relative improvement in percent predicted FEV$_1$	37	22	41	23	39	22
Odds ratio 95% CI P value	2.1 1.3, 3.3 p=0.002	- - -	2.4 1.5, 3.7 P<0.001†	- - -	2.2 1.6, 3.1 p<0.001	- - -

Abbreviations: CI, confidence interval; IVA, ivacaftor every 12 hours; LUM, lumacaftor every 12 hours.
† p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy.
Bold text indicates statistical significance.

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A21. The need for hospitalisation and other treatments are included as outcomes in the NICE scope. Please provide any data on hospitalisations (additional to those already presented for pulmonary exacerbations) and other treatments.

LUM-IVA is intended for use as an adjunct to SoC and as such, will not replace SoC treatments in clinical practice.

Among the Safety Set, differences were analysed between the placebo-treated and LUM-IVA-treated patients in terms of medications taken during the treatment emergent period.

Prior to first dose, 113 (30.5%) patients in the placebo arms and 144 (39.0%) patients in the LUM-IVA arms were not using inhaled antibiotics. During the treatment-emergent period, 24 (21.2%) of the non-users in the placebo arm and 21 (14.6%) of the non-users in the LUM-IVA arm went on to use inhaled antibiotics chronically, which is defined as use during 25% or more of the treatment-emergent period).

Prior to first dose, 29 (7.8%) patients in the placebo arms and 29 (7.9%) patients in the LUM-IVA arms were not using an inhaled bronchodilator. During the treatment-emergent period, 4 (13.8%) of the non-users in the placebo arm and none of the non-users in the LUM-IVA arm went on to use an inhaled bronchodilator chronically.

In addition to the hospitalisation data on pulmonary exacerbations reported in the original submission, Table 13 details hospitalisations not related to pulmonary exacerbations that occurred during TRAFFIC and TRANSPORT.

Table 13: **Hospitalisations not related to pulmonary exacerbations that occurred during TRAFFIC and TRANSPORT**

	Placebo		LUM-IVA	
	No. of Patients	**Events (Event Rate/Year)**	**No. of Patients**	**Events (Event Rate/ Year)**
Planned Hospitalisations for CF	18	18 (0.10)	13	17 (0.09)
Unplanned Hospitalisations	19	20 (0.11)	18	19 (0.10)

A22. An observational study for the lumacaftor and Ivacaftor Combination (Study to Evaluate Lumacaftor and Ivacaftor Combination Therapy in Subjects 12 Years and Older with Advanced Lung Disease (https://clinicaltrials.gov/show/NCT02390219)) is currently in progress, and includes patients with advanced lung disease, therefore potentially more severe than patients recruited to the TRAFFIC and TRANSPORT trials and who are homozygous for the F508del mutation. Are there any interim results available? If not, please could you provide the protocol for this study?

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The primary objective of study VX14-809-106 is to evaluate the safety and tolerability of LUM-IVA combination therapy in CF subjects 12 years and older and advanced lung disease and who are homozygous for the F508del-CFTR mutation; the secondary objective of this study is to evaluate the efficacy of LUM-IVA combination therapy. This study is ongoing and interim results are not yet available. The protocol is attached for your information.

One should note though that subpopulation analyses confirmed that in both pivotal studies (TRAFFIC/TRANSPORT), and in the pooled analysis, LUM-IVA combination therapy resulted in improvements in ppFEV$_1$ regardless of baseline spirometry measurements, with 81 patients in total with an FEV$_1$ < 40% predicted at baseline in the phase 3 studies TRAFFIC and TRANSPORT (and 24 patients in the LUM-IVA 400/250mg Q12h group), similar in magnitude to the overall population.

Section B: Clarification on cost-effectiveness data

Health related quality of life:

B1. **Priority question**: Why were utility decrements not assigned to adverse events other than pulmonary exacerbations, either by including decrements directly to events or including treatment arm as a covariate in the regression equation for utility (Section 5.4.6.1 P107 of company submission). Please rerun this model including treatment as a covariate and report whether there are any differences in utility between the arms not explained by ppFEV$_1$ and pulmonary exacerbations.

The impact of adverse events are implicitly applied via the utility regression equation, however this does not explicitly account for differences between the two treatment arms. A utility regression model was run that included ppFEV$_1$, pulmonary exacerbation status and treatment arm. The coefficient associated with treatment arm was small (0.003) and was not statistically significant (p=0.698) indicating that treatment arm was not a strong predictor of EQ-5D index value in these clinical trials after taking ppFEV$_1$ and pulmonary exacerbation status into account. The coefficient associated with the treatment arm could be considered conservative as the coefficient is positive and would ascribe additional benefit to LUM-IVA.

B2. Please provide a list of excluded studies for the review of health-related quality of life information. There appear to be two excluded studies which have used a condition-specific measure in people with cystic fibrosis.

The articles that were excluded during the second pass are reported in Table 14*.*

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Table 14: Articles excluded from the health related quality of life systematic literature review

Author	Title	Reference
Abbott J., Baumann U., Conway S., Etherington C., Gee L., Von Der Schulenburg J.M., Webb K.	Cross cultural differences in health related quality of life in adolescents with cystic fibrosis.	Disability and rehabilitation (2001) 23:18 (837-844). Date of Publication: 15 Dec 2001
Acaster S., Pinder B., Osmond J., Mukuria C.	Mapping the Cystic Fibrosis Questionnaire-Revised (CFQ-R) to a preference based utility index	Journal of Cystic Fibrosis (2013) 12 SUPPL.1 (S129)
Bermudez C.A., Norihisa S., Diana Z., Annette D.D., Jay B., Maria C., Joseph P., Cynthia G., Sappington P., Jonathan D.	Contemporary outcomes of lung transplantation using extracorporeal membrane oxygenation as bridge	Journal of Heart and Lung Transplantation (2013) 32:4 SUPPL. 1 (S266). Date of Publication: April 2013
Blackwell L.S., Quittner A.L.	Daily pain in adolescents with CF: Effects on adherence, psychological symptoms, and health-related quality of life	Pediatric Pulmonology (2014). Date of Publication: 2014
Boling W.	The health of chronically ill children: Lessons learned from assessing family caregiver quality of life	Family and Community Health (2005) 28:2 (176-183). Date of Publication: April/June 2005
Britto M.T., Kotagal U.R., Hornung R.W., Atherton H.D., Tsevat J., Wilmott R.W.	Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis	Chest (2002) 121:1 (64-72). Date of Publication: 2002
Cebrian M., Sole A., Ansotegui E., Pastor A., Pastor J., Peiro S., Pena M.	Comparative study of three health related quality of life instruments in Cystic Fibrosis patients	Journal of Cystic Fibrosis (2010) 9 SUPPL. 1 (S99). Date of Publication: June 2010
Cramm JM;Strating MMH;Roebroeck ME;Nieboer AP;	The Importance of General Self-Efficacy for the Quality of Life of Adolescents with Chronic Conditions	Social Indicators Research
Driscoll K.A., Schatschneider C., McGinnity K., Modi A.C.	Application of dyadic data analysis in pediatric psychology: cystic fibrosis health-related quality of life and anxiety in child-caregiver dyads.	Journal of pediatric psychology (2012) 37:6 (605-611). Date of Publication: Jul 2012
Eidt-Koch D., Mittendorf T., Greiner W.	Cross-sectional validity of the EQ-5D-Y as a generic health outcome instrument in children and adolescents with cystic fibrosis in Germany	BMC Pediatrics (2009) 9 (55) Article Number: 1471. Date of Publication: 28 Aug 2009
Feeley C., Leu R., Rogers A.E.	Sleep in caregivers and children with a chronic illness	Sleep (2015) 38 SUPPL. 1 (A386-A387). Date of Publication: 2015
Feltrim M.I.Z., Rozanski A., Borges A.C.S., Cardoso C.A., Caramori M.L., Pego-Fernandes P.	The Quality of Life of Patients on the Lung Transplantation Waiting List	Transplantation Proceedings (2008) 40:3 (819-821). Date of Publication: April 2008
Finlen Copeland C.A., Vock D.M., Palmer S.M.	The quality of life benefit of lung transplantation: A prospective multi-center analysis	American Journal of Respiratory and Critical Care Medicine (2011) 183:1 Meeting Abstracts. Date of Publication: 1 May 2011
Garriga M., De Blas A., Burreros M., Guallarte P., Perez-Aragon A., Lamas A., Del Campo R., Suarez L.	Probiotic intake improves the gastrointestinal health of cystic fibrosis patients	Journal of Cystic Fibrosis (2013) 12 SUPPL.1 (S6)
Gee L., Abbott J., Conway S.P., Etherington C., Webb	Validation of the SF-36 for the assessment of quality of life in	Journal of Cystic Fibrosis (2002) 1:3 (137-145). Date of Publication:

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Author	Title	Reference
A.K.	adolescents and adults with cystic fibrosis	September 2002
George S., Hoey H.M.C.V., Costigan C., Murphy N., Roche E.F., O'Riordan S.M.P.	Improved health-related quality of life with insulin therapy in children with cystic fibrosis-related diabetes: A prospective cohort study	Hormone Research in Paediatrics (2014) 82 SUPPL. 1 (103). Date of Publication: September 2014
Giraldo Duque I., Navalpotro B., Guarner L., Giralt J., Molero X.	Long term toxicity in patients with chronic pancreatitis treated with single-dose radiotherapy	Radiotherapy and Oncology (2010) 96 SUPPL. 1 (S367). Date of Publication: September 2010
Gloeckl R., Kenn K., Soennichsen A., Sczepanski B., Winterkamp S., Boensch M., Welte T.	Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation	European Respiratory Journal (2014) 44 SUPPL. 58. Date of Publication: 1 Sep 2014
Goldbeck L., Schmitz T.G.	Comparison of three generic questionnaires measuring quality of life in adolescents and adults with cystic fibrosis: The 36-item short form health survey, the quality of life profile for chronic diseases, and the questions on life satisfaction	Quality of Life Research (2001) 10:1 (23-36). Date of Publication: 2001
Gorinova Y., Simonova O., Vinyarskaya I., Samsonova M., Chernikov V.	The measurement of quality of life in children with cystic fibrosis with using russian version of health utility index (HUI) questionnaire	Value in Health (2012) 15:7 (A554). Date of Publication: November 2012
Gorinova Y.V., Samsonova M.S., Simonova O., Vinyarskaya I.V., Chernikov V.V.	First results of health status assessment in children with cystic fibrosis using Russian version of HUI Questionnaire	Journal of Cystic Fibrosis (2012) 11 SUPPL. 1 (S136). Date of Publication: June 2012
Groen H., Van Der Bij W., Koeter G.H., TenVergert E.M.	Cost-effectiveness of lung transplantation in relation to type of end-stage pulmonary disease	American Journal of Transplantation (2004) 4:7 (1155-1162). Date of Publication: July 2004
Hofer M., Fiechter Lienert B., Kurowski T., Boehler A.	Correlation of physical performance and quality of life in adult patients with cystic fibrosis	Respiration (2011) 82:1 (94). Date of Publication: June 2011
Ingerski L.M., Modi A.C., Hood K.K., Pai A.L., Zeller M., Piazza-Waggoner C., Driscoll K.A., Rothenberg M.E., Franciosi J., Hommel K.A.	Health-Related Quality of Life Across Pediatric Chronic Conditions	Journal of Pediatrics (2010) 156:4 (639-644). Date of Publication: April 2010
Janse A.J., Sinnema G., Uiterwaal C.S.P.M., Kimpen J.L.L., Gemke K.J.B.J.	Quality of life in chronic illness: Perceptions of parents and paediatricians	Archives of Disease in Childhood (2005) 90:5 (486-491). Date of Publication: May 2005
Janse A.J., Sinnema G., Uiterwaal C.S.P.M., Kimpen J.L.L., Gemke R.J.B.J.	Quality of life in chronic illness: Children, parents and paediatricians have different, but stable perceptions	Acta Paediatrica, International Journal of Paediatrics (2008) 97:8 (1118-1124). Date of Publication: August 2008
Janse A.J., Uiterwaal C.S.P.M., Gemke R.J.B.J., Kimpen J.L.L., Sinnema G.	A difference in perception of quality of life in chronically ill children was found between parents and pediatricians	Journal of Clinical Epidemiology (2005) 58:5 (495-502). Date of Publication: May 2005
Kenn K., Gloeckl R., Soennichsen A., Sczepanski B., Winterkamp S., Boensch M., Welte T.	Predictors of Success for Pulmonary Rehabilitation in Patients Awaiting Lung Transplantation	Transplantation (2014). Date of Publication: 12 Nov 2014

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Author	Title	Reference
Lahiri T., Herrington H., Diehl S., Landrigan G.	The effect of intranasal dornase alfa on chronic sinusitis in patients with cystic fibrosis: A pilot study	Pediatric Pulmonology (2012) 47 SUPPL. 35 (354). Date of Publication: September 2012
Linertova R., Lopez-Bastida J., Serrano-Aguilar P., Posada-de-la-Paz M.	Social economic burden and health-related quality of life in patients with rare diseases in Europe (BURQOL-RD project). Spanish results	Value in Health (2012) 15:7 (A516-A517). Date of Publication: November 2012
Monti F., Lupi F., Gobbi F., Agostini F., Miano A., Gee L., Abbott J.	Validation of the Italian version of the Cystic Fibrosis Quality of Life Questionnaire (CFQoL), a disease specific measure for adults and adolescents with cystic fibrosis	Journal of Cystic Fibrosis (2008) 7:2 (116-122). Date of Publication: March 2008
Pentek M., Baji P., Pogany G., Brodszky V., Boncz I., Gulacsi L.	Health related quality of life of patients and their caregivers in rare diseases results of the BURQOL-RD project in Hungary	Value in Health (2014) 17:7 (A538). Date of Publication: November 2014
Quittner A.L., Buu A.	Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and *P. aeruginosa* infection	Pediatric Pulmonology (2002) 33:4 (269-276). Date of Publication: 2002
Simonova O., Gorinova Y., Vinyarskaya I., Chernikov V.	Validation of Russian version of health utility index questionnai re in children with cystic fibrosis	Value in Health (2014) 17:7 (A731). Date of Publication: November 2014
Singer J.P., Katz P.P., Dean M.Y., Chen J., Su B., Kern R., Leard L.E., Hays S.R., Kukreja J., Blanc P.D.	Frailty is common in lung transplant candidates and associated with poorer health-related quality of life	Journal of Heart and Lung Transplantation (2013) 32:4 SUPPL. 1 (S43). Date of Publication: April 2013
Smeritschnig B., Jaksch P., Scheed A., Klepetko W.	Qualityof life after lung transplantation in patients with cystic fibrosis: A cross-sectional study	Journal of Heart and Lung Transplantation (2012) 31:4 SUPPL. 1 (S181). Date of Publication: April 2012
Stirling R.G., Pender S., Hore-lacy F., Marshall J.M., Wilson J.	Social participation and social support in adult cystic fibrosis: Important quality of life determinants	Respirology (2012) 17 SUPPL. 1 (41). Date of Publication: April 2012
Suri R;Metcalfe C;Lees B;Grieve R;Flather M;Normand C;Thompson S;Bush A;Wallis C;	Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial.	
Tappenden P., Harnan S., Uttley L., Mildred M., Carroll C., Cantrell A.	Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic *P. aeruginosa* lung infection in cystic fibrosis: Systematic review and economic model	Health Technology Assessment (2013) 17:56 (a-204). Date of Publication: 2013
Targett K., Bourke S., Nash E., Murphy E., Ayres J., Devereux G.	Employment in adults with cystic fibrosis	Occupational medicine (Oxford, England) (2014) 64:2 (87-94). Date of Publication: 1 Mar 2014
Walter E., Kasper D.C.	Cost-effectiveness-analysis of the new-born screening in Austria	Value in Health (2014) 17:7 (A343). Date of Publication: November 2014
Yi M.S., Tsevat J., Wilmott R.W., Kotagal U.R., Britto M.T.	The impact of treatment of pulmonary exacerbations on the health-related quality of life of patients with cystic fibrosis: Does hospitalisation make a difference?	Journal of Pediatrics (2004) 144:6 (711-718). Date of Publication: June 2004

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Author	Title	Reference
Ziaian T., Sawyer M.G., Reynolds K.E., Carbone J.A., Clark J.J., Baghurst P.A., Couper J.J., Kennedy D., Martin A.J., Staugas R.E., French D.J.	Treatment burden and health-related quality of life of children with diabetes, cystic fibrosis and asthma	Journal of Paediatrics and Child Health (2006) 42:10 (596-600). Date of Publication: October 2006

Trial adherence and discontinuation:

B3. **Priority question**: The trial adherence rate of 96.5% was assumed to be too high for standard practice, and thus lowered to 90% for the model. Please provide a justification for including such a reduction, but continuing to use the clinical data based on 96.5% adherence in the trial (effectiveness would presumably be lower with 90% adherence, but this has not been taken into account).

This assumption was driven by real world adherence data for ivacaftor (Kalydeco®) in patients with at least one G551D-CFTR mutation. It is acknowledged this value is lower than that which produces the treatment effect observed in the TRAFFIC and TRANSPORT trials. However, the 2014 cystic fibrosis registry annual report (11) showed that in practice the efficacy of ivacaftor was consistent with the efficacy observed in the trial while having lower adherence (10.5% increase in ppFEV$_1$ in real world evidence (11) compared to 10.6% in the phase 3 trial (12)).

It is assumed that the same efficacy-adherence relationship will be true for LUM-IVA in a homozygous F508del population.

B4. **Priority question**: In the company submission it appears that no further patients would discontinue from treatment after the first 24 weeks. Is there any reason to assume people who persist for the first 24 weeks of treatment would then be at no risk of future discontinuations? Please provide any available trial data for discontinuations in weeks 0-24 and 24-48?

During the 24 weeks of TRAFFIC and TRANSPORT, 25 (6.8%) patients discontinued treatment with LUM-IVA and 9 (2.4%) discontinued treatment with placebo. The pharmacoeconomic model accordingly assumes that 6.8% of patients assigned to LUM-IVA discontinue over the first 24 weeks of treatment.

During the first 24 weeks of PROGRESS, 13 (7.4%) patients who received placebo during TRAFFIC or TRANSPORT discontinued LUM-IVA treatment during PROGRESS. Of those patients who were already receiving LUM-IVA during TRAFFIC or TRANSPORT and who continued to receive it during PROGRESS, 22 (6.5%) discontinued treatment during the first 24 weeks of PROGRESS.

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As described in the original submission, it is difficult to predict a long-term rate of discontinuation based on these short-term data. This inherent uncertainty has been addressed through scenario analysis: The scenario detailed in Section 5.8.3.5 makes the assumption that cumulatively 30% of patients discontinue LUM-IVA treatment within 15 years of treatment initiation, with no further discontinuation beyond that point. The results of the base case and the scenario described above thus provide a range of results that might be expected for different levels of LUM-IVA discontinuation.

Costs:

B5. **Priority question**: Please provide a rationale for assuming the availability of a generic drug in 12 years and an assumed 89% price reduction for lumacaftor and ivacaftor. The cited publication includes these figures, but does not contain any justification for choosing these values. Were any sensitivity analyses undertaken varying these figures?

This assumption has been based on the previous review by Whiting et al. (13) that evaluated ivacaftor as treatment for the G551D mutation.

Similarly to ivacaftor, LUM-IVA is a small molecule and is anticipated to be easy to replicate. Therefore it is realistic to expect there will be generic versions available soon after patent expiry. The 12-year period represents the anticipated residual patent from time of commercialisation.

The 89% price reduction equates to an annual cost of £11,440, which is an approximate price reduction aligned with Whiting et al (13). The 89% price reduction was not included in sensitivity analysis, however reducing the price reduction to 80% resulted in an ICER of £231,504 (Table 15).

Table 15: Model results applying an 80% price reduction following generic entry*

Treatment	Total Cost	Total Life Years	Total QALY	Incremental Cost	Incremental Life Years	Incremental QALY	ICER
SoC	£377,632	10.32	8.92				
LUM-IVA	£1,176,973	13.78	12.38	£799,341	3.46	3.45	£231,504

**these results include the change to disease management costs discussed in question B6.*

B6. What elements primarily make up the 'other costs' in table 56 (page 119 of the company submission)? Is there a reason why 'other costs' appear to be lower for people with $ppFEV_1$ < 40% than for the other two groups?

Costs are derived from the following data from Lambrelli et al.

- *Lambrelli et al 2012 (14) – resource use by disease severity for hospitalisations*
- *Lambrelli et al data on file (15) - cost data for cystic fibrosis patients*

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Lambrelli et al. (14) published a poster in 2012 that detailed the resource implications of cystic fibrosis, the poster suggested the types of resource studied included pharmacotherapy, health care professional visits, hospitalisations, surgical and diagnostic procedures. Costs are reported as "hospitalisation cost" and "other cost"; based on access to raw data from this study. Thus all resources included in the list above, less the hospitalisations, were included within the "other cost" category.

Whilst answering this question a mathematical error was identified in the calculation of the hospitalisation costs. Table 16 below details the updated costs inputs after the mathematical error was corrected.

Table 16: Disease management direct medical costs (inflated to 2014 GBP)

ppFEV$_1$	**Categories**	**SoC**	**LUM-IVA + SoC**
ppFEV$_1$ > 70%*	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
ppFEV$_1$ 40-69%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
ppFEV$_1$ < 40%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]

As the hospitalisation costs are lower than in the original submission, the cost-offsets associated with LUM-IVA are reduced. The impact of this change is approximately a £14,000 increase in the ICER, the results are shown in the table below in Table 17.

As this change impacts all cost-effectiveness results, a new set of analyses containing a new base case (Section 1), PSA (Section 2.1), OWSA (Section 2.2) and scenario analyses (Section 2.3) are presented below.

1. Base-case results

1.1 Base-case incremental cost effectiveness analysis results

Using base-case assumptions the model projects that LUM-IVA + SoC will lead to an improvement in projected median survival of 7.69 years and increase mean residual life expectancy (undiscounted life-years gained) by 9.42 years. The median survival with SoC is projected to be 36.15 years, which is consistent with the projected median survival of 40.1 years reported in the UK CF Trust Registry (11), when considering patients who are homozygous for the *F508del* mutation and alive at age 12 years of age for a comparison of

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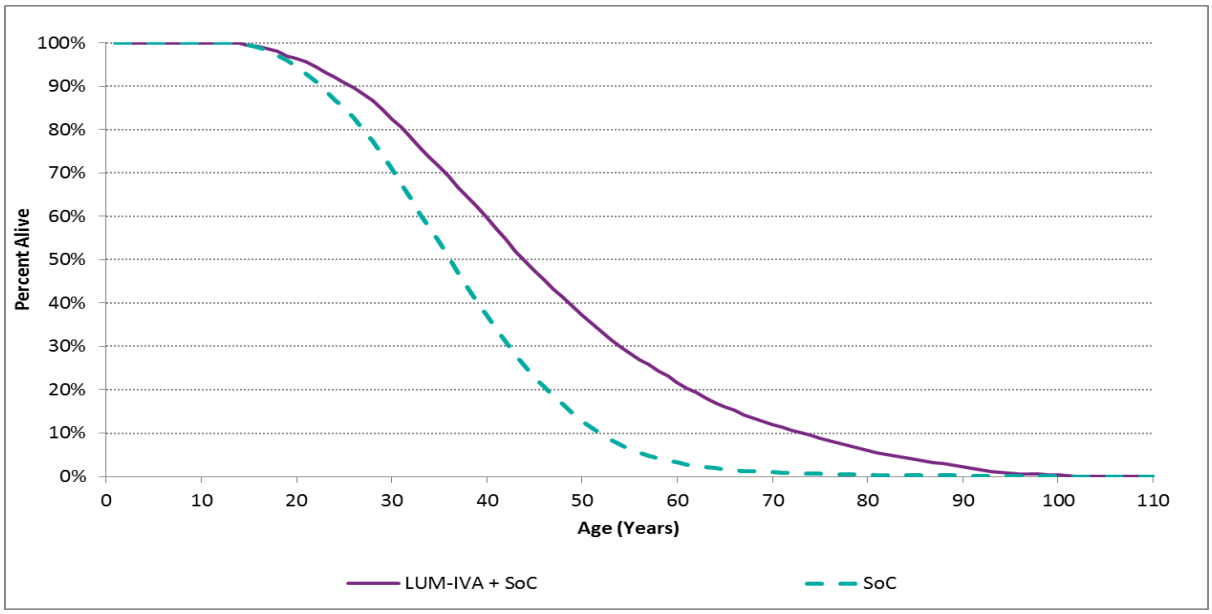
characteristics of the study patients with the whole of the UK CF registry). The projected 8-year increase in projected survival for patients treated with LUM-IVA represents a significant advancement in the care of patients with CF age 12 years and older who are homozygous for the *F508del* mutation.

The base case survival predicted from the model is shown in Figure 2.

Figure 2: Base case survival



Model results suggest that treatment with LUM-IVA will provide a survival benefit across all patient age groups, with LUM-IVA improving mean life years by at least 44%. This projected survival benefit is larger in younger cohorts, highlighting the importance of treating early. The mean residual life years for the different age groups is shown in Figure 3.

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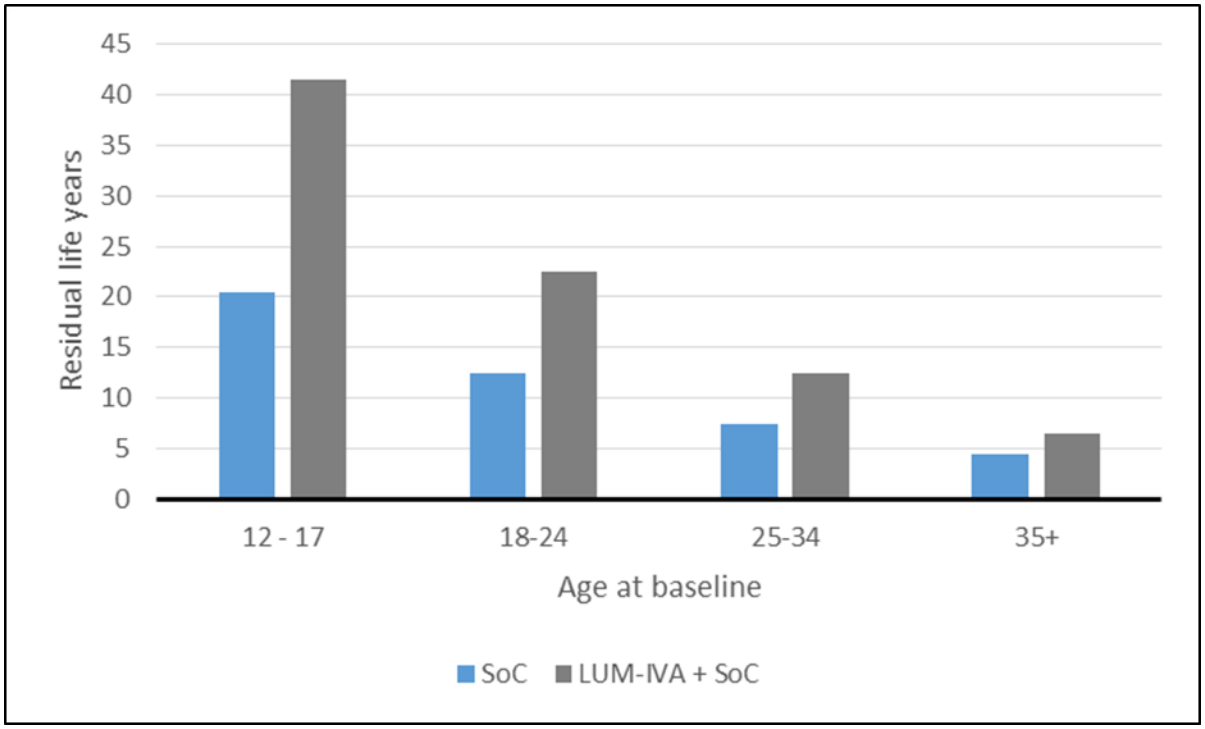
Figure 3: Mean residual life years by baseline age category



Abbreviations: SoC, standard of care.

The base case cost-effectiveness results are presented in Table 17. The results show that LUM-IVA + SoC is associated with improved health outcomes. LUM-IVA + SoC is associated with 12.38 discounted QALYs compared to 8.92 QALYs in the SoC arm. Costs are higher in the LUM-IVA + SoC arm than the SoC arm, with incremental costs equal to £753,570. The incremental cost in combination with the incremental QALYs result in an ICER equal to £218,248. The results based on a cost per life year gained are also shown in Table 17, these results show the discounted incremental life years to be 3.46 and an ICER of £217,627 per life-year gained.

Table 17: Base-case results

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92					
LUM-IVA	£1,131,202	13.78	12.38	£753,570	3.46	3.45	£217,627	£218,248

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost effectiveness analysis

1.2 Clinical outcomes from the model

Results suggest that patients on LUM-IVA preserve 8.37 percentage points of $ppFEV_1$ over their lifetimes, losing an average of 13.51 percentage points compared to 21.89 percentage

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points for patients on SoC. The model projects that LUM-IVA increases the amount of time spent with $ppFEV_1$ in the normal/mild range ($ppFEV_1 \geq 70\%$) and reduces the time spent with $ppFEV_1 < 30\%$, a common $ppFEV_1$ threshold for recommendation of lung transplantation. The annual exacerbation rate is reduced by 63% representing the combined impact of LUM-IVA on $ppFEV_1$ and pulmonary exacerbations. The model predicts that the percentage of patients undergoing lung transplantation is reduced by 73% with LUM-IVA + SoC compared to SoC and more than doubles the time to transplant among those who receive a lung transplant (Table 18).

Table 18: Health outcomes

Comparator	LUM-IVA + SoC	SoC	Incremental
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 $ppFEV_1 \geq 70\%$	4.08	1.14	2.94
Mean Years with $ppFEV_1$ between 70% and 40%	17.10	8.84	8.26
Mean Years with $ppFEV_1$ between 40% and 30%	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 Undergoing Lung Transplant	1.82%	6.80%	-4.98%
Mean Years Until Lung Transplant	46.49	19.34	27.14

Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second.

The detailed cost result table (

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Table 19) shows that the majority of increased costs are due to LUM-IVA. The incremental drug cost was £757,776, in comparison to the total incremental cost of £753,570. Over the lifetime, LUM-IVA + SoC will reduce transplantation costs by £9,442. Lower disease management costs are estimated for patients treated with LUM-IVA + SoC vs. SoC despite the projected increase in survival. Liver function testing and AE related costs are marginal.

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Table 19: Summary of predicted resource use by category of cost

Item	Cost LUM-IVA + SoC	Cost SoC	Increment	Absolute increment	% absolute increment
Drug Cost	£757,776	£0	£757,776	£757,776	98.10%
Disease Management Cost	£371,202	£366,556	£4,647	£4,647	0.60%
Lung Transplant Cost	£1,097	£10,539	-£9,442	£9,442	1.22%
Adverse Event	£995	£537	£458	£458	0.06%
Liver Function Test	£131	£0	£131	£131	0.02%
Total	£1,131,202	£377,632	£753,570	Total absolute increment	100%

Abbreviations: SoC, standard of care

2. Sensitivity analyses

2.1 Probabilistic sensitivity analyses

A scatter plot of the output from the probabilistic sensitivity analysis is shown in Figure 4. This shows 1,000 iterations and the associated uncertainty. Of the 1,000 iterations most of the data points fall between 1 and 6 QALYs gained and £500,000 and £1,000,000 incremental costs, with simulations leading to higher QALYs also leading to higher costs, reflecting the survival benefit of LUM-IVA. In every simulation, SoC is associated with less cost and fewer QALYs than the LUM-IVA treatment arms.

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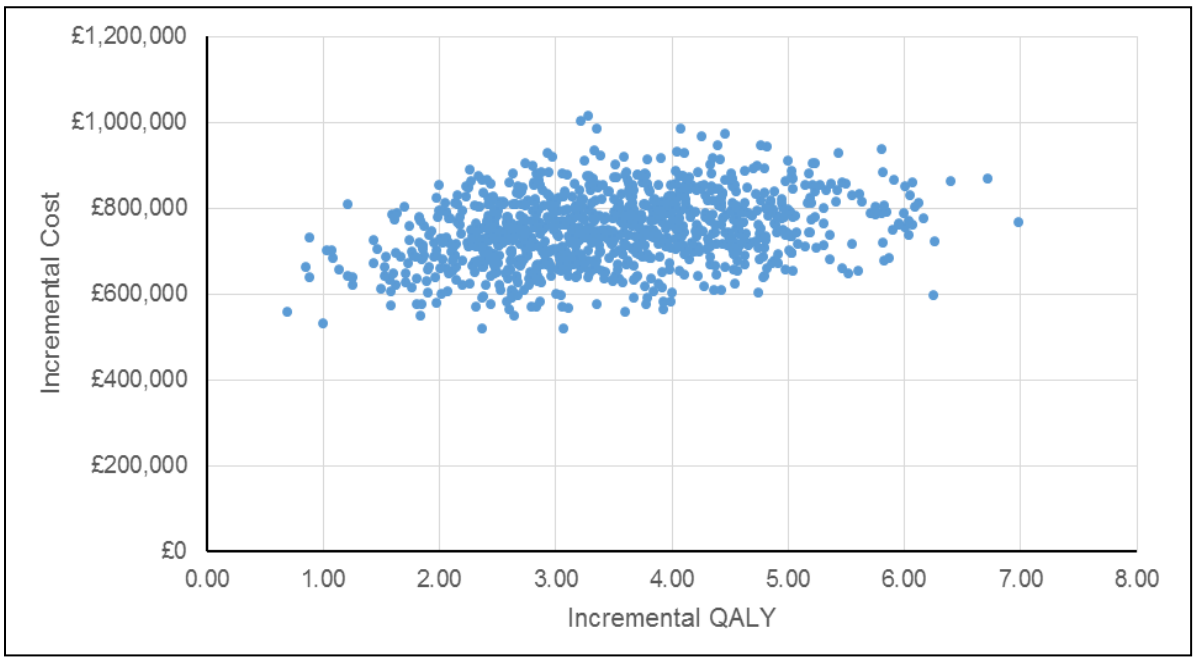
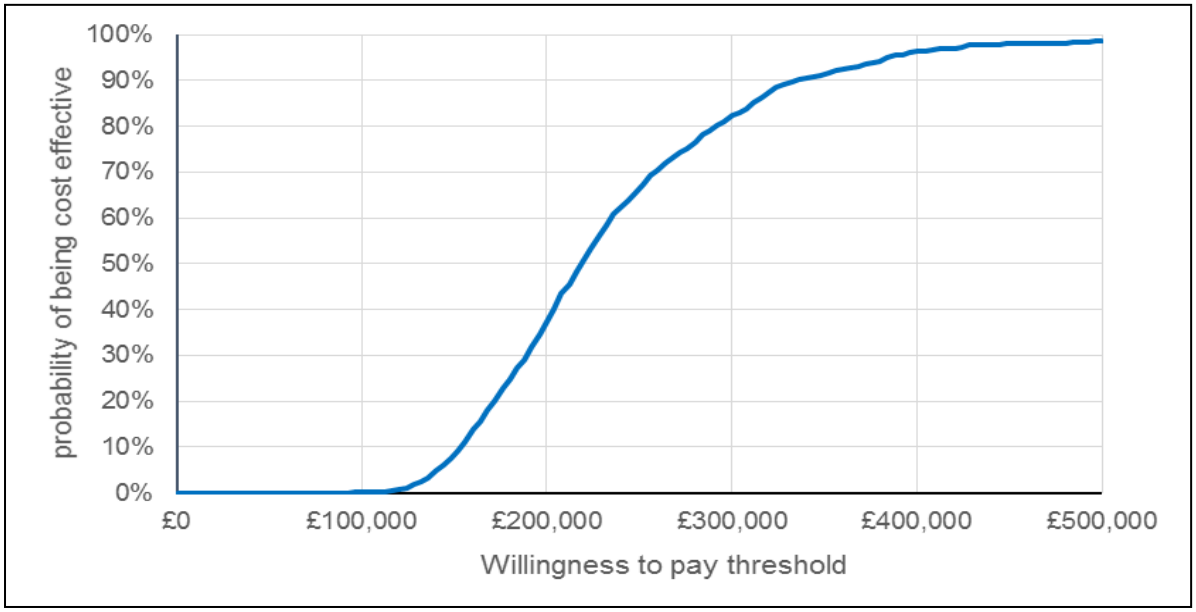
Figure 4: Cost Effectiveness Scatter Plot



Abbreviations: QALY, quality adjusted life years

To determine the probability of LUM-IVA + SoC being cost-effective at different cost-effectiveness thresholds, a cost effectiveness acceptability curve (CEAC) is reported in Figure 5. The CEAC shows that for a threshold above £220,000, LUM-IVA + SoC is likely to be a cost effective treatment (at a threshold of £220,000 there is a 50.9% probability that LUM-IVA + SoC is cost effective) and at a threshold of £336,000, LUM-IVA + SoC has a >90% probability of being cost-effective.

Figure 5: Cost Effectiveness Acceptability Curve



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The mean results of the probabilistic analysis are comparable to the base case results (Table 20). This demonstrates the results of the probabilistic analysis are robust.

Table 20: Mean Results from the Probabilistic Sensitivity Analysis

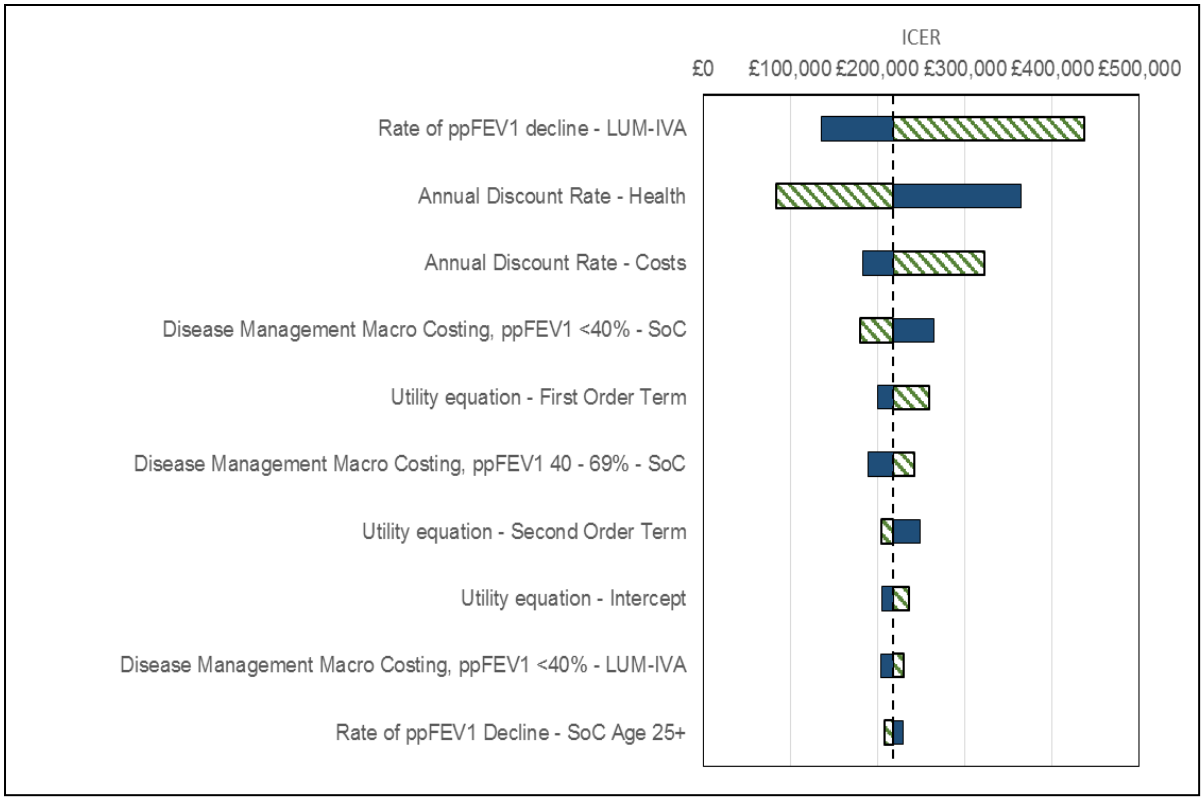
Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,152	10.34	8.94				
LUM-IVA + SoC	£1,125,946	13.82	12.42	£748,794	3.48	3.49	£214,838

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care.

2.2 Deterministic sensitivity analysis

Tornado diagrams have been presented in Figure 6 for the comparison between LUM-IVA + SoC vs SOC alone. The tornado diagrams are presented in order of impact on the ICER.

Figure 6: One-way sensitivity analysis



Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second; ICER, incremental cost effectiveness analysis.

The one-way sensitivity analysis shows that the model is most sensitive to the rate of decline for LUM-IVA, discount rates and disease management costs.

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2.3 Scenario analysis

A series of scenario analyses are included to test for uncertainties around assumptions and data limitations.

2.3.1 Discount rates

The model sensitivity to discount rates is due to the sustained health impacts of LUM-IVA for CF patients homozygous for the *F508del* mutation over a long time horizon, and the projected survival benefit, part of which occurs far in the future. Thus in accordance with the NICE decision support unit for products that meet these criteria a discount rate of 1.5% was tested (16).

The model has been shown to be sensitive to the discount rate, see Figure 6. Using a discount rate of 1.5% across both health outcomes and costs reduces the ICER by over £60,000 compared to the base case.

Table 21: Scenario Analysis – annual discount rate of 1.5%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£467,146	12.60	10.83				
LUM-IVA + SoC	£1,381,148	18.50	16.56	£914,001	5.90	5.72	£159,678

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.2 Rate of ppFEV$_1$ decline

To test the long term extrapolation of ppFEV$_1$ two alternative scenarios have been considered, one that that uses an alternative rate of decline for LUM-IVA and second that alters rate of decline for SoC.

The first scenario uses the only available data beyond one year for a CFTR modulator therapy. The data is based on treatment with ivacaftor in a population of patients with a *G551D CFTR* mutation (17). Sawicki et al. conducted an analysis where *G551D* patients receiving ivacaftor in the PERSIST clinical trial were compared with an aged-matched and propensity score matched control group of homozygous *F508del* patients who were not receiving any CFTR modulator therapy. Patients were followed up over a three-year period. The analysis found that the mean rate of ppFEV$_1$ decline in the ivacaftor-treated group was 53% lower than that of the control group. 48-week data from the LUM-IVA PROGRESS clinical trial saw a ppFEV$_1$ rate of decline very similar to that seen in the first year of PERSIST, which suggests that LUM-IVA could also have a similar ppFEV$_1$ trend for subsequent years. As such, assuming the same relative impact of rate of decline for LUM-IVA (53% reduction in rate of decline compared to standard of care) was tested in a scenario analysis.

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The results show that when using the data from ivacaftor, the results are in a similar range as the base case. The comparability in results is expected due to the comparability of rates of $ppFEV_1$ decline estimated by the two approaches. The results are shown in Table 22.

Table 22: Scenario Analysis – Sawicki et al. Rate of $ppFEV_1$ decline

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92				
LUM-IVA + SoC	£1,126,882	13.50	12.10	£749,250	3.19	3.17	£236,284

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

An alternative scenario was tested using a different reference to inform the SoC rate of decline for patients 18+ years of age (annual rate of decline of -2.47). In this scenario the rate of decline for SoC was derived from an analysis by de Boer et al. This study assessed exacerbations and rate of decline in 446 patients over a 3-year time horizon. The patients were from Ontario, Canada. A mean $ppFEV_1$ was calculated from the publication using a weighted average of the estimates reported. The results from using the rate of decline calculated from de Boer et al. are shown in Table 23.

Table 23: Scenario Analysis – de Boer et al. Rate of $ppFEV_1$ decline

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£350,697	9.41	8.07				
LUM-IVA + SoC	£1,131,202	13.78	12.38	£780,505	4.37	4.30	£181,366

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Two alternative scenarios have been conducted to test a plausible range around the rate of decline. The current rate of decline is associated with a large confidence interval, it is likely that as PROGRESS reports more observations the confidence interval will be reduced. A range of ±20% around the mean has been tested.

Table 24: Scenario Analysis – +20% Rate of $ppFEV_1$ decline for LUM-IVA

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92				
LUM-IVA + SoC	£1,121,358	13.45	12.04	£743,727	3.13	3.11	£238,795

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

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Table 25: Scenario Analysis – -20% Rate of ppFEV$_1$ decline for LUM-IVA

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92				
LUM-IVA + SoC	£1,140,078	14.16	12.76	£762,446	3.84	3.83	£199,003

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

The results show that increasing the rate of decline by 20% increases the ICER by £20,000 whereas decreasing the rate of decline by 20% reduces the ICER by £19,000.

2.3.3 Pulmonary exacerbations

Pulmonary exacerbations are a composite of patient signs and symptoms that often result in the need for aggressive treatment, including the use of IV antibiotics that may or may not require hospitalisation. To date, there is no generally accepted objective definition of a pulmonary exacerbation.

A rate ratio of 0.61 for the rate of pulmonary exacerbation in patients treated with LUM-IVA +SoC vs. SoC was calculated from the pooled results of the TRAFFIC and TRANSPORT trials where exacerbations were defined using the modified Fuchs criteria. The model uses an equation published by Goss et al. to predict the rate of pulmonary exacerbation for each patient in each cycle. However, the definition of pulmonary exacerbations used in the TRAFFIC and TRANSPORT trials is different from that used in the study conducted by Goss et al. The latter defined a pulmonary exacerbation as a CF-related pulmonary condition requiring admission to hospital or use of home IV antibiotics. Therefore, the base case adopted the pulmonary exacerbation rate ratio (0.442) of LUM-IVA +SoC vs. SoC derived from post-hoc analyses of the TRAFFIC and TRANSPORT trial data based a pulmonary exacerbation definition that closely mirrored that used in the study conducted by Goss et al. (18).

As a more conservative assumption than the base case, the rate ratio of 0.61 in the risk of pulmonary exacerbation (any type) calculated from the pooled results of all exacerbations recorded in TRAFFIC and TRANSPORT is applied to the predicted pulmonary exacerbation rate for patients on LUM-IVA + SoC for the entire model time horizon until treatment discontinuation. The results are shown in Table 26.

Table 26: Scenario Analysis – Pulmonary exacerbation rate ratio from TRAFFIC and TRANSPORT results using all protocol-defined pulmonary exacerbations

Technologies	Total costs	Total	Total	Incremental	Incremental	Incremental	ICER

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		LYG	QALYs	costs (£)	LYG	QALYs	versus baseline (QALYs)
SoC	£377,632	10.32	8.92				
LUM-IVA + SoC	£1,114,588	13.50	12.09	£736,957	3.19	3.16	£233,018

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.4 Utility

The utility equation described has been used in the base case as this represents the data from the LUM-IVA studies and provides the best source of evidence for utilities in this patient population. However, a paper by Tappenden et al., (2014) was identified in the quality of life literature reviews. The paper by Tappenden et al. (19) reported utilities by $ppFEV_1$ strata, which have been tested as an alternative. The utility values tested are reported in Table 49 of the submission. The results of this scenario are reported in Table 27.

The results show the ICER to be slightly higher that the base case, this is due to the utilities being lower but having a wider range between health states.

Table 27: Scenario Analysis – Utility Values Tappenden et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	7.97				
LUM-IVA + SoC	£1,131,202	13.78	11.09	£753,570	3.46	3.13	£241,109

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

As well as the paper by Tappenden et al. (19) a paper by Acaster et al., (20) which reported health state utilities for patients with CF was identified. These utility values have been tested in a scenario analysis, and results are shown in Table 28. The results show the ICER to be approximately £70,000 higher than the base case.

Table 28: Scenario Analysis – Utility Values Acaster et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	6.86				
LUM-IVA + SoC	£1,131,202	13.78	9.52	£753,570	3.46	2.66	£283,458

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

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The utility values used by Whiting et al. have been tested in the model. These values were derived from a study by Gee et al (21). The methodology used to calculate these utilities is unclear and there is little discrimination between higher and lower $ppFEV_1$ categories. Therefore, the results from this analysis should be considered with caution, these results are shown in Table 29.

Table 29: Scenario Analysis – Utility Values Whiting et al.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	7.61				
LUM-IVA + SoC	£1,131,202	13.78	10.39	£753,570	3.46	2.78	£270,870

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

As an alternative to the base case assumption, an additional scenario was tested using EQ-5D data from the TRAFFIC and TRANSPORT trials. This additional scenario uses the EQ-5D index values by $ppFEV_1$ strata. The results are shown in Table 30.

Table 30: Scenario Analysis – EQ-5D index values by $ppFEV_1$ strata from TRAFFIC and TRANSPORT

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	9.25				
LUM-IVA + SoC	£1,131,202	13.78	12.52	£753,568	3.46	3.27	£230,769

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.5 Rate of discontinuation

In reality, patients may discontinue LUM-IVA treatment for various reasons. Although deriving appropriate discontinuation rates over long periods of time is difficult, a scenario is tested that includes discontinuation beyond the trial period. This scenario makes the assumption that cumulatively 30% of patients discontinue LUM-IVA treatment within 15 years of treatment initiation, with no further discontinuation beyond that point. An annualised discontinuation rate of 1.9% is applied to each year following the 24-week trial period until the end of year 15.

For patients who discontinue LUM-IVA during the first 24 weeks, treatment efficacy is assumed to be the same for patients who remain on treatment by week 24. No efficacy loss is applied for the initial 24-week period. Beyond 24 weeks, after a patient discontinues LUM-IVA treatment, $ppFEV_1$ decline is assumed to be the same as for patients on SoC.

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Treatment impact on pulmonary exacerbation rate is stopped immediately after LUM-IVA treatment discontinuation.

The results are shown in Table 31. The results show increasing the discontinuation in the model improves the cost effectiveness results, this is due to removing patients from treatment and subsequently reducing the drug cost.

Table 31: Scenario Analysis – Rate of discontinuation

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,092,338	13.68	12.27	£714,705	3.36	3.34	£213,910

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.6 Survival curves

To test the uncertainty in the underlying survival function for the UK CF Registry population, the Gompertz parametric curve has been tested. The results are shown in Table 32. Using this Gompertz parametric curve reduces incremental projected median survival by about two years (5.7 years when using Gompertz compared to 7.7 when using the base case), and subsequently reduces the incremental QALYs and incremental cost. Despite the reduction in survival estimates, costs and QALYs are reduced by similar proportions and therefore the ICER calculated in this scenario is comparable to the ICER obtained when using the Weibull curve in the base case.

Table 32: Scenario Analysis – Gompertz Curve

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£292,406	8.23	7.18				
LUM-IVA + SoC	£939,058	11.08	10.00	£646,653	2.85	2.83	£228,830

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.7 Excluding disease management costs incurred during additional survival

Based on the base case modelling results, treatment with LUM-IVA + SoC increased the projected median survival by 7.7 years, during which time patients receiving LUM-IVA also incurred disease management costs. This scenario omits any additional disease management costs that would be incurred as a consequence of extending life for patients treated with LUM-IVA. Any of those disease management costs which are accrued for each

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individual patient on LUM-IVA, past the time at which the patient's "clone" on SoC dies, are omitted. The purpose of this scenario is to remove possible penalties for extension of life. Drug costs of LUM-IVA continue to be included over the patient's lifetime.

The results are shown in Table 33. This analysis shows that when excluding the disease management costs incurred during the incremental survival reduces the ICER to £186,361.

Table 33: Scenario Analysis – Omission of disease management costs incurred during additional survival

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92				
LUM-IVA + SoC	£1,021,104	13.78	12.38	£643,473	3.46	3.45	£186,361

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

2.3.8 Adherence

A scenario has been included testing the TRAFFIC and TRANSPORT level of adherence, observed at 96.5%. The base case uses a level of 90% adherence, based on observed adherence levels for Kalydeco.

Table 34: Scenario Analysis – Adherence 96.5 %

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,633	10.32	8.92				
LUM-IVA + SoC	£1,185,593	13.78	12.38	£807,960	3.46	3.45	£234,000

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

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3. Subgroup analysis

The TRAFFIC and TRANSPORT trials analysed pre-specified subgroups, as shown in Wainwright et al. it is expected that all patients will benefit from treatment. The cost effectiveness model tests the same subgroups, with the exception of pseudomonas aeruginosa infection status as the model does not differentiate between positive and negative patients.

For each subgroup, the treatment effect for $ppFEV_1$, BMI, weight-for-age z-score and rate ratio for pulmonary exacerbations were analysed. In addition to this, the patients sampled from the patient cohort is restricted to reflect the subgroup, e.g. for the subgroup of Male patients the cohort was restricted to male patients only. The inputs used for the subgroups are shown in Table 35.

Table 35: Subgroup Analysis Inputs

Subgroup	LUM-IVA Sample size from TRAFFIC and TRANSPORT	Mean Absolute Change in FEV_1 Percentage Points From Baseline by 16 Weeks	Pulmonary Exacerbations Rate Ratio	Mean Weight-for-age z-score Change From Baseline by 24 Weeks	Mean BMI Change From Baseline by 24 Weeks
Overall	352	2.81	0.44	0.068	0.24
Age ≥ 12 to <18	93	2.98	0.29	0.06	0.33
Age ≥ 18	259	2.79	0.47	0.07	0.21
$ppFEV_1$ <70%	239	3.26	0.48	0.06	0.17
$ppFEV_1$ ≥ 70%	108	1.86	0.09	0.08	0.34
$ppFEV_1$ < 40%	28	3.3	0.67	0.09	0.29
$ppFEV_1$ ≥ 40%	324	2.77	0.36	0.06	0.23
Male	178	3.19	0.38	0.07	0.24
Female	174	2.46	0.47	0.07	0.24

Abbreviations: BMI, body mass index; $ppFEV_1$, Percent predicted forced expiratory volume in 1 second

3.1 Gender

Sub-analysis by gender shows the ICER does not vary by more than £6,500 from the base case. The projected life-year gain (discounted) for a male population is slightly higher than for a female population, the results are shown in Table 36 and Table 37.

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Table 36: Subgroup Analysis – Male

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£395,492	10.93	9.48				
LUM-IVA + SoC	£1,177,060	14.62	13.16	£781,568	3.68	3.68	£212,205

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 37: Subgroup Analysis – Female

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£374,971	10.18	8.79				
LUM-IVA + SoC	£1,131,958	13.63	12.22	£756,987	3.46	3.43	£220,734

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

3.2 Age

The results for patients stratified by baseline age, show that treating patients earlier results in a lower ICER. The results for the patients aged between 12 and 18 is approximately 20% lower than the base case, the results are shown in Table 38. The results for treating patients with a baseline age greater than 18 is approximately 10% higher than base-case and shown in Table 39.

Table 38: Subgroup Analysis – Age between 12 and 18

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£552,642	14.99	12.86				
LUM-IVA + SoC	£1,459,048	20.10	18.10	£906,406	5.12	5.24	£172,845

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

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Table 39: Subgroup Analysis – Age greater than 18

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£314,107	8.63	7.50				
LUM-IVA + SoC	£1,014,311	11.55	10.35	£700,204	2.92	2.85	£245,279

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

3.3 *Baseline ppFEV$_1$*

The subgroups stratified by baseline ppFEV$_1$ show the highest variance in ICER, however it is important to note that the patient numbers for the baseline ppFEV$_1$ < 40% are very small as these criteria fall outside the inclusion criteria from the TRAFFIC and TRANSPORT trials.

Table 40: Subgroup Analysis – baseline ppFEV$_1$ > 40%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£393,337	10.85	9.40				
LUM-IVA + SoC	£1,176,340	14.53	13.07	£783,003	3.67	3.67	£213,336

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 41: Subgroup Analysis – baseline ppFEV$_1$ < 40%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£231,284	4.92	4.05				
LUM-IVA + SoC	£745,575	6.76	5.76	£514,290	1.84	1.71	£300,688

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 42: Subgroup Analysis – baseline ppFEV$_1$ > 70%

Technologies	Total costs	Total	Total	Incremental	Incremental	Incremental	ICER

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		LYG	QALYs	costs (£)	LYG	QALYs	versus baseline (QALYs)
SoC	£493,464	15.12	13.34				
LUM-IVA + SoC	£1,366,094	19.35	17.72	£872,630	4.24	4.37	£199,481

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Table 43: Subgroup Analysis – baseline ppFEV$_1$ < 70%

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£334,864	8.55	7.30				
LUM-IVA + SoC	£1,053,685	11.81	10.48	£718,821	3.26	3.18	£225,907

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care; ICER, incremental cost effectiveness analysis.

Subgroup analyses demonstrate that in all scenarios LUM-IVA leads to incremental improvements in health outcomes. Results by subgroup do not vary considerably, with ICERs varying between £172,000 and £300,000, which is within the general uncertainty of the model (based on one-way, scenario, and probabilistic sensitivity analyses).

4. Interpretation and conclusions of economic evidence

A lifetime individual patient microsimulation model was constructed to estimate the clinical outcomes (disease progression, residual years of life and QALYs) and direct medical costs (including LUM-IVA cost, disease management, lung transplant and adverse events) of a population of patients with CF age 12 years and older who are homozygous for the *F508del* mutation. The clinical outcomes and costs of patients receiving LUM-IVA in addition to SoC were compared with those receiving SoC alone to reflect projected real world use of LUM-IVA as adjunct therapy, and mimic the clinical studies of LUM-IVA which demonstrated the multiple clinically-meaningful benefits of LUM-IVA above and beyond SoC alone. Patients treated with LUM-IVA were assumed to continue to have access to the same level of SoC, including recommended medications and physical therapy as patients treated with SoC alone.

The individual patient microsimulation found LUM-IVA + SoC to be associated with improved health outcomes, including increased projected median survival, more time spent in higher ppFEV$_1$ states and fewer lung transplants. Specifically, LUM-IVA + SoC is projected to increase median survival by 7.7 years (9.4 undiscounted life-

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years gained) leading to incremental discounted QALYs of 3.45. When considering the incremental cost associated with LUM-IVA + SoC the resulting ICER is £218,248. The results of the model are considered to be generalisable to the CF population indicated for LUM-IVA in England, with UK CF data used where possible. Only in cases where there was a lack of available evidence relevant to England was an alternative reference used. The model was found to validate well when comparing the projected survival produced from the model for a cohort of patients representing the UK CF registry population with the parametric curve fitted to the UK CF registry (see Figure 17).

Sensitivity analysis found the model results to be sensitive to the long term extrapolation of $ppFEV_1$, discount rates and utility values. Several scenario analyses were tested using alternative data sources and the range of ICERs using these alternatives was £280,000 to £160,000. However as described in this section, inputs used in the base-case, and thus corresponding results, utilize the most robust data available. Probabilistic sensitivity analysis showed that the model results were robust, as the mean results were comparable to the base case results.

The utility values generated from the utility equation are based on the EQ-5D values from the TRAFFIC and TRANSPORT studies. Considering the impact CF has on patient's lifestyles and the burden of disease, patients with CF score higher than expected, with a median score of 1. This is a phenomenon that is common in CF and several studies suggest that whilst the utility values from the equation are high, these higher-than-expected values may accurately reflect CF patients' assessments of their own HRQoL. Furthermore, they represent the best available data for the subset of CF patients *F508del* homozygous and 12+ years of age.

As shown in the one-way sensitivity analysis, the key assumption in the model is the impact of LUM-IVA on rate of $ppFEV_1$ decline after the study period, which is due to the large amount of uncertainty in this parameter. However, the only and best data available to estimate the effect of LUM-IVA on $ppFEV_1$ rate of decline over time is the calculated rate of decline from the 48 week combined TRAFFIC, TRANSPORT and PROGRESS studies. Rate of decline was tested extensively in scenario and one-way analyses leading to ICERs increasing to £238,000 in the most conservative scenario tested. The model includes several conservative assumptions, one of which is that after the 24-week study period the model does not assume any changes in weight-for-age z scores, although continued increases were observed after 24 weeks. Another conservative assumption is using the most robust data source for SoC rate of decline when other studies suggest these rates could be higher (22).

As the only available treatment that targets the underlying cause of disease in CF patients homozygous for the *F508del*-CFTR mutation, LUM-IVA offers meaningful and sustainable clinical and HRQoL benefits to these patients. By targeting the underlying cause of disease and improving multiple clinically meaningful outcomes, the model projects that LUM-IVA will lead to substantial improvements in long-term

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health outcomes, including increased time in better health states, significant reduction in pulmonary exacerbations and lung transplants, and ultimately improving the life expectancy for these patients.

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

As stated in the UK 2015 CF registry (11), it is anticipated that 2,748 patients will be eligible for treatment with LUM-IVA in England in the first year.

This figure is based on the sum of paediatric and adult patients estimated to be eligible for treatment with LUM-IVA:

- There are 4,455 actively treated adult patients (>16 years old) in England and 50.6% of these patients being homozygous *F508del* patients. This results in 2,254 active adult patients eligible for LUM-IVA.
- It is also estimated that of the paediatric patients (<16 years old), 27% will be aged between 12 and 15, therefore of the 3,621 paediatric patients 975 are assumed to be within this age range. Of these patients 50.6% are assumed to be *F508del* homozygous, resulting 494 paediatric patients eligible for treatment with LUM-IVA.

The distribution of patients by age is shown in Table 44.

Table 44: Distribution of CF patients by age

Age	Patient numbers
2	288
3	276
4	279
5	239
6	278
7	248
8	217
9	238
10	225
11	226
12	201
13	237
14	231
15	258
16	246

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Total	3441
Total ≥ 12	927

Source: Annual CF registry report (11)

The calculation of the eligible patient numbers is shown in Table 45.

Table 45: Calculation of prevalent patient number

Population	Active CF Patients in England	Active CF patients in England aged 12+	Active CF patients who are aged 12+ and *F508del* homozygous in England
Adult	4,455	4,455	2,254
Paediatric	3,621	975*	494

*based on 927 patients aged > 12 and <16 out of 3441 paediatric patients. 927/3441 = 27%

Source: Annual CF registry report (11)

From the UK CF registry, it is known how many patients are aged 11, 10, 9 and 8 (11). These patient numbers represent the incidence of patients becoming eligible for LUM-IVA. Table 46 shows how the incidence has been calculated in years 2 to 5.

Table 46: Calculation of incidence

Year	Current age	Active CF Patients in England	Homozygous *F508del*	Incidence
2	11	226	50.6%	114
3	10	225	50.6%	114
4	9	238	50.6%	120
5	8	217	50.6%	110

Market uptake of LUM-IVA has been incorporated into the budget impact model, it is assumed 40% market share in the first year and 60% in the fifth year, with a 5% increment each year. The budget impact model compares two alternate treatment scenarios, one where LUM-IVA is available in the market place and another where there is no LUM-IVA. The patients not on LUM-IVA will receive SoC and patients on LUM-IVA are assumed to continue treatment with SoC.

The budget impact model, considers the same annual costs considered in the cost effectiveness model, except lung transplant. To align with the cost effectiveness model, an adherence rate of 90% has been applied to LUM-IVA patients. The costs per patient per year are shown in Table 47. The costs and resource use are discussed in section **Error! Reference source not found.**. The model accounts for patient survival based on output from the cost effectiveness model.

Table 47: Annual cost per patient per year within the budget impact model

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Treatment	LUM-IVA Drug cost	Disease management	Adverse event management	Liver function tests
LUM-IVA + SoC	£104,000	[redacted]	£72	£21
SoC	£0	[redacted]	£52	£0

The treated patient numbers in the two scenarios are shown in Table 48.

Table 48: Treated patient numbers

		LUM-IVA Available		LUM-IVA Not Available	
	Patient population	Patients treated with LUM-IVA + SoC	Patients treated with SoC alone	Patients treated with LUM-IVA + SoC	Patients treated with SoC alone
Year 1	2748	1099	1649	0	2748
Year 2	2814	1266	1548	0	2814
Year 3	2832	1416	1416	0	2832
Year 4	2868	1577	1291	0	2868
Year 5	2889	1733	1156	0	2889

The budget impact results are presented in Table 49. The results show the annual budget impact remains within the same region after the first year, when market uptake is stable. The total budget impact over 5 years is £567,571,728.

Table 49: Budget impact results

	After LUM-IVA introduced into the market place	Without LUM-IVA introduced into the market place	Incremental budget impact
Year 1	£190,306,859	£97,680,243	£92,626,616
Year 2	£199,990,345	£96,763,442	£103,226,903
Year 3	£209,673,691	£95,946,032	£113,727,659
Year 4	£219,112,467	£95,106,577	£124,005,891
Year 5	£228,487,702	£94,323,043	£134,164,659
Total	£1,047,571,066	£479,819,338	£567,751,728

The model is based on simplifying assumptions, the first one being the exclusion of lung transplant from the budget impact model. The exclusion of lung transplant is considered conservative as it is estimated that the SoC arm would incur more lung transplants, providing a cost offset for LUM-IVA. Additionally, the expected number of patients receiving a lung transplant has not been factored into the patient numbers, to align with the exclusion in the costs, it is likely that accounting for lung transplant

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would reduce the budget impact. Another simplifying assumption is the assumption of an equal rate of mortality between the two treatment arms.

B7. Information on resource use was collected from a UK-based cystic fibrosis population, which included people carrying the G551D mutation or F508del homozygous mutation. Please explain why the disease management costs between these two groups are expected to be similar.

The dataset used to estimate costs was derived from a chart review study of CF patients with the G551D mutation in the CFTR gene or F508del homozygous mutation. The low open channel probability that characterises the G551D mutation is functionally similar to the quantity and functional defect of F508del homozygous, leading to a similar phenotype across these populations. As CF disease progression is similar between these two groups and resource use has been shown to be comparable (23), the entire dataset was used to estimate costs in order to utilise what was publically available and maximise sample size.

McKone et. al. (24) analysed US Cystic Fibrosis Foundation Patient Registry data including patients with a G551D mutation and patients homozygous for the F508del mutation. This study found similarities between these two patient groups on clinical characteristics including sweat chloride and pulmonary function. Standardised mortality rates among the two groups were also comparable, suggesting similar rates of disease progression.

Wyatt et. al. (23) analysed two years of chart data for 200 UK patients with CF who were either homozygous for the F508del mutation or had at least one copy of the G551D mutation. This study found that patients in both groups received similar treatment intensity and exhibited high resource utilisation. This study found that both number of hospitalisations and number of hospitalisation days were higher among F508del homozygous patients, suggesting that the resource use data included in the base case may be conservative. This Wyatt study utilises the same dataset used to generate cost data for this NICE submission.

Other:

B8. Please explain why all patients in the model are assumed to be pancreatic insufficient. Please provide any data which supports this assumption from the baseline characteristics of the TRAFFIC and TRANSPORT studies?

Of the patients in the TRAFFIC and TRANSPORT trials approximately 94% of patients were pancreatic insufficient. As the assumption is applied to both treatment

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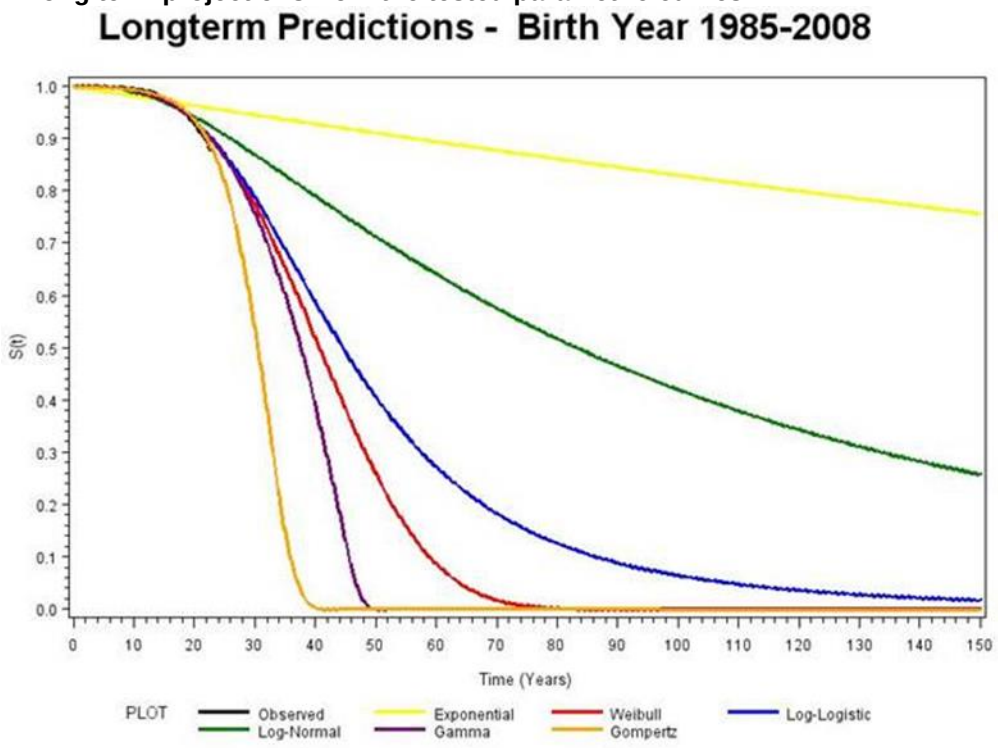
arms in the model, it isn't a big driver of the results. Hence the simplifying assumption that all patients would be pancreatic insufficient was made.

This assumption was validated with clinicians at an advisory board.

B9. Table 42 (page 90 of the company submission) suggests that the log-logistic model is also a plausible fit to the data, but only the Weibull, Gamma and Gompertz are considered further. Please explain why the log-logistic model was excluded at this stage.

While the log-logistic model exhibits a good statistical fit to the observed short-term data, it projected long-term survival that was not clinically plausible. The log-logistic model projected that >10% of the general CF population would survive past 80 years and that some patients would live past 100 years (Figure 7). Therefore, the log-logistic model was excluded from further consideration based on long-term survival estimates.

Figure 7: Long term projections from the tested parametric curves



B10. Adverse events, other than mortality, as a result of people receiving lung transplantation, were not considered in the model. Please explain why these events have been excluded and provide details of any peri/post-operative events?

These events are not included due to the low number of lung-transplants that occur in the model and consequently the low impact this additional complexity would have

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on model results. Additionally, these events are implicitly captured within the post-lung transplant mortality, costs and utility inputs with any further incorporation of these events as separate states likely to lead to double counting.

B11. For one of the distributions in the probabilistic sensitivity analysis, the mean value appears to lie outside of the credible interval: Liou equation reference value – mean pancreatic sufficiency (yes = 1) -0.126 [normal distribution (CI 0.16 - 0.17)]. Please explain this result?

This is a minor error (wrong digit entered in derivation of beta). The correct interval is: 0.1221 – 0.1300

The updated results presented in question B6 incorporate this change. To test the impact of this on the sensitivity analysis a scenario has been tested using the mid-point of the incorrect 95% confidence interval. The results of this analysis are shown below.

Table 50: Model results using the midpoint of the credible interval*

Treatment	Total Cost	Total Life Years	Total QALY	Incremental Cost	Incremental Life Years	Incremental QALY	ICER
SoC	£377,005	10.30	8.91				
LUM-IVA	£1,130,111	13.76	12.36	£753,106	3.46	3.45	£218,243

these results include the change to disease management costs presented in B6 Error! Reference source not found.***

Section C: Textual clarifications and additional points (New submission on Jan 8th Agreed with NICE project team)

C1. **Priority Question**: Please provide the list price for the lumacaftor and ivacaftor combination therapy if available. According to the confidentiality checklist you submitted with the company submission the price would be available in December 2015.

C2. **Priority Question**: Please remove the 'commercial in confidence' confidential marking from the following:

a. Total costs, incremental costs and ICERs for the for the lumacaftor and ivacaftor combination therapy in your submission. Unless NICE is able to make explicit reference to this material in our publicly available documents, it will not be possible for us to provide a complete and transparent account of the Committee's decision-making and be in line with NICE processes.

b. The information included in the EPAR, trial design (e.g. location, methods, outcomes) and statistical analyses. The EPAR is now in the public domain and as such this information cannot be marked as confidential.

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C3. **Priority Question:** Please also remove the 'academic in confidence' marking from the following:

a. The description of comparative results of HRQoL data because the EQ-5D data are transparent.

b. Primary outcomes, for example 'relating to pulmonary exacerbations', unless an intended publication date and location can be provided in the checklist. The same applies to any other data marked as AiC in the company submission and appendices (for example Table 10, page 35 of company submission). If these details are not provided the information cannot be marked as AIC.

C4. Please ensure all confidential information is marked appropriately:

a. Ensure it is underlined as well as highlighted (see instruction on the first page of this letter).

b. Ensure that table and figure titles and row and column titles in tables are not marked as confidential as it must be transparent within your documents what data are being presented even if they are confidential. Ensure that the page numbers in your updated checklist correspond to the confidential information in your submission

c. Ensure that confidential information contained in your appendices (Appendix 1: SmPC, Appendix 2: Subgroup analyses) is included in the checklist.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Cystic Fibrosis Trust
Your position in the organisation: [redacted]
Brief description of the organisation: We are the UK's only national charity dealing with all aspects of cystic fibrosis. We fund research to improve cystic fibrosis care and treatment, and aim to ensure appropriate clinical care and support for people with cystic fibrosis.

The Trust has not received any funding from Vertex Pharmaceuticals for work related to issues relevant to this submission. All Cystic Fibrosis Trust funding received from pharmaceutical manufacturers are carefully considered to ensure they do not breach best practice guidance regarding commercial funding agreements.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Cystic fibrosis is a multi-system, progressive, debilitating and life-limiting disease. Cystic fibrosis kills. The median age at death is just 28. Many will die as teenagers or younger.

In October 2015, the Cystic Fibrosis Trust surveyed 1426 people whose lives are affected by cystic fibrosis: people with the condition (n=248), families, partners and friends.

Our findings confirmed that cystic fibrosis imposes significant and often devastating daily challenges from birth, which affect everyone connected to the person with cystic fibrosis, that get worse with age, and make it difficult to grow, develop and plan for the future.

Additionally, the Cystic Fibrosis Trust hosts and manages the UK CF Registry, which monitors health data from over 10,000 people with cystic fibrosis in the UK, representing over 99% of the patient population. Our submission draws on data from this resource.

Cystic fibrosis necessitates a heavy burden of formal and informal care that has a wide-ranging impact and progressively increases in line with health deterioration and additional complications, such as CF-related diabetes and osteoporosis.

46% of adults with the condition told us that, on average, they will spend more than 3 hours each day on their CF treatment regime (Fig. 1 in Appendix 6).

One person with cystic fibrosis told us: “It's exhausting. I try to carry on working and want to do this for as long as possible, however my treatments are getting more and more and massively eat into my day. My wife works two jobs and then has to spend time doing my physio and help with antibiotics. We would like to have a family which means fertility treatment and I want to be there for any potential child, however the time I spend doing treatments or being very ill concerns me.”

When asked where cystic fibrosis had impacted on their lives in the past year, our respondents highlighted that family life (67%), social life (74%), planning ahead (69%), and holidays (67%) had all suffered (Fig. 2).

70% of responders to our survey who have cystic fibrosis or support someone with cystic fibrosis told us that the condition negatively affects their financial situation (Figs 3 & 4).

In explaining this situation, a typical response would highlight the impact of frequent and costly trips to specialist care centres, the cost of providing a healthy high-calorie diet, and, most significantly, reduced earnings through a reduced ability to secure full-time employment that is commensurate with qualifications and experience, due to periods of illness or care responsibilities. Both people with the condition and their support networks report extensive underemployment, necessitated by the demands of managing the condition.

One person with cystic fibrosis said: “I'm only able to work part time as, when working full-time, my health declined rapidly due to not having time to do my treatments properly, or to exercise before work. When working full time I was earning a good salary, but finding good quality part time work is incredibly difficult, and finding good part time work which will also further your career is next to impossible. This means I end up jumping from contract to contract, earning far less than I could otherwise. But I have to put my health first, so there is no option other than to accept any part time work I can find.”

Despite the myriad challenges that people with cystic fibrosis face in work and education, the UK CF Registry records that 70% of adults with cystic fibrosis are in full- or part-time work or a student.

The psychological and emotional impact of the disease was the second most frequently referenced topic – after the burden of care – that responders mentioned when we asked what it is like to live with the condition. Symptoms of stress, insecurity, anxiety and depression are elevated in both people with cystic fibrosis and parents, with a prevalence 2 to 3 times higher, compared with the rest of the population. (A Quittner et al: Thorax, Sep 2014)

The triggers and manifestations of these symptoms are highly complex and diverse. Psychological symptoms in both individuals with cystic fibrosis and parent caregivers have been associated with decreased lung function, lower body mass index, worse adherence, worse health-related quality of life, more frequent hospitalisations and increased healthcare costs. (A Quittner et al: Thorax, Oct 2015)

In the experience of one person with cystic fibrosis: “Every day is unpredictable which means living day by day. Hardly ever making plans for too far ahead. Also sleepless nights due to various CF related things and also mental health issues. Hate being a burden and often feel sad at relying on others to help with simple things. Also being in public and coughing. My worst nightmare.”

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most

important? If possible, please explain why.

Standard cystic fibrosis care, which until the advent of a new class of highly-innovative drugs that target improved functioning of the abnormal protein that causes the symptomatic expression of cystic fibrosis, had sought solely to manage and contain symptoms.

We asked what treatment outcome is most desired when looking to tackle a chest infection and the outcome with the largest support from both people with the condition and their families told us that an increase in lung function (measured as FEV_1% predicted), followed by reduced breathlessness, increased energy, and reduced coughing symptoms (Figs. 5 & 6).

However, when asked about what factors influence choices about treatments, the same groups, collectively and separately, scored a treatment's potential to protect future health and wellbeing marginally higher than a treatment with the potential to immediately reduce symptoms and make one feel better (Figs. 7 & 8)

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Even with an optimal treatment regime, people with cystic fibrosis develop frequent chest infections and exacerbations that will often require intravenous antibiotic therapy (IV therapy) to treat infection, inflammation and to help prevent further damage to the lungs. In 2014, the UK CF Registry recorded that 47% of patients required IV therapy with a median length of treatment of 28 days. 38.5% of patients received inpatient IV therapy with a median length of treatment of 15 days.

In our survey, IV therapy was considered by nearly 30% of responders with the condition to be the CF treatment that had the greatest adverse effect on their lives, alongside physiotherapy (32%) and nebuliser therapy (20%) (Figs. 9 & 10). When asked to rate the importance of a series of care outcomes, fewer exacerbations (86%) and fewer courses of IVs (79%) were rated as 'very important', behind an increased life expectancy (90%) but ahead of reduced symptoms, daily treatment burden, socialising, education and work (Figs. 11 & 12)

IV therapy is typically seen as the most disruptive treatment option in respect of planning ahead, maintaining work and education opportunities, and socialising. Hospital inpatient therapy is generally regarded as a "last resort", as the risk of cross-infection, the subsequent isolation, and the hospital setting carry an emotional and psychological burden for all involved.

One parent says: "Our daughter hates being admitted to hospital. It can be very lonely as patients cannot mix with each other because of cross-infection. Often family and friends do not visit as the hospital is far away from where we live. She feels isolated, bored and becomes depressed."

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

We asked people directly what benefits they expected eligible patients to gain from the lumacaftor/ivacaftor therapy.

- Improved disease progression/life expectancy scored highest (96%), followed by improved physical symptoms (91.90%), Improved quality of life (91.70%), greater capacity to do daily tasks (78%), better psychological/mental health (68%), and greater convenience/ease of use (62%)

Clinical trials show lumacaftor/ivacaftor therapy significantly reduces chest infections. We asked what a reduction in chest infections leading to intravenous antibiotic therapy would mean to the carer or the person with cystic fibrosis. The data below are extrapolated from free text:

- Improved quality of life scored highest (50%); followed by increased opportunity for employment/education (48%); improved physical and mental well-being (23%); fewer symptoms and exacerbations (14%); ability to exercise more (11%); improved life expectancy (7%) and reduced treatment burden and weight stabilisation.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Lumacaftor/ivacaftor is a relatively low burden treatment that may reduce dependence on high burden treatments, such as IV therapy, and keep people with cystic fibrosis out of hospital.

Lumacaftor/ivacaftor therapy is a twice-daily, orally-administered tablet. Only 3% of survey respondents consider tablets the most burdensome treatment. (Figs. 9 & 10)

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

No comment.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please see Answer 3(b).

Please list any concerns patients or carers have about the treatment being appraised.

A strong theme emerged from our questions in this area: the benefits outweigh the disadvantages. Some said it depended on the side effects, others that side effects are inevitable. Below are some key statistics that reflect this:

We asked people if they had any concerns about potential side-effects or disadvantages of the therapy.

- 75% of respondents had concerns about potential side-effects
- 50% had concerns about aspects of their condition that this therapy cannot help or might make worse
- 21% had concerns about difficulty in taking or using the therapy

We then asked if respondents consider these disadvantages to be an acceptable part of the treatment. 88% felt they would be acceptable.

We then asked why potential disadvantages were an acceptable part of the treatment. Respondents typically suggested that side effects where acceptable if, on balance, the therapy delivered net benefit in preferred treatment outcomes, including: lung function, life expectancy and quality of life. Many responses highlighted that clinicians would be able to support them to make informed decisions on the relative benefit/disadvantage ratio of the therapy.

One respondent commented: “As an adult with CF, time is not on our side. Any new treatment is worth trying.”

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No comment.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

No comment.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No comment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

No comment.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The pivotal Phase III clinical trials for the lumacaftor/ivacaftor combination therapy, TRAFFIC and TRANSPORT, captured important treatment outcomes for people with cystic fibrosis. The importance of FEV_1 and pulmonary exacerbations as outcome measures have been discussed, and Body Mass Index (BMI) is associated with resilience to infection and health stability.

As discussed, improved quality of life rates highly as a desired treatment outcome, with 95% of adults with the condition saying they consider it an important factor in deciding which treatments they take (Fig. 13). The Phase III trials did seek to measure effect on quality of life by collecting data on patient-reported respiratory symptoms through the CF questionnaire-revised (CFQ-R) – a clinically validated instrument.

However, the Cystic Fibrosis Trust believes this measure generally does not accord with the way people with the condition and their families think about quality of life and will not be sensitive enough to understand the impact of the treatment and cannot be used in isolation to draw conclusions about the impact of the therapy on quality of life.

For people with cystic fibrosis and their loved ones, quality of life may mean: liberation from daily maintenance treatment, freedom from regular exacerbation, greater resilience, ability to plan for the future, better energy levels, sleeping better, and a more general sense of functional fitness.

These are basics of security and independence, and by measuring respiratory symptoms through the CFQ-R alone, they are significantly overlooked in valuing the impact of this therapy on quality of life. Further study that utilises a more sensitive and person-centred instrument is necessary to assess real impact on quality of life.

One person commented: "[The trial endpoints] are clinically important but, for patients, factors such as quality of life are more important e.g. I went to a comedy show and I was able to laugh without coughing. FEV_1 won't measure this. It's the qualitative factors which matter most to people with CF."

An additional significant limitation of the trial data, in the context of its mode of action and effect, is its relatively short-term nature. For a therapy with a protective effect on health status, much longer-term data are the only way to achieve a clearer picture of clinical benefit or to understand the impact on quality of life. The Trust's views on this subject are discussed further in the section for issues for the Appraisal Committee to consider.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No comment.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

Please see appendices.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No comment.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No comment.

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The technology is the first disease-modifying therapy available to this patient group, targeting the cause, not the symptoms, of the disease. In this respect, it must be considered a 'step-change' therapy, and as a new, original and advanced mechanism of therapy in cystic fibrosis must be classed as highly innovative.

The treatment's health-related benefits are a result of partial correction of the specific dysfunctional protein that causes cystic fibrosis, as opposed to combating the abnormal symptomatic expression of the protein's faulty functioning.

This constitutes a fundamental shift in approach for both patients and clinicians and has been described as the beginning of effective therapy for cystic fibrosis associated with the most common mutant form of CFTR (P Davis – NEJM, Jul 2015).

Are there any other issues that you would like the Appraisal Committee to consider?

The Cystic Fibrosis Trust recognises that this therapy is a typical rare disease product in that it targets a small population with significant unmet need, has an innovative mechanism of action, and has an immature body of data that naturally cannot describe the full-extent of the clinical potential of this novel and innovative therapy.

However, the product has sufficiently demonstrated safety and efficacy through well-powered and executed Phase III clinical trials. As such, the Cystic Fibrosis Trust

believes that clinicians should be given the opportunity to prescribe this treatment with minimum delay.

Given the opportunities that present themselves in cystic fibrosis care – a defined patient population, a high-quality patient data registry, and a well-established network of specialist care centres with well-established protocols and routines for data collection – it is imperative that the Appraisal Committee explore how these assets can be innovatively used, within the assessment process, by all parties, to support negotiated access to this safe and effective therapy and to facilitate improved understanding of the therapy.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The therapy is safe and effective, and targets clinical outcomes that are most associated with disease progression and early death.
- The therapy reduces the number of pulmonary exacerbations, which are causal events directly linked to treatments viewed by people with cystic fibrosis and carers as the most burdensome and disruptive to daily life.
- The UK CF Registry and network of specialist care providers is a unique environment for further drug efficacy evaluation and must be utilised.
- The therapy is highly-innovative and unique in this patient population as the first and only licensed disease-modifying therapy.
- Clinicians should be given the opportunity to prescribe this treatment with minimum delay.

Uploaded to 'NICE Docs / Appraisals', alongside this submission are the following appendices:

- **Appendix 1** – Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK, 2nd edition – December 2011
- **Appendix 2** – UK Cystic Fibrosis Registry 2014 Annual Data Report
- **Appendix 3** – Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers (A Quittner et al: Thorax, Oct 2015)
- **Appendix 4** – CFF and ECFS consensus statements for screening and treating depression and anxiety (A Quittner et al: Thorax, Oct 2015)
- **Appendix 5** – Another Beginning for Cystic Fibrosis Therapy (P Davis: NEJM, Jul 2015)
- **Appendix 6** - Charts and figures from Oct 2015 survey
- **Appendix 7** – Full survey
- **Appendix 8** – What's it like to live with cystic fibrosis - https://vimeo.com/145843717

We ask that these appendices are made available to the Appraisal Committee.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Cystic fibrosis is treated in designated specialist CF Centres in accordance with agreed Standards of Care Guidelines and Service Specifications, with Peer Review processes in place to ensure a high standard of care. New treatments are introduced via specialist CF centres, and can be closely monitored via the UK CF Registry.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The F508del/F508del mutation is a severe mutation causing progressive lung disease and premature death.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology

be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is currently no treatment which addresses the basic genetic defect in patients with the F508del/F508del mutation. The lumacftor+ivacaftor combination is therefore a very innovative treatment which represents a step-change in the treatment of CF.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Adverse reactions, reported in the clinical trials, appear to be minor and mild.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Quality-adjusted life year analysis may be difficult to apply to a disease such as cystic fibrosis (by comparison with cancer, for example) as patients with a chronic disease adapt to the disease and maintain quality of life.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Nursing
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? No

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **Yes – CF Clinical Nurse Specialist, Member of the RCN**

- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Cystic fibrosis (CF) patients who would be suitable for the Lumicaftor and Ivacaftor combination therapy are currently treated with conventional CF medication and therapy, such as antibiotics, mucolytics, physiotherapy etc. This medication would be a completely novel treatment for this group of patients. It is possible that they may be able to reduce the need for some of the current treatments, such as intravenous antibiotics, but it is likely they will need to continue on a significant number of current therapies, to be taken in conjunction with the Lumicaftor/ivacaftor.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Lumicaftor/ivacaftor combination therapy is recommended for patients who are homozygous for the Phe508del CFTR mutation. This is the commonest mutation in CF affecting approximately 51.3% patients (CF Trust 2014). It is possible that there may be a subgroup of patients within the Phe508del group who may benefit more than others but we not aware of any evidence for this yet.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Lumicaftor/ivacaftor will presumably be in the ultra-orphan drug category (as is Kalydeco (Ivacaftor)). Currently, Kalydeco is prescribed within secondary care and funded by the New Medicines Fund (Scotland). The author is currently unsure of the funding arrangements in England/Wales. It may be necessary to have similar funding arrangements for Lumicaftor/ivacaftor. There should be no requirements for additional professional input, once the patient is established on the medication apart from routine clinical surveillance.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This is not available yet.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

There are no published guidance yet regarding Lumicaftor/Ivacaftor.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is no comparable treatment for Lumicaftor/Ivacaftor as this is a targeted medication for CF patients with specific genetic mutations.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Any patient started on this medication would need careful surveillance for clinical improvement and adherence. Patients on Ivacaftor (with G551D mutations) are monitored in this way and will be taken off the medication if there is no evidence of clinical improvement or if they are not taking the drug regularly as prescribed. Monitoring would also be required for side effects, such as deranged liver function blood results.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The author is aware of two phase 3 randomised double blind placebo controlled trials have been conducted to assess Lumicaftor/Ivacaftor (New England Journal of Medicine, 2015). Although improvements in FEV1 were not as significant as with Ivacaftor (used for patients with the G551D mutation), there were clinically meaningful reductions in the rates of protocol defined pulmonary exacerbations. It is difficult to predict long term outcomes from these studies.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In the trials, adverse event reporting was similar across the Lumacaftor/Ivacaftor group to the placebo group. 4.2% of the Lumacaftor/Ivacaftor group discontinued the medication due to an adverse event. Adverse events included elevation of creatinine kinase level, haemoptysis, bronchospasm, dyspnoea, pulmonary exacerbation and rash. No deaths were reported.

The medication is not yet in routine clinical practice.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None known at this stage.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

With the exception of ensuring close clinical surveillance of patients taking the medication, at present, the author cannot envisage that any additional resources would be required.

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

The cost of Lumicaftor/Ivacaftor could have implications for some patients to have access to this medication. It is imperative to have a fair and consistent funding strategy in place for all eligible CF patients within the UK. The cost of this drug is not yet known in the public domain, but it will be the cause of much anxiety and concern within the CF population.

Appendix G – NHS organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation ID786]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Clinical Commissioning Groups (CCGs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a CCG perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation - Cystic Fibrosis Clinical Reference Group, for NHS England

Please indicate your position in the organisation:

[redacted]

[redacted]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Patients are all looked after in Specialist CF Centres (some children also in their local hospitals acting as Network centres supervised by their Specialist centre). There is

currently no treatment available that specifically targets the commonest gene mutation (F508del) that causes CF. This drug combination is the first to do so. Current treatment simply manages symptoms and complications of the disease as had been outlined in the Scope's background section. This involves a high burden of care for the patients/carers, with daily treatments at home and frequent hospital visits and in-patient admissions. Despite this, lung disease progresses relentlessly, resulting in a need for lung transplantation, or death in early adulthood.

Is there significant geographical variation in current practice?

No - management of CF is similar across the UK, and generally follows national and European guidelines, national Standards of Care, and the Service Specification of NHSE.

Are there differences in opinion between professionals as to what current practice should be?

Inevitably there are some minor differences, but as above, all important management issues are generally agreed upon.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is no alternative to this new drug in terms of correcting the CF basic defect in patients homozygous for F508del mutation. We can only attempt to treat complications and symptoms; standard treatments are nutritional supplements, vitamins, enzyme replacement for every meal time and snack, twice daily physiotherapy, long term oral and inhaled antibiotics, inhaled mucolytics, inhaled bronchodilators. There are even more drugs for other complications, as well as admissions for intravenous antibiotics during chest exacerbations.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

It is not currently used.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

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The immediate impact for the patient is taking a pill twice a day with a fatty meal. The patients would continue with their usual clinic visits, so delivery of care would largely be unchanged, as they would need to continue with their current therapies. In time it is hoped that they would have less hospital admissions for treatment of pulmonary exacerbations with intravenous antibiotics. There would be no impact in terms of staffing levels or infrastructure needed for CF care in the specialist centres.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Specialist CF centres only.

Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

It would be an extra medication in Pharmacy but that should have minimal impact once the prescribing and commissioning arrangements are in place. Extra sweat tests may be carried out (perhaps just one) and liver function tests in clinic for efficacy and safety monitoring**.**

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

This largely depends on what the company decide to charge the NHS, but undoubtedly the budgetary impact will be huge, considering around 3500 patients would be eligible for the treatment. Current US pricing is $259,000 per patient per year.

Drug costs will be offset to an extent by improvements in lung health, particularly if the reduction in exacerbations seen in the study (around 30%) is maintained in real life practice. Exacerbations are damaging to the lungs and require expensive treatments with intravenous antibiotics and prolonged hospital stays (usually 2 weeks in-patient care).

Furthermore, any reduction in exacerbations is likely to improve the child/young person's ability to attend education and thus increase their options for a productive working life/career.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

It would have to come from new funding and could not possibly be taken from existing CF funding, so trade-offs would be for the NHS as a whole. Some costs to the whole NHS may be offset though as per above paragraph.

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Would there be any need for education and training of NHS staff?

This would be minimal; the medication would be prescribed by medical staff who would need to be aware of indications, contraindications, side effects etc. Pharmacists would need to be aware of the drug, The CF multidisciplinary team would also need to be made aware of the drug and particularly what side effects to look out for.

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

This is not relevant.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

Due to the publicity around this drug, there is great expectation amongst people with CF, and carers of children with CF who are aware that a new medication has become potentially available, and they will all know it is currently in use in all relevant patients in the USA. It is certainly a breakthrough in terms of our ability to correct the basic defect in those with the commonest CF genotype (around 50% CF population), although results are not as spectacular as with the use of ivacaftor for CF patients with the gating mutations (around 5% CF population).

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Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr. Peter Barry

Name of your organisation: Manchester Adult Cystic Fibrosis Centre, University Hospital of South Manchester

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Currently patients with cystic fibrosis are cared for in specialist units throughout the United Kingdom. Patients who are homozygous for the Phe508del mutation represent close to half of people with CF in the UK. Current treatment provided for patients carrying this mutation is directed at the downstream consequences of the genetic mutation in the CF gene which gives rise to a dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein.

Dysfunction of the CFTR protein results in the formation of thicker secretions in the respiratory tract, which are difficult to clear and provide an ideal environment for the acquisition and persistence of respiratory pathogens. This in turn gives rise to a cycle of inflammation and destruction of pulmonary tissue. Current respiratory therapies are targeted at reducing the tenacity of the secretions, reducing the bacterial load of these secretions, attenuating inflammation or assisting in airway dilatation.

Other treatment in CF is targeted at the consequences of CFTR dysfunction in other organ systems including among others the gastro-intestinal tract and musculo-skeletal system. Representative treatments are targeted at replacing pancreatic enzymes, vitamin and nutritional supplements. Perhaps most importantly the treatment of people with CF is co-ordinated and delivered through centre with multi-disciplinary expertise such as dietetics, physiotherapy, psycho-social, medical and nursing teams. These teams alongside published clinical guidelines have minimised any geographical or professional differences in treatment across treatment centres.

The proposed combination drug acts in a novel way by aiming to restore functional CFTR activity in patients homozygous for the Phe508del mutation. This represents a fundamentally different approach to current therapies and may therefore affect the multi-system consequences of the condition. In addition by targeting the basic defect CFTR modulation has the potential to effect disease progression. This potential has already been established in the sole other representation of CFTR modulation in CF. In patients carrying at least one copy of the Gly551Asp mutation, ivacaftor therapy has been shown to significantly reduce the rate of lung function decline compared to a control group not carrying that mutation. In addition, several lines of evidence suggest that CFTR modulation in contrast to other current therapies has the ability to positively affect the multi-system consequences of the condition. We await similar data with this combination product but data to date suggest that the approach of increasing CFTR activity in patients with CF will be beneficial. It should be noted that although ivacaftor for Gly551Asp patients represents the first ‘CFTR modulator’ in clinical practice, the current combination therapy has not been seen to affect CFTR to the same degree in an acute setting as witnessed by lower rise in FEV_1 compared to the combination product in question. Thus while the use of ivacaftor therapy in patients with cystic fibrosis but with a different genotype is an indication of the potential of CFTR modulation, it may not represent longitudinal responses to this combination product.

One consideration for this therapy is the consideration of who may best respond to therapy. The evidence to date and current application considers only the potential of this combination product for patients who are homozygous for the Phe508del

mutation. Phase 2 trial evidence did not suggest any meaningful benefit for patients who were heterozygous for this mutation. Patients homozygous for the Phe508del mutation tend to have 'classical' CF disease determined by respiratory abnormalities and exocrine pancreatic insufficiency. Differences in disease severity are not solely explained by gene mutations but this mutation combination is considered consistent with severe dysfunction of CFTR activity. A re-analysis of the phase III trial data of this combination product has failed to identify clear subgroups that are more responsive to the therapy.

This is consistent with previous evidence of ivacaftor monotherapy in suitable patients. Within this group it is notable that recent evidence has suggested that any initial response as measured by increases in lung function was not related to longitudinal responses (McKone NACFC). Furthermore, in severe patients we have noted that again using the ivacaftor monotherapy example, that increases in lung function are not related to subsequent reductions in exacerbations. In other terms this suggests that there is not a clearly identifiable responsive subgroup and that any single measure of response such as the measurement of lung function response at one time period may not be representative of longitudinal benefit. I must again stress that these examples are garnered from the utilisation of CFTR modulation in a different genetic mutation and we await evidence with this combination product.

This combination product would represent an additive product to the current standard of care for CF. There exists a potential for this product to reduce healthcare utilisation over time by reducing pulmonary exacerbations and improving lung function. There is a clear need for such therapies for patients homozygous for the Phe508del mutation.

The advantages and disadvantages of the technology

There is no suitable alternative medication available to people with CF homozygous for the Phe508del mutation. This therapy represents an addition to currently licensed therapies and was studied in this form in the phase III clinical trials.

Advantages
As an oral agent it should be acceptable to the majority of patients as evidenced by low discontinuation rates in trials. There exists the potential for drug interaction with some medications that are utilised in cystic fibrosis including the anti-fungal drugs itraconazole and voriconazole. Although other potential drug interaction potential exists, the majority of these have a low relevance for the routine treatment of CF patients.

The outcome measures of improvement in pulmonary function and reduction in pulmonary exacerbations demonstrated in the clinical trial are important and clinically relevant outcome measures for patients with CF. This may potentially have the benefit of reducing healthcare utilisation for the acute treatment of pulmonary exacerbations including as demonstrated in the phase III trial a significant reduction in the need for hospitalisation.

The evidence base for the use of this combination product is strong. Two phase 3 clinical trials represented the largest interventional clinical trials ever conducted in

CF. These clinical trials contained patients who were representative of the CF population as a whole and permitted all regular CF therapies. The patients included in the clinical trials were representative of patients treated in the United Kingdom.

Disadvantages
If tolerated by the individual, there does not appear to be any clear disadvantages to the use of this medication. Adverse events in the clinical trial were consistent with those seen in the majority of other clinical trials. There is a small risk of increased liver enzymes which needs to be monitored if patients were to start this combination therapy.

Stopping Criteria
As previously outlined there is not a clear subgroup that will benefit from this medication once the qualifying criterion of genotype is fulfilled. There is no evidence available to my knowledge, which can validate stopping the medication on the basis of any clinical criteria or response. We in fact must be cautioned by the fact that initial spirometric rises are unrelated to either longitudinal responses or reduction in pulmonary exacerbations in patients who received ivacaftor monotherapy. Thus stopping on the basis of a lack of spirometric response may potentially cause longitudinal harm. Additionally, previously the use of sweat chloride responses has been utilised to assess clinical response to ivacaftor therapy but this measure appears unrelated to clinical response. Furthermore the phase II trial data would suggest that there was a relatively small reduction in sweat chloride identified with the combination product, meaning this measure would be unsuitable for use as a marker of response. In my view the only robust stopping criteria would be clear evidence of non-adherence.

Equality and Diversity

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 this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

I do not have any concerns regarding equality for this product

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

With regards to this product recent re-analyses were presented at the North American Cystic Fibrosis Conference looking at the data with relation to open label prescription of lumacaftor and ivacaftor following on from the TRAFFIC and TRANSPORT trials. Also re-analyses have been presented with relation to examining response according to baseline pulmonary function (De Boeck et al)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No additional education or training would be required for staff. Clinical care for these patients should not alter significantly.

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Single Technology Appraisal (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Edward F Nash

Name of your organisation: West Midlands Adult Cystic Fibrosis Centre, Heart of England NHS Foundation Trust, Birmingham, B9 5SS, UK

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Cystic fibrosis (CF) is the most common inherited life limiting condition in the UK Caucasian population, affecting more than 10,000 people. CF is caused by mutations within the CF gene on chromosome 7, which causes a defect in the CFTR protein, an epithelial chloride channel. Defective CFTR causes reduced fluid secretion through all epithelial mucosal surfaces, including the airways of the lung and the digestive tract. Within the lungs, this results in thickened, sticky airway secretions, which causes a vicious cycle of progressive bacterial infection and inflammation. The resultant lung damage causes recurrent chest infections (exacerbations) and worsening respiratory failure, with a current median survival of 40 years of age.

Management of people with CF throughout the UK is provided by multi-disciplinary teams including specialist doctors, nurses, dieticians and physiotherapists, working within paediatric and adult CF centres. Prior to the last few years, treatments have primarily been aimed at helping patients to better clear their airway secretions, reducing airway infection and optimising nutrition. However, following intensive research efforts, treatments are now being developed which target the underlying cause of CF. This class of treatments, known as 'CFTR modulators' aim to improve CFTR function and thereby treat the underlying cause for CF. NICE previously approved funding for one such treatment (Ivacaftor) for people with CF caused by a relatively uncommon mutation referred to as a 'gating mutation'. This type of CF mutation only affects around 4% of people with CF but in patients with this mutation, Ivacaftor is very effective in improving lung function, symptoms, exacerbation frequency and body weight.

In approximately 52% of people with CF, the disease is caused by two copies of a mutation called F508del (referred to as homozygous F508del). This mutation causes severe CF due to almost complete absence of functional CFTR at the epithelial cell surface. The technology currently being assessed is aimed at treating people with CF caused by homozygous F508del. Orkambi is an oral medication (tablet) consisting of Lumacaftor (which aims to increased the amount of CFTR that reaches the cell surface) and Ivacaftor (which aims to improve the function of any CFTR that reaches the cell surface). Pre-clinical and early phase clinical trials have demonstrated that Orkambi is effective in increasing the amount and function of CFTR at the airway cell surface. A recent peer-reviewed publication reported the results of 2 multi-centre placebo-controlled clinical trials called TRAFFIC and TRANSPORT. The combined results included 1108 CF patients with homozygous F508 del aged 12 years or older, demonstrating significant improvements in lung function (the primary outcome measure)[1]. Specifically, the difference between active treatment and placebo with respect to the mean absolute difference in FEV1 ranged from 2.6 - 4% ($P<0.001$). Secondary outcomes showed a significant reduction in the rate of pulmonary exacerbations of 30-39%, with a significant reduction in hospital admissions and a small but significant weigh gain. Orkambi treatment was generally well tolerated, with no evidence of serious adverse effects.

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The main advantage of Orkambi is that it is the first available treatment for people with F508del homozygous CF that targets the basic defect. The combined results of the TRAFFIC and TRANSPORT studies show modest but statistically significant improvements in FEV1, which is the most important objective measure of severity of lung disease. The 30-39% reduction in exacerbations is not only highly statistically significant, but is clinically very relevant. CF exacerbations are very costly to the NHS, since patients often need to be admitted to hospital for 12-14 days, receiving intravenous antibiotics and specialist care. Orkambi is administered in the form of a tablet, which is of importance since people with CF already have a high treatment burden and tablets are relatively easy to administer.

The main clinical disadvantage of Orkambi is that it is only beneficial for patients with F508del homozygous CF mutations. Although this affects approximately 52% of patients, this limits the potential benefits. As mentioned previously, the improvement in FEV1 is relatively modest, but in my opinion this is offset by the significant reduction in rate of exacerbations and hospital admissions. The consequent potential cost savings associated with reduced hospital admissions, as well the potential financial benefits of reduced progression of the disease, need to be weighed against the not insignificant cost of Orkambi.

Reference

1. Wainwright et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med. 2015 Jul 16;373(3):220-31.

If made available, CF consultants working in CF centres would prescribe Orkambi. This would only be available for people with F508del homozygous CF, within its licensed indication.

The requirement for additional professional input as a result of the prescribing Orkambi would depend on the requirements placed upon prescribers. For instance, if patients were required to have a sweat test or eye test (both of which were required to enable patients to take part in the clinical trial), this would provide a significant challenge. Particularly for larger CF centres, this would introduce a significant extra expense to provide these screening tests and would delay implementation of the technology. There would also be additional time required from pharmacists supporting the CF team, since there are potential drug-to-drug interactions that will need to be assessed and managed. There will also be an increased burden placed on CF specialist doctors, since they will be expected to identify and counsel patients as well as monitor for adverse effects.

Since this is a relatively new technology, there are no relevant clinical guidelines for the use of Orkambi as yet. There were strict inclusion and exclusion criteria used in the clinical trials (such as FEV1 between 40-90% predicted) and if approved, NICE will need to decide whether to restrict use according to these guidelines. Interestingly, the criteria used in the relevant clinical trial were not adhered to when NICE approved the use of Ivacaftor and this has allowed patients not meeting those inclusion and exclusion criteria to be started on Ivacaftor.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

As already explained, Orkambi is the first and currently only medication that aims to correct the basic defect causing CF in people with F508del homozygous disease. There are therefore currently no alternative medications with which Orkambi can be compared. The currently available medications aim to palliate the symptoms of CF, rather than treating the basic defect, People with CF have been waiting for many years for a medication that works to correct the basic defect and there is therefore a great deal of interest from patients and carers in the potential availability of Orkambi.

In terms of practical considerations, patients starting Orkambi will need to have certain blood tests (such as liver function tests) to monitor for any evidence of adverse effects. In practice this is straightforward, since this can easily be arranged either at routine follow up visits at the CF centre or in the community. During the clinical trials, patients had to have an eye screening test before starting the trial and after completing the trial. This was because in pre-clinical trials there was noticed to be a potential for one of the drugs contained within Orkambi to cause cataracts in animals. I am not aware of any patients having developed cataracts in any of the trials of Orkambi, but if approved it will need to be decided whether eye screening is required before starting Orkambi. If so, this will cause additional expense and significant practical difficulties, particularly in larger CF centres.

Patients also had to have several sweat tests during the course of the trials and if approved by NICE, it will have to be decided whether this is requirement in clinical practice. This was included as a requirement when NICE approved the use of Ivacaftor and this has caused a great deal of additional expense and significant practical difficulties. Since I am not aware of any evidence that change in sweat test results is correlated with clinical outcomes, I would suggest that this should not be made a requirement in the case of Orkambi. This would cause major difficulties in larger CF centres, since availability of sweat testing can be very limited.

It would also need to be decided whether criteria are put in place for Orkambi to be stopped, for instance in the absence of clinical improvement. In practice this would be challenging to enforce, since the benefits of Orkambi are likely to manifest over the course of several years. The variable and unpredictable nature of CF will make it difficult to assess whether any clinical improvement or decline is related to starting Orkambi. Since the improvement in lung function (FEV1) was relatively modest in the clinical trials, this should not be used as a criterion to stop Orkambi. The significant reduction in rate of exacerbations is a much more compelling treatment effect, but again due to the variable and unpredictable nature of CF, it would be difficult to use this as an indication to stop the drug.

Orkambi interacts with certain other medications (such as anti-fungal drugs) and this may potentially be in an issue in a proportion of patients. However, this is a relatively minor concern since Orkambi can usually still be safely co-administered if the dosing frequency is altered accordingly. Orkambi can potentially adversely affect liver function and in the 5-10% of patients with CF liver disease, this may affect tolerability. Orkambi is not known to be safe in pregnancy and since it makes hormonal contraceptives less effective, female patients are advised to use alternative

methods of contraception. Female patients and their partners will need to be made aware of this advice.

It is unclear whether the treatment effects seen in the clinical trials will be replicated in clinical practice. By the very nature of clinical trials, this is not always the case. Since certain inclusion and exclusion criteria were used in the clinical trials, it will need to be decided whether these criteria are required in clinical practice. The main relevant criterion in my view is the requirement for FEV1 to be between 40-90% predicted in the clinical trials. This inclusion criterion was presumably put in place to select a group of patients that are most likely to benefit, since Orkambi might not have as much of an effect on FEV1 in patients with milder or more severe lung disease. If this criterion were used as a requirement in clinical practice, this would restrict the use of Orkambi based on the evidence base. However, the effect on exacerbation frequency may not be limited to patients with FEV1 between 40-90% predicted. If the 30-39% reduction in the rate of exacerbations was replicated in clinical practice, this could result in a significant cost saving for the NHS as well as resulting in patient benefits. Since we know that patients that experience more frequent exacerbations experience more rapid decline in lung function over time and have increased mortality, the clinical use of Orkambi could also feasibly result in prolonged survival by reducing exacerbation frequency. However, since the clinical trial data published to date were based on trials of a 6-month duration, any potential effect on slowing long-term lung function decline, or reducing mortality has not yet been observed.

Equality and Diversity

I do not feel that there are significant issues with regards to equality and diversity. Orkambi would only be available for people with certain CF mutations, but this is based on sound scientific principles and is not discrimination. I cannot foresee any reason why access to Orkambi could result in adverse impacts for people with any particular disability.

Any additional sources of evidence

There is currently an ongoing clinical trial, which assesses the longer-term effectiveness, safety and tolerability of Orkambi, but the results are as yet unpublished. Since Orkambi is not currently available clinically, there is no relevant data from registries or clinical audits.

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Single Technology Appraisal (STA)

Implementation issues

The requirements in terms of extra training or staffing will depend to a large degree on the requirements that NICE impose on prescribers of Orkambi. This particularly relates to the potential requirement for eye screening and sweat tests as mentioned previously. If eye screening or sweat tests are required, this will cause significant disruption and delay in the implementation of Orkambi, since both of those services are in limited supply. There would also be significant additional expense incurred. There would also be an increased burden placed on pharmacists working within or alongside CF centres. Since Orkambi has potential drug-to-drug interactions and this can require manipulation of the dosage and timing of the relevant drugs, this would place a significant increased burden on pharmacists. This is particularly the case in larger CF centres, where Orkambi could potentially be made available to several hundred patients. Since CF pharmacists are already extremely busy, this could significantly delay the implementation of Orkambi beyond 3 months. CF specialist doctors would also be impacted, since they would be required to identify and counsel potentially suitable patients, prescribe Orkambi and monitor for potential adverse effects. Since CF specialist doctors are already extremely busy, especially in larger CF centres, this could also delay the implementation of Orkambi.

On balance, the novel mechanism and potential clinical benefits of Orkambi make it a very compelling treatment. The potential reduction in rate of exacerbations, if replicated in clinical practice, will lead to significant benefits for patients in the short and medium term. There is also a potential that Orkambi will slow the progression of lung damage in the longer-term, although this has yet to be proven. These clinical and expected financial benefits clearly need to be weighed up against the cost of the medication.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Vicky Armstrong
Name of your nominating organisation: Cystic Fibrosis trust
Do you know if your nominating organisation has submitted a statement?

☐x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐x No

- a carer of a patient with the condition?

☐x Yes ☐ No

- a patient organisation employee or volunteer?
-

☐x Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I have a son aged 13 with cystic fibrosis along with 4 other healthy younger children. He presented at age 12 weeks when he developed a facial palsy which progressed from unilateral to bilateral facial weakness of the 7th cranial nerve. This has improved slightly over the years but he still can not smile and has reduced facial expression. This was thought to be due to the initial vitamin deficiency from malabsorption. He has had his ups and downs and struggled at times with bacterial infections and fungal infections. These have been managed with intravenous antibiotics at home, along with anti fungals and steroids. All of which come with the side effects and toxicities. More recently having issues with ABPA and steroid use which may have effected his growth. He struggles to gain weight and after a period of overnight naso gastric tube feeding which he inserted himself every night and removed in a morning. This allowed him to gain weight but had negative psychological effects on his body image and self esteem. He was not happy with the alteration in his appearance and this has now been stopped. He has lost the excess weight and is happier with his BMI. He is awaiting consultation from endocrinologist regarding puberty. He attends clinic every 6 weeks and in between when required. The overall management of this condition is relentless, you can not take your eye of the ball for a minute. Changes can be so unpredictable and very frustrating. The diligent planning of treatments and timings of medications have to be closely followed and the dedication to clinic attendance and close communications with CF team is paramountTo .

Dylan is a cooperative boy who understands fully the implications of this long term life limiting illness and endeavours to understand as best he can and can be independent in all therapies and medication requirements. He has not let this condition effects his quality of life as he participates in all sports and excursions with school. This has required an intense amount of care and support over his early childhood to equip him with these life long skills. However I am aware that this will not be the case for all children with the condition and limits are placed on quality of life. Dylan is aware that he will

have a constant up hill struggle to keep up with his peers and to fight every day to keep his self well.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

All treatment outcomes are important to improving both quality and quantity of life. To allow people with Cystic fibrosis to look ahead to the future without doubting it. The overall disease burden would be greatly reduced if the primary defect could be addressed and all associated symptoms would then be eased. Further exploration in to effectiveness of these drugs with even further trials in to wider mutation types benefitting from them would be a future expectation I would like to see. The improvements of current antibiotics and the toxicities of drugs are also an important factor in long term management of this condition.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

My son has required several courses of intravenous antibiotics these over the past 11 years have been done by me at home. This process has always gone smoothly with the initial dose being given at hospital following insertion of a line . This usually done in a timely way. I have a very good relationship with the consultant and the team and can discuss all treatment plans and have always agreed with each decision. Treatment for aspergillious and associated ABPA have been the most recent challenge and having tried all possible interventions being unable to tolerate any nebulised drug. The treatment was delayed due to quality of life issues of being on holiday and competing in sporting activities as the exposure to sun was contraindicated. Again this is an example of balancing the quality of life with these patients. Dylan will try and is willing to discuss new interventions and treatments but has his own say on acceptability. This does have a significant impact on relationships and coping mechanisms as a parent and carers. The transition in to adult hood and allowing Dylan to make all his decisions will be a future challenge we are aware of.

The only issue I have had is accessing a drug not available to CF patient's omiluzamab to treat ABPA in asthma patients. Dylan suffers with very similar traits and this has been improved with this. However this was not approved.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Improved quality of life.

Reduced burden of disease and physical symptoms

More time to enjoy life

Reduced periods of exacerbation and feeling less well.

More stable life style more flexible in daily regime and activities.

Improved physical function

Improved long term emotional and psychological state.

Reduced tablet load.

Less complex treatment regimes, reduced time.

Improved life expectancy and quality improved life measures.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

No other treatment offers direct correction of the underlying defect causing the disease.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I am aware that other children and young adults have a much poorer quality of life than my child. This is due to several underlying factors such as disease severity, infection, poverty, parents understanding, and patient compliance. For the whole population of these patients this will be improved as regardless of these factors if all patients were offered correction of the underlying defect than complications from the disease would be reduced.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My only concern regarding current treatment is the equity of treatments offered and the expertise of those prescribing them. These need to be standardised throughout the country to ensure best practice for all.

Please list any concerns you have about the treatment being appraised.

I am concerned that this treatment may be subject to funding in individual cases and not standard practice, I also would hope that further trials including other mutation types were explored.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Yes patients who do not understand the importance of intensive treatment currently required today would benefit from this drug and also the patients who do keep them selves well will hopefully have a overall significant improvement to their long-term survival.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Only those who do not comply

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical

trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No adverse effects

9. Other issues

Do you consider the treatment to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This drug is the first of its kind offering a correction to the primary defect for a wide proportion of patients.

Is there anything else that you would like the Appraisal Committee to consider?

Further research in to wider benefits for the people who will not fall in to this mutation types.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Improved quality and quantity of life
- Reduced disease burden
- Equitable treatment for all
- Life changing treatment
- Just the beginning

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

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- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Lynsey Beswick
Name of your nominating organisation: Cystic Fibrosis Trust
Do you know if your nominating organisation has submitted a statement?

☐x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?

☐x Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

Life with Cystic Fibrosis (CF) involves a huge daily burden of treatment, variable symptoms and regular specialist input. Every day involves taking numerous medications several times a day, physiotherapy, nebulisers, insulin, inhalers and regular exercise.

I attend a specialist unit for all of my Cystic Fibrosis care which is overseen by a multidisciplinary team. I make a 50 mile round trip every 6 to 8 weeks for outpatient appointments monitoring lung function (FEV1), weight (BMI), microbiological status, symptoms and to discuss any medical or psychosocial intervention where required.

My health is variable and can take a sudden turn, particularly if I have a chest exacerbation. I work full time, fitting my many treatments around my day, but admittedly sometimes with great difficulty due to the time taken. I am finding as I get older and my health declines, the burden of treatment continues to increase with additional CF related complications including asthma and CF related diabetes.

Increasingly I require more time off work to attend hospital appointments and for hospital care and treatments. I do worry longer term about my future, maintaining employment and being able to keep up with my peers.

Living with Cystic Fibrosis affects my life in other ways too. I cannot absorb my food properly so have to eat a high fat, high calorie diet, which can be hard to maintain; especially when I am unwell and my appetite is low. This pressure to retain weight can generate emotional stress, as my BMI is an important factor in my overall health and management of the condition.

The emotional impact of living with a long term condition means that I often feel stressed, embarrassed, frustrated and anxious at times about my health.

CF can affect my relationships and my independence too. I do sometimes (reluctantly) have to rely on my partner to help with my treatments or do normal tasks like preparing a meal if I am too unwell to do so myself.

The condition also affects my social life as I increasingly feel too tired or symptomatic to leave the house. I also avoid places where I know I may be more prone to pick up colds/infections.

CF is very unpredictable, making it difficult to plan ahead. In the short term, holidays have been postponed or cancelled because of sudden ill health and long term plans to start a family have now been ruled out.

CF has over the years has impacted on many of the important day to day and life decisions I have made and it is a consideration in everything I do. However, I am keen to try live as normal life as possible.

Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

For me the key treatment outcomes are lung function, BMI, reduced treatment burden, reduced exacerbations and increased life expectancy.

Living with Cystic Fibrosis I have a daily burden of treatment, but one of the worst aspects of treatment is intravenous antibiotics (IVs). IV treatment is exhausting and the drugs can often cause unpleasant side effects. Over time I have also become more resistant to certain antibiotics.

Intravenous treatment is the treatment I dread. It is often unplanned and extremely disruptive to work and family life. The treatment is a two week course delivered at home or as an inpatient or a combination of the two. The treatment is multiple times a year on top of my usual daily treatments.

The IV antibiotics I am routinely prescribed have to be administered 3 times a day 6-8 hours apart, plus an additional IV which is taken once or twice daily.

If I am in hospital, I will be very unwell, usually with a persistent productive cough, fatigue, breathlessness and chest pain. I have to take time off from my full time job and make arrangements for practicalities like pet care for the duration of my inpatient stay.

Due to cross infection risk I am confined to a single room on the specialist ward, which is lonely and isolating. This is exacerbated by the distance of the regional centre to my home city which limits visitors.

If I opt to have my IV treatment at home, intravenous antibiotics means that my life is effectively on hold for two weeks. I will still have symptoms but with the added burden of having to administer the drugs myself which is intensive and tiring.

The IV antibiotics often cause unpleasant side effects too. The treatment can also place strain on personal relationships as it is a stressful time.

My chest exacerbations usually occur multiple times a year and as I get older the frequency of treatment is gradually increasing. Fewer chest infections would help reduce damage to my lungs, thus helping to slow disease progression.

My lung function (fev1) is significant to me, as it is an indicator to my overall respiratory health and is monitored carefully by the CF team. It can fluctuate, which can be a source of anxiety and concern. Any increase is beneficial; a few percent increase can make a positive difference to me both physical and psychologically.

My Body mass index (BMI) is an important aspect of my CF. Managing my weight effectively can be a struggle and requires a huge effort (and expense) on my part to retain a healthy BMI. If my weight drops low, this can often be one of the first indicators of a chest infection.

Life expectancy is very important to me too. Psychologically it has had an impact on me and in particular my future plans and overall outlook on life. It is always in the back of my mind, especially as I get older. In an ideal world I want my health to be stable, have less symptoms and to reduce burden of care so that I can achieve a normal quality of life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Cystic Fibrosis is a condition that requires specialist care. Cystic Fibrosis care is delivered within a specialist centre. Specialist care is undertaken by a multi-disciplinary team. The team are my first point of contact and hold regular outpatient clinics to monitor the condition.

Current treatment for my condition includes a large burden of daily treatment to treat the symptoms of CF. These include digestive enzymes, nebulisers, inhalers, antibiotics, fat soluble vitamins and physiotherapy.

Some of these treatments are easier to take than others. For example, pills and inhalers are much simpler, faster and discreet than a nebuliser. A nebuliser would require sterilisation, preparation and then take a few minutes to administer. It also requires charging, replacement parts and maintain ace and is not as portable, convenient or discreet.

Another treatment which I tend to dread is Intravenous antibiotics (IVs) which are delivered in hospital or at home. I, like many people with CF do prefer home IV treatment where possible for convenience, in order to retain some normality, but the regime is intensive and tiring.

Increasingly hospital admission is required, which can be disruptive and isolating. Both IV treatment options present challenges in terms of work, family and social commitments and are in addition to the daily burden of treatment.

IV treatment is usually two weeks and can be either preventative or responsive and required multiple times a year. The drugs can also bring on side effects and frequent use can result in antibiotic resistance/allergies.

I would certainly welcome any treatment that will reduce symptoms (physically and psychologically), is less time consuming, avoids hospitalisation, slows decline and reduces the overall burden of care.

3. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

- Improved/less symptoms – including exacerbations
- Better clinical outcomes and reduced disease progression
- Reduced treatment burden such as the time spent taking IV antibiotics and hospital admissions
- Better overall health, including a steady weight and well-being which will enable me to have a better quality of life i.e.: be more active, continue to work, plan ahead/for future.
- Less exacerbations and an increase in lung function may result in a slower decline thus the possibility to potentially increase life expectancy.
- Less need for antibiotics may also be beneficial for longer term antibiotic resistance and side effects.
- I have mentioned physically health, but the treatment may also impact on my mental wellbeing too. Anything that can help improve physical

symptoms would inadvertently also help to improve the psychological impact of living with CF too.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

It is the only treatment available for my mutation group that treats the underlying cause and not just the symptoms.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I have read that some people are worried about potential side effects of the treatment and that the impact of the drug may be variable to each individual.

4. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

There is nothing like this in the NHS currently available that treats the underlying cause of CF.

Please list any concerns you have about the treatment being appraised.

That it may be perceived to be too high cost. So I am concerned that funding for the drug may be an issue.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

5. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Currently this will only be for those with double delf508. There may be some individuals who may have a higher perceived benefit than others, depending on their individual health, disease progression and personal circumstances.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

This treatment will initially be for only 50% of the UK CF population with Double DelF508.

6. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I have not used the treatment so cannot comment

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, I think some of the key clinical outcomes have been captured, however I am unsure if the potential wider impact of the drug is fully captured.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐x Yes ☐ No

If yes, please provide references to the relevant studies.

Cystic Fibrosis Trust survey.

7. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No.

8. Other issues

Do you consider the treatment to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It treats the underlying defect of CF. Previously other medications have only treated the symptoms. It is the first medication of its kind for this specific mutation group.

Is there anything else that you would like the Appraisal Committee to consider?

Anything that may improve clinical outcomes and/or quality of life and slowing of disease progression could be life changing.

9. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is first drug of its kind for this mutation; been waiting a lifetime for a treatment that will treat the underlying cause of CF

- Any reduction in symptoms will have such a positive impact both physically and psychologically to lead a more ‘normal’ life
- Reduced treatment burden and hospital care will enable more freedom; to plan ahead without boundaries or limitations
- Impact on disease progression and life expectancy will provide a real hope for the future

- In summary: Life changing!

Title: Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Produced by ERG: Warwick Evidence

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Please note that: Sections highlighted in yellow and underlined are ‘academic in confidence’. Sections highlighted in aqua and underlined are ‘commercial in confidence’.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CF	Cystic fibrosis
CFQ-R	Cystic fibrosis questionnaire-revised
CFTR	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
EQ-5D-3L	EuroQoL 5 Dimension 3 level
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IV	intravenous
IVA	Ivacaftor
LUM	Lumacaftor
LUM-IVA	Lumacaftor-ivacaftor combination
MCID	Minimum clinically important difference
$ppFEV_1$	Percent predicted forced expiratory volume in 1 second
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
SoC	Standard of care
VAS	Visual analogue scale

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The CS decision problem as stated matches the population, interventions and comparators described in the final NICE scope (Box 1), although the intervention in the company's decision problem also includes standard of care (SoC) However, there are some differences in outcomes (see below).

Box 1: NICE final scope

	Final scope issued by NICE
Population	People with cystic fibrosis aged 12 years and older who are homozygous for the *F508del* mutation
Intervention	Lumacaftor and ivacaftor combination therapy
Comparator (s)	Established clinical management without lumacaftor and ivacaftor combination therapy (Standard of Care)
Outcomes	• Mortality • Lung function • Body mass index • Respiratory symptoms • Pulmonary exacerbations • Frequency and severity of acute infections • Need for hospitalisations and other treatments • Adverse effects of treatment • Health-related quality of life

The intervention, lumacaftor and ivacaftor combination therapy (LUM-IVA), is indicated for the treatment of cystic fibrosis (CF) in people aged 12 years and over with diagnosed CF who have a genotype that is homozygous for the *F508del* mutation on the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene. The Company received marketing authorisation from the European Medicines Agency in November 2015. The recommended dose is 400 mg of lumacaftor with 250 mg of ivacaftor, taken twice daily, in addition to ongoing clinical management of CF (SoC).

The comparator is established clinical management, which is currently the standard of care for the management of CF. This was also the comparator (with placebo) in the included clinical evidence. Details of SoC were not reported in the CS.

1.2 Summary of submitted clinical effectiveness evidence

The CS included a systematic review to search for evidence to meet the decision problem. The ERG considered the systematic review to be of reasonable quality, though the chance of systematic error in the review was uncertain. This was due to lack of clarity in the processes undertaken, partly due to ambiguous inclusion and exclusion criteria and also due to the inclusion of outcomes in the search strategy.

The CS systematic review found six randomised trials, of which four tested LUM-IVA. One was a Phase 2 trial which the ERG regarded as not directly informative and thus excluded. Two placebo-controlled randomised trials, TRAFFIC and TRANSPORT, were pivotal phase 3 trials and were summarised in depth in the CS. These two trials were substantially identical in conduct and analytic method and the CS also presents data from a pre-planned pooled analysis. The fourth trial, PROGRESS, is an ongoing extension study for TRAFFIC and TRANSPORT. While information from PROGRESS was presented, only one arm (i.e., without a comparator) was relevant to the licensed indication and results were from a pre-planned interim analysis. Therefore the ERG interpret these data cautiously.

Many of the outcomes in the NICE scope are reflected in the clinical evidence. Specifically, in the pooled analysis for TRAFFIC and TRANSPORT, LUM-IVA administered at the recommended dose had several statistically significant effects on key outcomes at the primary trial endpoint, which was 24 weeks after initiation.

- **Lung function.** On percent predicted forced expiratory volume in one second ($ppFEV_1$), patients receiving LUM-IVA had an absolute change from baseline that was significantly greater than those in the placebo group (2.8%; 95% CI 1.8, 3.8). Relative change from baseline (i.e., as a percentage of the baseline value) was also significantly different between groups (4.8%; 95% CI 3.0, 6.6)
- **Body mass index (BMI).** Patients in the LUM-IVA group had a significant greater change in BMI from baseline than those in the placebo group (0.24; 95% CI 0.11, 0.37).
- **Pulmonary exacerbations.** Patients in the LUM-IVA group had a significantly reduced rate of pulmonary exacerbations as compared to those in the placebo group (rate ratio 0.61; 95% CI 0.49, 0.76).
- **Need for hospitalisations and other treatments.** Patients in the LUM-IVA group had a significantly reduced rate of pulmonary exacerbations requiring hospitalisation (rate ratio 0.39, $p<0.0001$) and of pulmonary exacerbations requiring IV antibiotics (rate ratio 0.44, $p<0.0001$) as compared to those in the placebo group.
- **Health-related quality of life.** On the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, patients in the LUM-IVA group were not significantly different from those in the placebo group (2.2; 95% CI 0.0, 4.5).
- **Adverse events.** The rate of any treatment-emergent adverse event (TEAE) between relevant study arms was similar, though placebo appeared to have a higher incidence of any serious adverse event. Of the TEAEs, placebo-treated patients had a greater risk of infective pulmonary exacerbation, cough, increase in sputum production and nasal congestion than

patients receiving LUM-IVA, whereas patients receiving LUM-IVA reported dyspnoea, diarrhoea, nausea and upper respiratory infection in greater numbers.

The frequency and severity of NICE scoped outcomes of acute infections, and respiratory symptoms, are not discussed directly in the CS. Some acute infections and respiratory symptoms are reported in the adverse events, but these do not record the severity of the events. Mortality is also not directly addressed, though only one death occurred in the relevant arms of TRAFFIC and TRANSPORT, and this was judged to be unrelated to the study.

1.3 Summary of the ERG's critique of submitted clinical evidence

The ERG appraisal of TRAFFIC and TRANSPORT, the pivotal phase 3 trials in the CS, substantially agreed with the CS appraisal, and the ERG agreed that the trials were of generally good quality. However, the ERG noted some evidence of selective reporting bias. The CS approach to pooling the phase 3 trials appeared reasonable, and the analytic methods used within both phase 3 trials also appeared to be appropriate.

The ERG noted several issues with the submitted clinical evidence:

- First, though the NICE scope did not specify severity of disease, both trials included only CF patients with mild to moderate CF (that is, with $ppFEV_1$ between 90% and 40% at screening). This means that clinical evidence may not generalise to those with 'end-stage' CF or those at the beginning of the disease course. The CS does not discuss this issue.
- Second, several outcomes addressed in the NICE scope were not adequately reflected in the included clinical evidence. Specifically, mortality was not directly addressed in the CS except as an adverse event; respiratory symptoms were only considered as adverse events; frequency of acute infections was only considered under adverse events, and severity of acute infections was not discussed; and results for EQ-5D-3L, a measure of health-related quality of life (HRQoL), were mentioned but not presented in the CS.
- Third, some outcomes were not adequately reported in the CS. Clarifications for these outcomes were requested and responses were generally useful, with some exceptions. Specifically, data presented on rates of pulmonary exacerbations were not clear regarding the unit of analysis, and numbers did not appear (based on the ERG's reading) to reconcile between different tables.

1.3.1 Strengths

This CS had several strengths:

- In the main, quality of the systematic review was reasonable, and assessment of study quality was appropriate.

- The quality of the included trials, TRAFFIC and TRANSPORT, was good.
- Patients in the included trials were considered to be generalisable to those in England by the ERG clinical advisor.
- The approach the CS used to pool studies appeared to be appropriate, though more specific details of the statistical methods used were not available.
- Expert statements noted that TRAFFIC and TRANSPORT were the largest trials of a CF therapy conducted to date.

1.3.2 Weaknesses and areas of uncertainty

However, this CS had several weaknesses:

- Eligibility criteria and searches for the systematic review were not completely clear and appropriate; for example, responses to clarification questions revealed that an exclusion criterion had been stated in error, and pilot studies were excluded. The search strategy also included outcomes that did not overlap with the NICE scope.
- There was evidence of selective reporting in respect of the outcome of 'response', though this was later addressed in the clarifications. However, questions remain as regards the number of pulmonary exacerbations in the placebo group and the consistency of reporting across tables. Data for the EQ-5D were not presented in the original submission.
- Related to this, data regarding adverse events had unclear sample sizes, especially given that in some analyses relating to PROGRESS, more participants were included than appeared to be randomised.
- The short-term nature of the trials meant that long-term effects are uncertain.
- Finally, it was unclear what constitutes a clinically meaningful difference for key outcomes, particularly for absolute change in FEV_1 and relative change in FEV_1. The ERG clinical advisor suggested that the former is more relevant to patients and clinicians.

1.4 Summary of submitted cost-effectiveness evidence

The company submitted a de novo Markov model with a lifetime horizon, and a cycle length of 4 weeks for the first 2 years and 1 year thereafter. Patient survival in each cycle of the model is based on an individual's $ppFEV_1$, pulmonary exacerbations, weight-for-age z-score, pancreatic sufficiency, diabetes, *B. cepacia* infection, *S. aureus* infection, age and sex. Additionally, probabilities of lung transplantation, adverse events and treatment discontinuation are applied in each model cycle.

The initial patient cohort in the model represents the population from the TRAFFIC and TRANSPORT studies, with identical populations simulated through the LUM-IVA and SoC arms of the model. Short-term data on differences between treated and untreated patients in $ppFEV_1$, pulmonary exacerbation rates and weight-for-age z-scores are taken from the TRAFFIC and

TRANSPORT studies. Long-term $ppFEV_1$ progression with LUM-IVA is based on 48-week data from the TRAFFIC, TRANSPORT and the open-label PROGRESS study. Long-term $ppFEV_1$ progression with SoC is based on a US and Canadian cohort study, and data on other long-term outcomes are derived from the UK CF registry, often using data from the whole population rather than the F508del mutation subpopulation. The benefits of treatment on $ppFEV_1$ progression and pulmonary exacerbation rates are assumed to persist as long as a patient is on treatment, and the benefits on weight-for-age z-score last for the duration of the model. It is assumed that no patients will discontinue treatment after the time horizon of the trials.

EQ-5D data were collected during the TRAFFIC and TRANSPORT studies, and an equation is estimated to link utility scores to $ppFEV_1$ values and recent pulmonary exacerbation. These utility values are then applied for the duration of the model, assuming no other differences in utility result from treatment. Probabilities of lung transplantation and outcomes post-transplant are assumed to be the same, regardless of prior treatment.

The full costs of LUM-IVA therapy are applied to people on treatment in the model for the first 12 year. It is then assumed that a generic alternative would become available, to which all individuals are immediately switched, which costs 11% of the pre-generic price. Costs of disease management are based on a study including individuals with the *G551D* mutation, and the 61% reduction in pulmonary exacerbation related hospitalisation with LUM-IVA treatment in the trials is applied to all hospitalisations in the model, for as long as an individual remains on treatment.

The company also conducted a range of sensitivity and scenario analyses, looking at the impact on cost-effectiveness of changing parameter values, using different model assumptions or modelling different subpopulations.

1.4.1 Base case results

The company base case results indicate that LUM-IVA will provide an additional 3.45 QALYs versus SoC and costs an additional £753,570, with an ICER of **£218,248 per QALY**. The parameters included in sensitivity analyses to which this estimate is most sensitive are the assumed rates of decline in $ppFEV_1$ in the LUM-IVA group, discount rates and disease management costs. At willingness-to-pay thresholds of £30,000 per QALY and £50,000 per QALY, there is a 0% probability of LUM-IVA being cost-effective versus SoC alone.

1.5 Summary of the ERG's critique of submitted cost-effectiveness evidence

1.5.1 Strengths

- The model constructed by the Company is clearly explained and logical. The model developed appears to capture important features of the disease (mortality, $ppFEV_1$, pulmonary exacerbations, lung transplantation).
- The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.
- The company model makes use of both short-term randomised trial data and longer-term cohort studies, to attempt to capture both short-term differences with treatment and the longer-term natural history of the condition.
- Other than two issues which the company has appropriately addressed (errors in the calculation of disease management costs and an incorrectly specified PSA distribution), no discrepancies were identified between the models reported in the company submission and the version supplied to the ERG, nor were any errors identified in running additional analyses.

1.5.2 Weaknesses and areas of uncertainty

- Since there are no long-term follow up studies comparing LUM-IVA to SoC alone, long-term extrapolations for the two arms are made separately based on different, un-randomised datasets. This may introduce bias that it is not possible to test or adjust for in the analysis.
- Many of the natural history parameters in the model are informed by data on the whole UK CF population, not data for the particular *F508del* mutation of interest.
- Long-term extrapolations of $ppFEV_1$ values with LUM-IVA treatment are based on data with a follow-up of only 48 weeks, meaning short term benefits are assumed to persist over much longer time horizons.
- The benefit of treatment with LUM-IVA on $ppFEV_1$ and rates of pulmonary exacerbations is assumed to remain the same as in the trial, for as long as a person remains on treatment. The benefits of treatment on weight-for-age z-scores is assumed to persist for the remainder of an individual's life.
- In the base-case, it is assumed that no patients will discontinue from LUM-IVA treatment after the time horizon of the trial.
- Quality of life for individuals with CF (pre-transplant) is assumed to depend only on $ppFEV_1$ values and recent pulmonary exacerbations, with treatment having no other effect (positive or negative) on quality of life.
- Disease management costs are estimated from a population including individuals with the *G551D* mutation, and the 61% reduction in pulmonary exacerbation hospitalisations from

TRAFFIC and TRANSPORT is assumed to apply to all hospital costs whilst patients remain on treatment.

- Whilst a justification is given for the incorporation of a generic price discount in the model, no clear reason is given for the particular discount chosen.

1.6 Summary of sensitivity and exploratory analyses undertaken by the ERG

The ERG ran an additional set of sensitivity analyses, based on the company's base-case model, looking at the impact of differing assumptions around the time until a generic alternative treatment becomes available, and the price discount this generic would provide. This produces a range of ICERs from £197,790 per QALY to £349,337 per QALY, depending on the assumptions used.

The ERG also ran a modified version of the company's base-case, incorporating the following different assumptions:

- Adherence rates to treatment for LUM-IVA are set to 96.5% for costing purposes. This means the same adherence level is used for both effectiveness and cost data.
- The new model incorporates discontinuations from LUM-IVA treatment after the time horizon of the TRAFFIC and TRANSPORT studies. Discontinuation rates for weeks 24-48 were taken from the discontinuation rates for individuals in the PROGRESS study who had previously received LUM-IVA during TRAFFIC or TRANSPORT (13.5% annually). Annual discount rates after this point are assumed to be 1.9%, in line with a scenario analysis in the CS.
- The placebo-adjusted mean change from baseline in $ppFEV_1$ is calculated using data from the 24-week time point, rather than the average of the 16-week and 24-week follow ups. This replaces the 2.8% absolute increase in the company's base-case model with a 2.45% absolute increase.

In the ERG's base case, LUM-IVA provides an additional 3.22 QALYs versus SoC and costs an additional £714,637, with an ICER of **£221,992** per QALY.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company describes cystic fibrosis (CF) and the F508del mutation on CS pp. 22-23 and the ERG clinical advisor agrees that this is an appropriate summary of the condition. The CS describes CF as a genetic disease that is rare, chronically progressive, and life-limiting in nature. Though it is multisystemic in its effects, CF most prominently affects the respiratory tract and respiratory failure is the largest cause of death in people with this condition. The specific CF-associated genotype relevant to this submission is in patients homozygous for the F508del mutation on the CTFR gene. As described on CS p. 23, this mutation has the effect of both preventing normal formation of the CFTR protein and of restricting the protein's function.

As described on pp. 22-23 of the CS, CF is characterised by ongoing progressive decline in lung function. This is measured by declines in percent predicted forced expiratory volume in 1 second ($ppFEV_1$). In addition, because CF results in the production of unusually thick respiratory secretions, CF progression is accelerated by the occurrence of pulmonary exacerbations. Finally, poor nutritional status due to deficiencies in gastrointestinal enzyme production is characteristic of CF. Citing evidence from cohort studies,[1, 2] the CS states, and the ERG clinical advisor agrees, that decline in $ppFEV_1$, pulmonary exacerbations and poor nutritional status are key drivers of mortality in CF. Thus, these three outcomes are targets for supportive therapy in CF.

The company states on p. 22 and again on p. 24 that median age of death for people with CF is 28 years. However, the ERG clinical advisor notes that median survival has improved over the last 20 years with improved standards of care, and that the median age of death does not reflect this. In total, 10,583 patients are included in the UK Cystic Fibrosis Registry. The company notes on p. 23 that of those living with CF in the UK, approximately 50% match the genotype for which this drug is indicated[3] (CS p.23), and that this corresponds to approximately 2,748 patients (CS p. 22). However, the submission for the Cystic Fibrosis Clinical Reference Group, for NHS England, suggests that the number of eligible patients would be closer to 3,500. The company notes that CF has extensive impacts on patients due to frequent and debilitating illness, treatment burden, and psychological effects on the patient and the patient's carers.

2.2 Critique of company's overview of current service provision

The company reviews current service provision for CF on pp. 24-25. It is noted that CF in patients with the relevant genotype is managed with supportive care to control symptoms and pulmonary exacerbations, and to prevent deterioration of lung function. The company further notes that there is no NICE guidance on management of CF, but that guidance has been published by the UK Cystic

Fibrosis Trust. The ERG clinical advisor agreed that management consists of supportive care, but also highlighted that the European Cystic Fibrosis Society has published relevant guidance. In response to clarification question A18, the company stated that LUM-IVA is intended for chronic use as an adjunct to the medications that are currently used as standard of care (SoC) for CF management and that it will not replace SoC treatments in clinical practice. Treatment with LUM-IVA can be initiated at any point in the patient treatment pathway in line with its licensed indication. Early initiation of treatment may benefit patients given the disease progression over time that is characteristic of CF.

2.3 Changes to service provision

The company notes changes to service provision on CS pp. 21-22, and again on p. 25. The company observes that LUM-IVA is intended to be used as an adjunct to SoC, and that the major modification to existing service delivery would be additional liver monitoring, which the company believes would be readily integrated into existing management. The ERG clinical advisor specifically notes that hepatic function tests are currently conducted on a yearly basis, so more frequent hepatic function testing during the first year of treatment (at 1, 3, 6, 9 and 12 months after initiation) would pose additional costs. Genotyping is currently undertaken routinely, and therefore there would be no additional costs in identifying people with the F508del mutation.

Eye screening was undertaken in the TRAFFIC and TRANSPORT trials, and participants were excluded if they had a history of cataract or lens opacity or evidence of cataract or lens opacity determined to be clinically significant by the ophthalmologist during the ophthalmologic examination at the screening visit. The ERG's clinical advisor noted that it may be likely that advice is issued to ensure children have an eye check before commencing the drug, which could introduce additional costs.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population in the decision problem matches the population described in the final scope. The population of interest is people 12 years of age or older diagnosed with CF and homozygous for the F508del CTFR mutation. However, the clinical evidence presented specifically included patients with mild to moderate CF; that is, with ppFEV$_1$ at screening of between 40% and 90%. In response to clarification A5, the company stated that *'as in virtually all clinical studies of CF, it was necessary to work within upper and lower limits of percent predicted FEV$_1$ as inclusion criteria in order to standardise the patient population'*, though the company noted that a number of patients had fallen to below 40% ppFEV$_1$ between screening and baseline and these patients were included. The ERG clinical advisor noted that testing in this population may not account for 'alternative' uses of the drug in patients with very mild CF, or with severe CF, e.g. in patients waiting for lung transplantation. Participants were also excluded if they had a history or observation of clinically significant cataract or lens opacity. However, the ERG clinical advisor noted that the population in the trials was similar to CF patients in England and Wales.

3.2 Intervention

The intervention in the company's decision problem is lumacaftor and ivacaftor combination therapy (LUM-IVA) plus SoC. The NICE scope does not specify SoC as part of the intervention, however its inclusion is appropriate as LUM-IVA is intended as an adjunct to SoC (see section 2.2). Lumacaftor is a CTFR corrector that improves the production of the CTFR protein, and ivacaftor is a CTFR potentiator that improves the protein's function at the cell surface. The CS outlines the technology on page 19. The ERG requested additional information from the company on the mechanism of LUM-IVA and this was provided in clarification point A19. Processing of respiratory secretions depends on the correct creation and positioning of specific proteins within bronchial cells (i.e., cells in the airways). In patients homozygous for the F508del mutation, the pathway of creation and positioning of these proteins is flawed in several respects. LUM-IVA is intended to correct several parts of this pathway. As confirmed by in vitro experiments, lumacaftor works within the cell by improving the structure of the proteins, increasing the amount of the proteins that is available for use, and prolonging the proteins' useful life in the correct position on the cell surface. Once the relevant proteins have been positioned at the cell surface, ivacaftor increases their capacity further. Cell culture experiments suggest that lumacaftor and ivacaftor have an additive effect in improving the function of bronchial cells. The ERG clinical advisor confirmed that the brief description of the chemical action of this therapy is correct.

LUM-IVA (lumacaftor 400 mg twice daily, ivacaftor 250 mg twice daily) has received marketing authorisation from the European Medicines Agency (19 November 2015). The Food and Drug Administration (FDA) released a regulatory decision on 2 July 2015 approving LUM-IVA for marketing. The FDA briefing noted that slightly different results were obtained through correction of stratification errors in the original analyses for the clinical evidence contained in the submission. The FDA reviewer noted that this did not change conclusions, but on $ppFEV_1$ (absolute change from baseline) figures are slightly off by 0.1 on either the point estimate or on upper/lower confidence intervals. This may have some minor implications for the accuracy of subsequent modelling as the CS contained the 'incorrect' estimates. Moreover, the FDA submission makes two findings about adverse events worth noting: first, that more people receiving LUM-IVA experienced hepatic severe adverse events; and second, that respiratory symptoms occurred at a higher rate in those receiving LUM-IVA, though these data come from examining both LUM-IVA dosing arms (i.e. one arm with the indicated dose, and one arm with a higher dose) jointly.

The CS does not summarise the findings of the FDA review. However, the company acknowledges on p 19 of the CS that the key issues raised in the draft CHMP marketing authorisation were the clinical relevance of the absolute change in $ppFEV_1$, long-term maintenance of effects, effects on pulmonary exacerbations, the benefit of this combination therapy for patients with rapidly progressing CF, and the benefit derived from LUM-IVA combination therapy in everyday clinical practice as opposed to in the pivotal trials included in the clinical evidence.

3.3 Comparators

The NICE scope specified the comparator to be established clinical management without LUM-IVA (such as, best supportive care including but not limited to, mannitol dry powder for inhalation, inhaled mucolytics, nebulised hypertonic saline, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and oral, nebulised and intravenous antibiotics). The company's decision problem (CS p.14) stated that the submission presents data for LUM-IVA in conjunction with patients' usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), referred to as SoC throughout the submission, versus SoC alone. As such, the comparison in the clinical evidence was LUM-IVA plus SoC versus placebo plus SoC. Mannitol dry power is the only specified comparator treatment that has been recommended by NICE as a treatment option for cystic fibrosis, although the indication is not identical to that of LUM-IVA.[4] However the CS does not report the use of mannitol dry powder for inhalation as part of SoC. The ERG clinical advisor stated that SoC used in the clinical trials is relevant to UK practice.

3.4 Outcomes

The outcomes in the scope mostly match those in the decision problem, though not all are presented in the clinical evidence. Specifically, lung function, body mass index, and pulmonary exacerbations, which are covered in the scope, are presented in the clinical evidence. Mortality, though addressed in the scope, is not directly reported in the clinical evidence (other than through assessment of adverse events), though the ERG believes this is likely due to the inability to capture mortality outcomes in a short-term trial. The outcomes of respiratory symptoms, frequency and severity of acute infections, and need for hospitalisations and other treatment are not *per se* addressed in the submission, though frequency of pulmonary exacerbations requiring hospitalisation and frequency of those requiring IV antibiotics are reported. The ERG clinical advisor noted that the outcomes reported in the clinical evidence would be appropriate measures of acute infections. Findings for EQ-5D-3L are discussed, but the treatment effect is not reported in the submission.

3.5 Other relevant factors

The CS makes a case for innovation, see section 7 for details.

4 CLINICAL EFFECTIVENESS

4.1 Critique of company's approach to systematic review

The CS conducted a systematic review for evidence of clinical effectiveness; the ERG's quality assessment of this is summarised in Table 1 below. The quality of the company's systematic review was reasonable, although the ERG had concerns regarding the inclusion of selected outcomes in the search strategy (see section 4.1.1). The process for study selection was adequate (two independent reviewers), but the processes for data extraction and quality assessment were not described in the CS. This was clarified by the company (clarification question A7) and was considered to be appropriate by the ERG.

The submitted evidence generally reflects the decision problem, although it should be noted that the trials were limited to mild to moderate cystic fibrosis and all outcomes in the scope were not explicitly addressed (e.g. mortality, need for hospitalisations and other treatments).

Overall, the chance of systematic error in the systematic review is uncertain due to lack of transparency in the processes undertaken.

Table 1 Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	ERG Response
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Uncertain - eligibility criteria are reported (CS Table 7 p. 27), however, there are some differences between these and the NICE scope. A second eligibility stage was applied to references reported to be included.
2. Is there evidence of a substantial effort to search for all relevant research?	Uncertain – the inclusion of some outcomes (but not all relevant outcomes), and including outcomes not listed in the scope, may have limited the searches and missed relevant research (see Section 4.1.1). A potentially relevant ongoing study was identified by the ERG (see 4.2.12).
3. Is the validity of included studies adequately assessed?	Yes – the CS uses the NICE recommended criteria and the quality of the TRANSPORT/TRAFFIC RCTs is generally good. The ERG agrees with the company's assessment, although notes that 'Response' was measured but not reported in the CS (data provided by the company following request by the ERG).
4. Is sufficient detail of the individual studies presented?	Yes – trial methodology (CS Table 10 p.35-39), statistical analysis (CS Table 11 p. 40-43), patient disposition (CS Table 12 p.45) and baseline characteristics (CS Table 13 p.46-47) were presented.

	However the pre-planned subgroups were not listed (although subgroups were not specified on the NICE scope), and some details such as method of randomisation were only available in the trial publication and CSR.
5. Are the primary studies summarised appropriately?	Yes – results for each RCT are presented in narrative form with tabulation of data. Where detail is lacking, such as 95% confidence intervals for some outcomes, data are available in the publication and CSR. Results for absolute and relative change in $ppFEV_1$, and absolute change BMI, weight and CFQ-R are presented in the CS as difference between groups in change from baseline values only. No statistical details were reported for EQ-5D-3L. Baseline values and change from baseline values for each group were provided by the company when requested by the ERG (clarification question A6). Methods used to pool the two RCTs are not provided in the CS, but further information is given in the appendix of the trial publication.

4.1.1 Description of company's search strategy

The company reports one set of searches for both published RCTs and published non-RCTs. These searches were undertaken on 29th July 2015 (EMBASE) and 3rd August 2015 (Cochrane) in the following medical databases (MEDLINE, MEDLINE In-process and Embase (via EMBASE.com); CDSR, DARE and CENTRAL (via the Cochrane Library)). These searches sought literature for lumacaftor monotherapy, ivacaftor monotherapy, LUM-IVA combination therapy, and SoC therapies for patients with CF, but the inclusion of a few selected outcomes (but not all relevant outcomes), and some outcomes not listed in the scope (see lines 11 to 17 of the EMBASE search strategy, CS Appendices p. 27) is a limitation for two reasons. Firstly, although unlikely, some records not retrieved by the search may have included one or more of the other relevant outcomes (i.e. those not included in the search). Secondly, it is common for study outcomes not to be mentioned at all in database records and therefore, the inclusion of any outcomes in a search can result in relevant research being missed. The search terms and lines were combined correctly. The searches were limited to the last 10 years. Conference proceedings were excluded from the electronic searches, which may have missed relevant research.

The Company searched the most recent year of one conference directly (European Cystic Fibrosis Society, 2015). A separate search of the manufacturer's database is mentioned (see CS p. 29), but no search for ongoing studies is reported.

The ERG checked three recent conferences (International Congress on Pediatric Pulmonology 2015, British Thoracic Society 2015 and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2015). No relevant studies were identified.

The ERG checked the studies reported in CS Appendix 3 for any additional studies of relevance to the decision problem. None were identified.

In addition, the ERG undertook several targeted searches for:

- Published RCTs in LUM-IVA combination therapy published in the last 2 years, without including any 'outcome' related terms. No additional studies were identified.
- Ongoing trials. One non-randomised single group study relevant to the decision problem was identified (see section 4.2.12 for further details).
- Published lumacaftor monotherapy, ivacaftor monotherapy and LUM-IVA combination therapy studies that include specific adverse effects. No additional studies were identified.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The inclusion criteria for the systematic review were in the main clearly stated (see CS Table 7 p. 27), though some important ambiguities exist. Inclusion criteria were stated as all mutations and all ages of cystic fibrosis (though case definition criteria are not specified), and the presence of either lumacaftor monotherapy, ivacaftor monotherapy, or LUM-IVA. The population (specifically, the mutations included) and intervention criteria appear to be broader than in the decision problem. There was no age limit specified in the NICE scope, however the proposed indication is for people 12 years and older. The indication is 400mg LUM, 250mg IVA every 12 hours, and the criteria are broader than this. This may have been to facilitate searching, but this is unclear.

Included comparators were SoC, with SoC 'not used in clinical practice' excluded. This reflects the NICE scope, i.e. established clinical management without LUM-IVA, however excluded types of SoC were not appropriately described. In response to clarification question A4, the company stated that 26 studies were excluded due to SoC, These were aztreonam (AZLI) (6 studies), ceftazidime (3 studies), gene therapy (2 studies), hyaluronic acid (2 studies), ataluren (2 studies), corticosteroids (2 studies), clarithromycin (2 studies), meropenem (2 studies), aminoglycoside (1 study), cysteamine (1 study), lucinactant (1 study), l-arginine (1 study) and glutathione (1 study). The ERG clinical advisor agreed that the exclusion of studies of these treatments was appropriate.

Specified outcomes were BMI, FEV_1, pulmonary exacerbations, sweat chloride levels, weight and z-score (likely BMI z-score based on reporting on CS p. 58). Outcomes specified in the search appear to be narrower in part and broader in part than those in the decision problem. The scope includes mortality, respiratory symptoms, frequency and severity of acute infections, need for hospitalisations

and other treatments, adverse effects, and HRQoL, none of which were in the review eligibility criteria. The review additionally included weight, which appears to be corollary to BMI as included in both the review and the decision problem, and sweat chloride, which is a marker of cystic fibrosis and not included in the decision problem or scope.

Included study designs were stated as observational and RCT, but crossover, individual case studies, pilot, retrospective and post-hoc, reviews/letters/comments, and time/dose comparisons were excluded. It was not clear what type of observational studies were eligible, and it is of note that no observational studies were ultimately included, whilst 90 studies were excluded due to study design (no further details reported in the original CS). In response to clarification question A2, the company stated that the exclusion code of study design '*encompassed other reasons for exclusion i.e. the focus or the purpose of the study was deemed not relevant'* and that details of the excluded study designs could not be provide in the timeframe for response. A justification for excluding crossover studies and pilot studies was not provided. In response to clarification question A1, the company stated that in fact crossover studies were not excluded and that this was an error in CS Table 7. The company also stated that pilot studies were excluded as '*a pilot study is not a hypothesis testing study and results may be prone to bias due to small sample sizes'*. The ERG does not agree that it is reasonable to exclude a relevant RCT due to it being a pilot study. The company was unable to provide information on the number of relevant pilot studies potentially excluded. Non-English studies were excluded, although justification for this was not provided. Quality limits were not placed on the RCTs, which is reasonable.

A PRISMA diagram (CS Figure 1 p. 28) summarised studies included and excluded, although a second stage of inclusion was applied and 28 studies were subsequently excluded for not reporting data on homozygous F508del mutation. These were not presented in the flow diagram or the eligibility criteria in CS Table 7 (p27). The studies were 14 of ivacaftor monotherapy and 24 of SoC (CS p29).

The company was not explicit about biases throughout the search process, perhaps most notably from their search strings including outcomes and from examining a different set of outcomes than in the decision problem, from excluding pilot studies and from ambiguities in study designs flagged for exclusion. Moreover, many studies nominally included in the systematic review were actually excluded because they did not report information on the homozygous F508del subgroup.

4.1.3 Identified studies

Included RCTs were summarised in CS Table 8, p. 30, and these included phase 2 and phase 3 studies. No non-randomised studies were included. In total, six RCTs were identified, of which two (TRAFFIC and TRANSPORT) were published in one paper[5] and of which one (PROGRESS) was

only presented as interim analysis (not identified in searches of the literature but from a separate search of the company's database). As discussed above, the CS excluded 28 studies from the main submission because the participants did not have homozygous F508del mutations (n=14 ivacaftor monotherapy, 24 SoC). These studies are not further summarised in the CS, although references are tabulated in CS Appendix 3, Table i. The ERG was provided with all relevant RCT reports electronically, including summaries of data from the CSRs. All Phase 2 and Phase 3 trials discussed in the submission were funded by Vertex Pharmaceuticals.

Three phase 2 trials are provided in CS Table 9 p. 32 in summary form. The ERG does not consider these studies to be of relevance to the NICE scope and the decision problem as they were either monotherapy studies (ivacaftor 150mg, n=1; lumacaftor n=1) or included lower doses of combination therapy (n=1). Although cohort 3 of phase 2 study 809-102 received the relevant LUM-IVA dose for 28 days, participants had previously been allocated to 28 days of lumacaftor monotherapy and were compared with a placebo group (combined placebo groups from cohorts 2 and 3) that contained both homozygous and heterozygous participants.[6] The phase 2 studies are not discussed further.

The three phase 3 trials are presented in CS Tables 10 (trial methods, including primary and secondary outcomes, CS p. 35), 11 (analysis methods, CS p. 40), 12 (patient disposition, CS p. 45), and 13 (baseline characteristics, CS p. 46), with outcomes presented in CS Tables 14-31. All key details of study samples, analysis, groups, patient disposition and related information are presented, with the exception of specific outcome data that appear to be missing or unclear, see Section 4.1.6 for details.

The two pivotal RCTs, TRANSPORT and TRAFFIC, were similar in their design. Both were 3-arm, 24-week placebo-controlled RCTs. As LUM-IVA is an adjunct to SoC the CS states (CS p. 44) that placebo and LUM-IVA participants continued SoC, and as such the placebo arm is a SoC comparator as per the decision problem. The ERG agrees that this is appropriate. Of note is that all three phase 3 trials included arms with different dosing from the indication (i.e. TRAFFIC, TRANSPORT and PROGRESS all investigated 600mg LUM-250mg IVA q12h alongside the 400mg LUM-250mg IVA for which this drug has specifically been licenced). These arms are not summarised in the CS. The ERG agrees with this omission from the CS and does not consider these arms further.

No flow charts of participant disposition were provided in CS Section 4.5, however key information is detailed in CS Table 12 (CS p. 45). The ERG has summarised the participant disposition in Table 2; the numbers in the TRAFFIC and TRANSPORT pooled safety set were confirmed in clarification response A16. For the full analysis set in the pooled LUM-IVA arms of the RCTs, there was a 1.9% loss from the number randomised. In the pooled placebo arms of the RCTs there was a 0.8% loss from the number randomised. The proportions completing the studies was 94.7% in the pooled LUM-IVA

groups compared with 98.1% in the pooled placebo groups. Reasons for discontinuation (other than adverse events) were not provided in the CS; however the ERG has reproduced these in Table 3 below from the trial publication.[5] The results for TRAFFIC and TRANSPORT were pooled (see below).

The third included phase 3 study (PROGRESS) is a long-term extension study (90 weeks) following on from TRAFFIC and TRANSPORT. 'Part A' of PROGRESS is presented in the CS; there is also a 'Part B' cohort that involves participants heterozygous for the F508del mutation and which is therefore excluded from the CS, the ERG agrees this is appropriate. The PROGRESS study is primarily a safety and tolerability study and is currently ongoing. At week 24, participants in the treatment groups of TRAFFIC and TRANSPORT continued in their allocated groups (LUM-IVA 400/250mg or 600/250mg doses) whereas participants in the placebo group were re-randomised to either of the LUM-IVA groups. Only the LUM-IVA 400/250mg group is of relevance to the decision problem and reported in the CS and the ERG report. As such the results of the PROGRESS study are considered as if from a single-arm study, although the interim results are presented for the first 24 weeks for those continuing with LUM-IVA (48 weeks of treatment) and those who have switched from placebo (24 weeks of LUM-IVA treatment).

The number of participants in PROGRESS is reported in CS Table 12, p. 45. For the participants continuing in their allocated LUM-IVA group the numbers do not concur with the numbers shown in the publication as rolling over to the PROGRESS trial (flow diagram suggests it should be 349,[5] however CS Table 12 states 341, see Table 2 below). Of the 341 reported, one participant did not receive treatment and 31 discontinued. The CS reports that 176 of the 358 placebo participants were allocated to the LUM-IVA 400/125mg group, and 18 had discontinued treatment by the time of the interim analysis (Table 3).

The ERG noted that there appeared to be more in the safety set in PROGRESS than were enrolled; that is, whereas the CS states on p. 36 that 341 subjects continued from the relevant LUM-IVA dose and that an additional 176 subjects were randomised to the relevant dose for a total of 517 subjects, several of the PROGRESS analyses include sample sizes of 544 (LUM-IVA n=368, placebo n=176, Table 2). The ERG requested participant flow charts for clarification (clarification question A16), but the company response did not provide these.

Table 2 Participant disposition from the included studies

	Pooled TRAFFIC and TRANSPORT		PROGRESS (Part A)	
	LUM–IVA 400/250mg BD	**Placebo**	**LUM–IVA 400/250mg BD**	**Placebo to LUM–IVA 400/250mg BD**
Randomised	376	374	341	176
Full Analysis set (% of randomised)	369 (98.1)	371 (99.2)	340 (99.7)	176 (100)
Safety Analysis set	369 (98.1)	370 (98.9)	368[a]	176[a]
Completed treatment	344	362	-	-
Completed study (% of randomised)	356 (94.7)	367 (98.1)	-	-

BD: Twice Daily (every 12 hours) [a]from CSR

Table 3 Reasons for discontinuation of treatment from the included studies

Pooled TRAFFIC and TRANSPORT		Progress (Part A)	
LUM–IVA 400/250mg BD	**Placebo**	**LUM–IVA 400/250mg BD**	**Placebo to LUM–IVA 400/250mg BD**
25 (AE: 17; refused further dosing: 2; did not meet eligibility criteria: 2; non-compliance with study drug: 2; Physician decision: 1; other: 1)	9 (AE: 6; refused further dosing: 2; required prohibited medication: 1)	31 (AE: 9; Refused further dosing: 15[a]; non-compliance with study drug: 1[a]; Other non-compliance: 1[a]; required prohibited medication: 2[a]; Pregnancy: 2[a]; Other: 1[a])	18 (AE 10; Refused further dosing: 3[a]; lost to follow-up: 1[a]; Physician decision: 2[a]; required prohibited medication: 1[a]; Pregnancy: 1[a])

AE: Adverse events; BD: Twice Daily (every 12 hours) [a]from CSR

There do not appear to be meaningful differences between treatment groups in baseline characteristics within the phase 3 trials (Table 4). Characteristics presented concur with the publication, but the publication does not report ethnicity or race and the CS does not report baseline mean percent predicted FEV_1 (reproduced by the ERG in Table 4 below).

Significance testing between trial arms on baseline characteristics was not presented for any of the included phase 3 trials; however the trial publication states the participants were well balanced between groups. Table 12 of the CS presents data for PROGRESS, but it is unclear whether data for

participants initially treated with placebo come from the first baseline (i.e. at randomisation to placebo) or at the point of randomisation to active treatment. The ERG identified from the CSR that these data are from the first baseline. The ERG agrees that participants appear to be similar between phase 3 trials, although assessment of this is complicated by the fact that two of the phase 3 trials feed into the third study.

4.1.4 Relevant studies not included in the submission

All relevant completed RCTs were identified by the CS.

One relevant ongoing study was identified by the ERG (see section 4.2.12 for further details). The study is a single-group open-label study in people aged 12 years and over, homozygous for F508del mutation and with advanced disease (Study VX14-809-106).

4.1.5 Description and critique of the approach to validity assessment

The CS included a quality assessment for five RCTs using criteria recommended by NICE. The trials assessed were two trials of monotherapy, phase 2 study 809-102 and a combined assessment of TRAFFIC and TRANSPORT. The combined assessment is appropriate as identical methods were used in the studies. The two trials of monotherapy and phase 2 study 809-102 were not relevant to the submission and have not been evaluated by the ERG. The quality assessment was presented in tabular format in CS Appendix 4 without any comment or discussion by the company.

The ERG quality assessment agrees with most of the company assessment of study quality for TRAFFIC and TRANSPORT. However the ERG notes that 'response' is not reported in the CS and as such there is evidence of selective reporting bias (data were provided by the company in response to clarification question A20). Modified ITT analysis appears to have been used for efficacy data by including all those who were dosed at least once in either arm, but it is unclear how missing data on study follow-up visits were handled other than imputation was not performed.

Table 4 Key baseline characteristics from included studies

	TRAFFIC		**TRANSPORT**		**Pooled**		**PROGRE point of fi**
	LUM-IVA 400/250mg BD N=182	**Placebo N=184**	**LUM-IVA 400/250mg BD N=187**	**Placebo N=187**	**LUM–IVA 400/250mg BD N=369**	**Placebo N=371**	**LUM–IV 400/250m BD N=34**
Mean Age (SD)	25.5 (10.09)	25.0 (10.80)	25.0 (9.03)	25.7 (10.02)	25.3 (9.56)	25.4 (10.41)	25.1 (9.33
Age groups, years, n (%)							
12 to <18	52 (28.6)	53 (28.8)	46 (24.6)	43 (23.0)	98 (26.6)	96 (25.9)	94 (27.6)
≥18	130 (71.4)	131 (71.2)	141 (75.4)	144 (77.0)	271 (73.4)	275 (74.1)	246 (72.4)
Female (%)	46.2	45.7	52.4	51.9	49.3	48.8	48.2
Mean (SD) BMI (kg/m^2)	21.68 (3.17)	21.03 (2.96)	21.32 (2.89)	21.02 (2.89)	21.5 (3.03)	21.0 (2.92)	21.4 (2.94
$ppFEV_1$ Mean (range)	60.5 (34.8, 94.0)	60.5 (34.0, 88.0)	60.6 (31.3, 96.5)	60.4 (33.9, 99.8)	60.5 (31.3, 96.5)	60.4 (33.9, 99.8)	60.4 (SD 14.20)[a]

BD: Twice daily (every 12 hours); [a]from CSR

Table 5 Company and ERG assessment of trial quality for TRAFFIC and TRANSPORT

Item	**Judgement**	
1. Was randomisation carried out appropriately?	**CS:**	Yes
	ERG:	Yes
Comment: randomization was stratified according to age (<18 vs ≥18 years), sex and ppFEV$_1$ at screening (<70 vs ≥70)		
2. Was concealment of treatment allocation adequate?	**CS:**	Yes
	ERG:	Yes
Comment:-		
3. Were groups similar at outset in terms of prognostic factors?	**CS:**	Yes
	ERG:	Yes
Comment: -		
4. Were care providers, participants and outcome assessors blind to treatment allocation?	**CS:**	Yes
	ERG:	Yes
Comment: -		
5. Were there any unexpected imbalances in drop-outs between groups?	**CS:**	No
	ERG:	No
Comment: a slightly higher proportion of participants receiving at least one dose in the LUM-IVA arm discontinued treatment compared with participants receiving at least one dose in the placebo arm (TRAFFIC 5.5% vs 2.2%; TRANSPORT 8.0% vs 2.7%), but proportions completing the study and rolling over to PROGRESS were high in both trials (TRAFFIC 96.7% vs 98.9%; TRANSPORT 96.3% vs 98.9%)		
6. Is there any evidence that authors measured more outcomes than reported?	**CS:**	No
	ERG:	Yes
Comment: Response (≥5% increase in average relative change in ppFEV$_1$) not reported (data provided by the company in response to clarification question A20).		
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**CS:**	No
	ERG:	Appears to be a modified ITT analysis for efficacy
Comment: 'Full Analysis Set' included all randomised patients who received at least one dose of study drug, patients were analysed as part of the study group to which they were randomly assigned'. States 'no imputation of missing data was performed'. The safety set included all patients who received any amount of study drug, patients were analysed according to the patients' actual study group regardless of the group to which they had been assigned. In response to clarification question A16, the company clarified differences between the full analysis set and the safety set in terms of group numbers.		

4.1.6 Description and critique of company's outcome selection

The NICE scoped outcomes were mortality, lung function, BMI, respiratory symptoms, pulmonary exacerbations, frequency and severity of acute infections, need for hospitalisations and other treatments, adverse effects and HRQoL. The CS reports in the decision problem (CS p. 14) that the implications of LUM-IVA on all of these outcomes is discussed. Outcomes from the pivotal phase 3 trials (TRAFFIC and TRANSPORT) and the extension study (PROGRESS) include measures of lung function (absolute and relative change in $ppFEV_1$); BMI (both absolute and as a z-score); pulmonary exacerbations (both overall and including those requiring hospitalisation, those requiring intravenous (IV) antibiotics, time to first event, risk of having at least one event and duration of events); adverse effects and HRQoL (while data were presented for the CFQ-R respiratory domain as a measure for HRQol, EQ-5D data were collected but not presented, though data were provided by the company in response to clarification question A6; see also below).

The absolute change from baseline $ppFEV_1$ at week 24 was calculated by averaging the mean absolute change at week 16 and week 24 to reduce known variability. The ERG clinical expert advised that this approach is becoming common in cystic fibrosis trials and is acceptable. The average of weeks 16 and 24 weeks was also used for the relative change from baseline $ppFEV_1$. The CS reports that the outcome was measured by spirometry according to published guidelines. No other details are provided in the CS. The FEV_1 is the maximum volume of air exhaled in the first second of a forced expiration from a position of full inspiration. In the CSR the definition for absolute change and relative change were Post-baseline value – Baseline Value and 100 × (Post-baseline value – Baseline value) / Baseline value, expressed as a percentage respectively. The CS does not report how the percent predicted values were calculated. In the CSR it is reported that the calculation of the $ppFEV_1$ was by published standards. There is no discussion of what is a clinically significant difference in absolute or relative $ppFEV_1$, though elsewhere in the CS and the CSR a threshold of 5% is used for determining response to the treatment. The company clarified that the 5% difference in $ppFEV_1$ with LUM-IVA relative to placebo was used as an arbitrary measure of effect size to assess the probability of a Type 1 error and estimate sample size for the trials (clarification question A10). In response to clarification question A15, the company confirmed that there is no empirically agreed minimum clinically important difference for absolute and relative changes in $ppFEV_1$. The ERG clinical advisor stated that absolute change is more clinically relevant than relative change, and that an absolute change in $ppFEV_1$ of 5% or more would be clinically important.

The number of pulmonary exacerbations is a secondary outcome in both trials. The other outcomes relating to pulmonary exacerbations are additional outcomes. No definition of a pulmonary exacerbation is provided in the CS. In the CSR pulmonary exacerbations are defined as a new or change in antibiotic

therapy (IV, inhaled, or oral) for any four or more of the following signs/symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection. The ERG clinical advisor agrees that this definition of pulmonary exacerbation is appropriate.

Although not specifically discussed as a separate outcome, the NICE scoped outcome of respiratory symptoms is likely to be covered by the events of cough, dyspnoea, sputum increase, haemoptysis, abnormal respiration, upper respiratory tract infection, nasal congestion, rhinitis and reduced pulmonary function test seen in the adverse event reports from the studies. The frequency and severity of acute infections are not discussed directly in the CS. Some acute infections are reported in the adverse events, but these do not record the severity of the events.

Other than pulmonary exacerbations requiring hospitalisations and those requiring IV antibiotics, the final NICE scoped outcome of 'need for hospitalisations and other treatments' is not discussed in the CS, although some data were provided in response to clarification question A21 (presented in section 4.2.7). Mortality is briefly addressed on CS p. 61 and 69.

HRQoL was measured in the TRAFFIC and TRANSPORT trials using the EQ-5D-3L and Euroquol Visual Analogue Scale (VAS), and the CFQ-R. The EQ-5D-3L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses from no problems to extreme problems. The VAS records an individual's rating for their current HRQoL state. Few details are reported in the CS; in the CSR it states that the self-report questionnaires were completed by the participants or their parents/caregivers. The CS on p. 60 states that assessing HRQoL with a generic measure can be difficult with a lifelong disease as people may perceive their HRQoL to be equivalent to those without CF. The ERG clinical expert agrees that there is good evidence for this assertion. The CFQ-R is a measure of HRQoL specifically for CF patients. The score ranges from zero to 100 with higher scores representing better health, and difference of at least 4 points is considered the minimal clinically important difference (MCID) for the absolute change from baseline. The ERG is not aware of evidence for the validity or reliability of CFQ-R as a measure of HRQoL.

Some specific outcome data appear to be missing from the CS or are unclear. There are no data presented for the EQ-5D in the CS (CS p. 60) (although data were provided by the company in response to clarification question A6, see section 4.2.8), there are ambiguities about patients and event rates in CS

Tables 16 and 17 that were unresolved by responses to clarification questions A11 and A12 (see section 4.2.5), and data in Tables 18 and 19 lacked confidence intervals. Information on duration of pulmonary exacerbations (CS p. 54) is presented narratively without a meaningful estimate of treatment difference, either in CS Table 20 or in the text.

As well as scoped outcomes noted above that were not reported, the CS did not report the proportion of participants with response (≥5%) on the $ppFEV_1$ which was reported in the trial publication, or the FEV_1 in litres.

4.1.7 Description and critique of the company's approach to trial statistics

Data from TRAFFIC and TRANSPORT were final data, while the data from the PROGRESS extension study are from a pre-planned interim analysis of the treatment cohort at 24 weeks (after up to 48 weeks LUM-IVA for the original treatment cohorts, up to 24 weeks for the original placebo cohorts). This study will continue for 96 weeks. Data are currently unpublished and are presented as AIC data.

The CS reports data from TRAFFIC and TRANSPORT for a full analysis set, which reflects all randomised participants who received at least 1 dose of the study drug. This modified ITT analysis excluded 7 participants from the LUM-IVA arms and 3 participants from the placebo arms. It appears that the final analysis set and the safety set are not completely identical. In response to clarification question A16, the company clarified that the two analysis sets are different on the placebo arms by one subject because at least one placebo patient received the active dose and was thus assigned to the active arm in the safety set.

A mixed-effect model for repeated measures (MMRM) was used for the analysis of the primary outcome, with least squares means, 95% CIs and p values obtained. A Bonferroni correction was applied to account for multiplicity. A hierarchical testing procedure was used for primary and five key secondary outcomes, where a statistically significant treatment effect was considered when the $p \leq 0.025$. The methods appear to be reasonable. The studies appear to be adequately powered to detect a treatment difference.

Details of the analysis method taken to pool the TRAFFIC and TRANSPORT studies are reported below in section 4.1.8.

The CS provides details of the planned analyses for the PROGRESS extension study. Analysis of PROGRESS was based on a similar approach to TRAFFIC and TRANSPORT, but within-group estimates were used instead of between-group estimates. This means that PROGRESS data do not include a relevant comparator. As described in 4.1.3, there appears to be more participants in the safety set in

PROGRESS than were enrolled. The ERG requested clarification on this (A16) but the company did not provide the requested participant flow charts.

Subgroup analyses were reported in the CS, although few details were provided. Subgroups were not identified in the NICE scope.

4.1.8 Description and critique of the company's approach to the evidence synthesis

A narrative review of the evidence is presented in the CS. Where possible the ERG has checked key data presented in the CS against those in the publications and CSRs provided by the company. On reading CS Table 16 and CS Table 17, which report pulmonary exacerbations, the ERG noticed several potential inconsistencies. In CS Table 16, the number of events experienced by the pooled placebo arms in the first 24 weeks of the study was 251, but the number of events experienced by the pooled placebo arms is 237 in CS Table 17. This is accompanied by slight differences in the corresponding annualised rates (1.14 vs. 1.19). The ERG sought clarification in questions A11 and A12. While the discrepancies in annualised rates were explained (the model used to generate the data in the former analysis excluded treatment group from the model), the company did not explain why different raw data were presented for what to the ERG's reading were identical arms. EQ-5D-3L and VAS were reported narratively only. In Table 25 (treatment emergent adverse events, TEAEs) incorrect data has been inserted for nasal congestion for the TRANSPORT groups. The ERG assumes this is a typographical error as the pooled numbers are correct.

The two RCTs with identical methods, TRAFFIC and TRANSPORT, were pooled in pre-specified analysis using primary data pooling (i.e. all data were treated as one study). Details were not provided in the CS but the publication appendix[5] states that the statistical methodology was prepared prior to unblinding of study results, and that 'standard statistical adjustment was applied for the pooled analysis given that the real trial results may have been against the similarity assumption'. The trial authors also state that a meta-analytic approach could alternatively have been applied. The ERG agrees that meta-analysis is an option and that pooled analysis is appropriate in this situation. However, a justification is not provided for the choice of method of pooling, and there is no assessment of statistical heterogeneity. Further details of the methods used for pooling the studies were requested by the ERG (clarification question A8). The company stated that data from TRAFFIC and TRANSPORT were integrated in two common databases, one for pooled efficacy and one for pooled safety. However, the company did not offer further details regarding the statistical methods used to pool studies. While the ERG believes that the method used to pool study findings was likely appropriate, it is unable to offer an unequivocal critique in this regard.

The hierarchical testing procedure used for the individual studies was not used for the pooled analyses.

The company did not pool the data from those originally given placebo and then given LUM-IVA in the PROGRESS for the clinical effectiveness outcomes, which the ERG considers to be appropriate. However, as described in section 4.1.7, the numbers included in the safety set for PROGRESS were unclear.

Each of the presented primary and secondary outcomes for the two studies were pooled. The treatment effect was presented as the mean treatment difference (absolute change and/or relative change as specified for the primary and secondary outcomes) with 95% confidence intervals and P values. The 95% confidence intervals for the rate ratios in CS Tables 16, 18 and 19 were not presented and were provided by the company in response to clarification request A17.

Pre-planned subgroup analyses were presented for absolute change in $ppFEV_1$, pulmonary exacerbations and BMI. The subgroups were age (≥12 to <18 years vs ≥18 years), $ppFEV_1$ (screening <70 vs ≥70; baseline <40 vs ≥40), sex, inhaled antibiotic use prior to first dose, inhaled hypertonic saline use prior to first dose, and P. *aeruginosa* status. Data were presented in a figure only in an Appendix, and a statistical test of interaction was not provided. CS page 50 and 61 state that there were no characteristics that were strong predictors of response and the ERG agrees based on observation of the figures.

The publication appendix[5] also presented the following subgroups for absolute change in $ppFEV_1$: region, inhaled bronchodilator use prior to first dose and inhaled corticosteroids use prior to first dose. Subgroup analysis of the CFQ-R respiratory domain was presented in a CIC reference (Vertex Pharmaceuticals, data on file, CS reference 21) provided by the company but not included in the CS. This reference also provided additional subgroups for pulmonary exacerbations, BMI and CFQ-R respiratory domain (region, inhaled bronchodilator use prior to first dose and inhaled corticosteroids use prior to first dose).

4.2 Summary of submitted evidence

A summary of results for the primary outcome and key secondary outcomes of the TRAFFIC and TRANSPORT trials is presented in Table 6. All outcomes are individually discussed below as listed in the NICE scope.

Table 6 Summary of results from TRAFFIC and TRANSPORT: primary outcome and key secondary outcomes at 24 weeks

Mean treatment difference vs placebo (95% CI)[b]	**TRAFFIC N = 366**	**TRANSPORT N = 374**	**Pooled N = 740**
Absolute change from baseline in $ppFEV_1$ (percentage points) (Primary outcome)	2.6 (1.2, 4.0) p<0.001	3.0 (1.6, 4.4) p<0.001	2.8 (1.8, 3.8) p<0.001
Relative change from baseline $ppFEV_1$ (percentage points)	4.3 (1.9, 6.8) p<0.001	5.3 (2.7, 7.8) p<0.001	4.8 (3.0, 6.6) p<0.001
Absolute change from baseline in BMI (kg/m^2)	0.13 (-0.07, 0.32) p=0.19	0.36 (0.17, 0.54) p<0.001	0.24 (0.11, 0.37) p<0.001
Absolute change from baseline in EQ-5D	0.0095 (-0.0109, 0.0298) p=0.36	-0.0009 (-0.0192, 0.0174) p=0.92	Not reported
Absolute change from baseline in CFQ-R respiratory domain (points)	1.5 (-1.7, 4.7) p=0.36	2.9 (-0.3, 6.0) p=0.07	2.2 (0.0, 4.5) p=0.05
Number of pulmonary exacerbations, rate ratio (95% CI from CSR)	0.66 (0.47, 0.93) p=0.02[a]	0.57 (0.42, 0.76) p<0.001[a]	0.61 (0.49, 0.76) p<0.001

Mortality [a] p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy. [b] Pulmonary exacerbations are reported as rate ratio (95% CI).

4.2.1 Mortality

The number of deaths occurring during the trials was reported (see section 4.2.11). One death occurred in the group receiving the relevant dose of LUM-IVA, and this was judged to be unrelated to the study drug. The 24-week duration of the TRAFFIC and TRANSPORT trials plus 24 weeks interim analysis from the PROGRESS extension study is unlikely to have adequately addressed mortality.

4.2.2 Lung function

The primary outcome, absolute change from baseline in $ppFEV_1$ at week 24 (calculated by averaging the mean absolute change at week 16 and week 24; Table 7), was statistically significant in both trials, with a mean treatment of difference of 2.8 percentage points (95% CI 1.8 to 3.8, p<0.001) for LUM-IVA compared with placebo in the pooled analysis. It is unclear if this is a clinically meaningful difference (see section 4.1.6). In addition, it is noted from CS Figure 3 p. 49 that the absolute change in $ppFEV_1$ at 24 weeks was lower than that at 16 weeks, therefore using change from baseline to week 24 would produce a less favourable result. Interim analysis at week 24 of the PROGRESS extension study (LUM-IVA group only, total 48 weeks of treatment) produced a LS mean absolute change from baseline in $ppFEV_1$ of 2.6 percentage points (95% CI 1.6 to 3.5 (CSR Table11-1), p<0.0001). There was not a placebo group for comparison in the PROGRESS extension study.

Relative change from baseline in $ppFEV_1$ at week 24 (average at week 16 and week 24) was also statistically significant in both trials (Table 7), with a mean treatment difference of 4.8 percentage points (95% CI 3.0 to 6.6, p<0.001) for LUM-IVA compared with placebo in the pooled analysis. It is unclear if this is a clinically meaningful difference (see section 4.1.6). Interim analysis at week 24 of the PROGRESS extension study (LUM-IVA group only, total 48 weeks of treatment, no placebo group for comparison) produced a LS mean relative change from baseline in $ppFEV_1$ of 4.7 percentage points, p<0.0001).

Table 7 Absolute change and relative change from baseline in ppFEV1, FAS population (average of week 16 and week 24)

	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA N = 182	**Placebo N = 184**	**LUM-IVA N = 187**	**Placebo N = 187**	**LUM-IVA N = 369**	**Placebo N = 371**
Absolute change (percentage points)						
Within-group Change, LS mean (SE)	2.16 (0.53) P<0.0001	-0.44 (0.524) P = 0.40	2.85 (0.54) P<0.0001	-0.15 (0.539) P = 0.77	2.49 (0.38) P<0.0001	-0.32 (0.376) P = 0.40
Mean treatment difference vs placebo (95% CI)	2.6 (1.2, 4.0) p<0.001		3.0 (1.6, 4.4) p<0.001		2.8 (1.8, 3.8) p<0.001	
Relative change (percentage points)						
Within-group change, LS mean (SE)	3.99 (0.92) P<0.0001	-0.34 (0.91) P = 0.71	5.25 (0.96) P<0.0001	0.00 (0.96) P = 0.9983	4.64 (0.67) P<0.0001	-0.17 (0.66) P = 0.80
Mean treatment difference vs placebo (95% CI)	4.3 (1.9, 6.8) p<0.001		5.3 (2.7, 7.8) p<0.001		4.8 (3.0, 6.6) p<0.001	

CS Table 14 p. 49, CS Table 15 p. 50 and clarification question A9.

The number of patients with a response, defined as ≥5% increase in average relative change from baseline in $ppFEV_1$ at week 16 and week 24 was also assessed in the trials; see section 4.1.6 for a discussion of the limitations of this outcome. Data were provided by the company in response to clarification question A20 and are presented in Table 8. The odds of achieving this threshold were statistically significantly greater with LUM-IVA than placebo.

Table 8 Patients with ≥5% increase in average relative change from baseline in ppFEV1 at Week 16 and Week 24, FAS population

Response	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA N = 182	Placebo N = 184	LUM-IVA N = 187	Placebo N = 187	LUM-IVA N = 369	Placebo N = 371
Number of patients	37	22	41	23	39	22
Odds ratio (95% CI) P value	2.1 (1.3, 3.3) p=0.002		2.4 (1.5, 3.7) p<0.001†		2.2 (1.6, 3.1) p<0.001	

Clarification response A20. Abbreviations: CI, confidence interval; IVA, ivacaftor every 12 hours; LUM, lumacaftor every 12 hours.
† p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy.

4.2.3 Body mass index

There was no statistically significant difference in absolute change from baseline BMI between LUM-IVA and placebo in the TRAFFIC trial at 24 weeks (Table 9). However, an improvement in BMI was observed in the TRANSPORT trial and this was demonstrated in the pooled analysis (mean difference 0.24 kg/m^2, 95% CI 0.11 to 0.37, p<0.001). It is unclear if a difference in BMI of this magnitude is clinically meaningful. The LS mean absolute change from baseline in BMI at Week 24 of PROGRESS was 0.56 kg/m^2 (p<0.0001) for the LUM-IVA group.

A similar pattern was observed for absolute change in weight (CS Table 22 p. 58, not reproduced) and, for a subset of patients < 20 years of age, for absolute change in BMI z-score (data not reported in CS).

Table 9 Absolute change from baseline in BMI at Week 24, FAS population

Absolute change (kg/m^2) at 24 weeks	**TRAFFIC**		**TRANSPORT**		**Pooled**	
	LUM-IVA N = 182	**Placebo N = 184**	**LUM-IVA N = 187**	**Placebo N = 187**	**LUM-IVA N = 369**	**Placebo N = 371**
Within-group Change (SE)	0.32 (0.071) P<0.0001	0.19 (0.070) P = 0.0065	0.43 (0.066) P<0.0001	0.07 (0.066) P = 0.2892	0.37 (0.048) P<0.0001	0.13 (0.048) P = 0.0066
Mean treatment difference vs placebo (95% CI)	0.13 (-0.07, 0.32) p=0.19		0.36 (0.17, 0.54) p<0.001		0.24 (0.11, 0.37) p<0.001	

CS Table 21 p. 57 and clarification question A9.

4.2.4 Respiratory symptoms

Respiratory symptoms were only considered under adverse events in the CS. See section 4.2.11 for details.

4.2.5 Pulmonary exacerbations

Number of pulmonary exacerbations

See section 4.1.6 for the definition of pulmonary exacerbations. The reduction in rate of pulmonary exacerbations in both TRAFFIC and TRANSPORT in the LUM-IVA group compared with the placebo group was not considered statistically significant within the framework of the testing hierarchy (see section 4.1.7 for further details). The testing hierarchy was not applied for the pooled analysis, which found a 39% (95% CI 24% to 51%) (p<0.001) reduction in the rate of pulmonary exacerbations with LUM-IVA (Table 10).

As noted above in section 4.1.8, there were several inconsistencies in the data presented between CS Table 16 and CS Table 17 (Table 10 and Table 11 below). Though the company provided an explanation of discrepancies in the arm-specific annualised rates (clarification response A12), they did not explain the differences in the number of events in the pooled placebo arm (251 in Table 10 and 237 in Table 11).

Table 10 Number of pulmonary exacerbations through Week 24, TRAFFIC and TRANSPORT, FAS population

Pulmonary exacerbations, 24 weeks	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (rate per 48 weeks)	73 (0.71)	112 (1.07)	79 (0.67)	139 (1.18)	152 (0.70)	251 (1.14)
Rate ratio (95% CI)	0.66 (0.47, 0.93) p=0.02[a]	-	0.57 (0.42, 0.76) p<0.001[a]	-	0.61 (0.49, 0.76) p<0.001	-

CS Table 16 p. 51 and clarification A17. Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care. [a] p value ≤0.025; however, it was not considered statistically significant within the framework of the testing hierarchy.

Table 11 Number of pulmonary exacerbations: Up to 48 weeks of active treatment, PROGRESS (pooled analysis)

Group	Number of patients with events	Number of events	Event rate/year (annualised rate)
TRAFFIC/TRANSPORT placebo + SoC (24 weeks)	152	237	1.19
LUM-IVA + SoC (TRAFFIC/TRANSPORT and PROGRESS (48 weeks)	146	249	0.64
Placebo + SoC to LUM-IVA + SoC (24 weeks)	48	61	0.61

CS Table 17 p. 51. Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care.

Time to first pulmonary exacerbation through week 24

The proportion of patients who remained free from pulmonary exacerbations for a longer period of time was higher in the LUM-IVA group as compared to placebo group in the individual studies (TRAFFIC: rate ratio 0.69, p=0.0385 and TRANSPORT: rate ratio 0.53, p=0.0003) and the pooled analysis (data presented in a figure only, CS Figure 5 p. 54).

Risk of having at least one exacerbation through week 24

The risk of having at least one pulmonary exacerbation was lower with LUM-IVA compared with placebo in both studies (TRAFFIC: rate ratio; 0.64, p=0.0512 and TRANSPORT: rate ratio; 0.44, p=0.0002) and the pooled analysis (rate ratio; 0.5327, p<0.001).

Duration of pulmonary exacerbations at week 24

The mean total duration of pulmonary exacerbations was shorter with LUM-IVA in each of the trials. In the pooled analysis, this was around 8 days less in the LUM-IVA group than the placebo group [8.14 (SD 17.4) days versus 15.67 (SD 24.8) days, p<0.0001]. Duration of pulmonary exacerbations was not included as an outcome in the PROGRESS extension study.

Table 12 Normalised total duration of pulmonary exacerbations, FAS population

Number of days with pulmonary exacerbation, 24 weeks follow-up	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
n	55	73	54	88	109	161
Mean (SD)	7.81 (15.91)	13.07 (22.27)	8.45 (18.78)	18.23 (26.86)	8.14 (17.41)	15.67 (24.79)
LUM-IVA vs placebo	p<0.0001		p<0.0001		p<0.0001	

CS Table 20 p. 54. Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SD, standard deviation; SoC, standard of care.

4.2.6 Frequency and severity of acute infections

Acute infections were only considered under adverse events in the CS. See section 4.2.11 for details.

4.2.7 Need for hospitalisation and other treatments

The CS reported the number of pulmonary exacerbations requiring hospitalisation and the number of pulmonary exacerbations requiring IV antibiotics. Hospitalisation due to other causes and need for other treatments were not reported in the CS, but were provided to the ERG in response to clarification question A21.

Hospitalisations not related to pulmonary exacerbations

Hospitalisations not related to pulmonary exacerbations were similar between LUM-IVA and placebo groups (pooled analysis, Table 13).

Table 13 Hospitalisations not related to pulmonary exacerbations that occurred during TRAFFIC and TRANSPORT (pooled)

	LUM-IVA		Placebo	
	No. of Patients	**Events (Event Rate/ Year)**	**No. of Patients**	**Events (Event Rate/Year)**
Planned Hospitalisations for CF	13	17 (0.09)	18	18 (0.10)
Unplanned Hospitalisations	18	19 (0.10)	19	20 (0.11)

Clarification response A21.

Pulmonary exacerbations requiring hospitalisation

A statistically significant reduction in the rate of pulmonary exacerbations requiring hospitalisation was found in both trials for LUM-IVA compared with placebo, with a reduction of 61% compared with placebo in the pooled analysis (Table 14). The event rate per year through 48 weeks of treatment with LUM-IVA in the PROGRESS extension study was reported as 0.19 (no placebo group for comparison).

In the pooled analysis, the mean number of days patients were hospitalised for a pulmonary exacerbation was 2.48 days and 7.64 days in the LUM-IVA group and placebo group, respectively ($p<0.0001$).

Table 14 Number of pulmonary exacerbations requiring hospitalisation through Week 24, FAS population

Pulmonary exacerbations requiring hospitalisation, 24 weeks follow-up	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	17 (0.14)	46 (0.36)	23 (0.18)	59 (0.46)	40 (0.17)	105 (0.45)
LUM-IVA vs placebo, Rate ratio[a] (95% CI)	0.38 (0.22, 0.67) p=0.0008		0.39 (0.24, 0.64) p=0.0002		0.39 (0.26, 0.56) p<0.0001	

CS Table 18 p.52 and clarification A17. Abbreviations: IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; SoC, standard of care. [a] Figures are rounded to 2 decimal places

Pulmonary exacerbations requiring IV antibiotics

The event rate per year of pulmonary exacerbations requiring IV antibiotics could not be estimated for the TRAFFIC trial because the negative binomial distribution model did not converge. A statistically significant reduction in the rate of pulmonary exacerbations requiring IV antibiotics was found in the TRANSPORT trial when LUM-IVA was compared with placebo (Table 15), with a reduction of 56% compared with placebo in the pooled analysis.

The event rate per year through 48 weeks of treatment with LUM-IVA in the PROGRESS extension study was reported as 0.26 (no placebo group for comparison).

In the pooled analysis, the mean number of days on IV antibiotic therapy for a pulmonary exacerbation was 3.79 days and 10.13 days in the LUM-IVA group and placebo group, respectively (p<0.0001).

Table 15 Number of pulmonary exacerbations requiring IV antibiotics through Week 24, FAS population

Pulmonary exacerbations requiring IV antibiotics, 24 weeks follow-up	TRAFFIC		TRANSPORT		Pooled	
	LUM-IVA + SoC N = 182	Placebo + SoC N = 184	LUM-IVA + SoC N = 187	Placebo + SoC N = 187	LUM-IVA + SoC N = 369	Placebo + SoC N = 371
Number of events (event rate per year)	33 (no estimate[b])	62 (no estimate[b])	31 (0.23)	87 (0.64)	64 (0.25)	149 (0.58)
LUM-IVA vs placebo, rate ratio[a] (95% CI)	NA - p=0.0050		0.36 (0.24, 0.54) p<0.0001		0.44 (0.32, 0.59) p<0.0001	

CS Table 19 p53 and clarification A17. Abbreviations: IV, intravenous; IVA, ivacaftor 250 mg every 12 hours; LUM, lumacaftor 400 mg every 12 hours; NA, Not applicable, SoC, standard of care. [a] Figures are rounded to 2 decimal places. [b] The event rate per year could not be estimated because the negative binomial distribution model did not converge.

Medications taken during the treatment emergent period

In response to clarification question A21, the company reported inhaled antibiotic use and inhaled bronchodilator use in people not taking these medications at baseline (Table 16). A greater proportion of people not taking inhaled antibiotics or bronchodilators at baseline went on to use these medications during the study and up to 28 days after the last dose of study drug. Statistical analysis was not provided.

Table 16 Medications taken during the treatment-emergent period in patients not using prior to first dose

	LUM-IVA	Placebo
Patients NOT using inhaled antibiotics prior to first dose, n (%)	144 (39.0)	113 (30.5)
Patients using inhaled antibiotics chronically[a] during treatment emergent period, n (% of non-users)	21 (14.6)	24 (21.2)
Patients NOT using inhaled bronchodilator prior to first dose, n (%)	29 (7.9)	29 (7.8)
Patients using inhaled bronchodilator chronically[a] during treatment emergent period, n (% of non-users)	0	4 (13.8)

Clarification response A21. [a] defined as use during 25% or more of the treatment-emergent period. The treatment-emergent period was defined as the period at or after the initial dosing of study drug to 28 days after the last dose of study drug.

4.2.8 Health-related quality of life

CFQ-R respiratory domain score

There was no statistically significant or clinically important (MCID ≥ 4 points) difference between LUM-IVA and placebo in absolute change from baseline in CFQ-R respiratory domain score at Week 24, in the individual trials or the pooled analysis (Table 17). However, the difference between LUM-IVA and placebo was statistically significant at week 4, 8 and 16 in the pooled analysis (CS Figure 8 p. 60).

The LS mean absolute change from baseline in the CFQ-R respiratory domain score at Week 24 of the PROGRESS extension study was 6.3 (p<0.001) for the LUM-IVA group (total 48 weeks of treatment, no placebo group for comparison).

Table 17 Absolute change from baseline in CFQ-R respiratory domain score at Week 24, FAS population

Absolute change (points), 24 weeks	**TRAFFIC N = 366**		**TRANSPORT N = 374**		**Pooled N = 740**	
	LUM-IVA N = 182	**Placebo N = 184**	**LUM-IVA N = 187**	**Placebo N = 187**	**LUM-IVA N = 369**	**Placebo N = 371**
Baseline, mean (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, LS mean (SE)	2.60 (1.192) p=0.0295	1.10 (1.161) p=0.3423	5.66 (1.169) p<0.0001	2.81 (1.153) p=0.0152	4.10 (0.834) p<0.0001	1.88 (0.818) p=0.0213
Mean treatment difference vs placebo (95% CI)	1.5 (-1.7, 4.7) p=0.36		2.9 (-0.3, 6.0) p=0.07		2.2 (0.0, 4.5) p=0.05	

CS Table 23, p59 and clarification question A9.

EQ-5D-3L

HRQoL was described narratively on CS p. 60, however EQ5-D data were not presented in the submission. The company provided data on request by the ERG (clarification point A6); reasons for missing data were not provided (Table 18). There was no clinically meaningful or statistically significant treatment effect on quality of life measured by EQ-5D-3L (Table 18). Pooled analysis of TRAFFIC and TRANSPORT was not provided. EQ5D-L was not included as an outcome in the PROGRESS study.

Table 18 Absolute change from baseline in EQ-5D-3L at 24 weeks

	TRAFFIC		TRANSPORT	
	Placebo N=184	LUM-IVA N=182	Placebo N=187	LUM-IVA N=187
N	179	170	183	176
Baseline Mean (SD)	0.9237 0.104)	0.9217 (0.098)	0.9171 (0.10837)	0.9267 (0.10462)
Absolute change at week 24 [LS mean (SE)]	0.0006 (0.0074)	0.01 (0.0076)	0.0117 (0.00673)	0.0108 (0.00683)
LS mean Diff, (95% CI), p value	0.0095 (-0.0109, 0.0298) p=0.36		-0.0009 (-0.0192, 0.0174) p=0.92	

4.2.9 Subgroup analysis results

Pre-planned subgroup analyses of LUM-IVA versus placebo were undertaken for the outcomes $ppFEV_{1,}$ number of pulmonary exacerbations, BMI and CFQ-R, according to age, sex, disease severity ($ppFEV_1$ at screening and baseline), prior use of CF medications, and *P. aeruginosa* infection status. None was considered to be a strong predictor of clinical response.

In the pooled analysis, 28 patients in the LUM-IVA group had $ppFEV_1$ values that had fallen to <40% of predicted at baseline (as stated on CS p. 50, but 29 patients according to CS Table 13 p. 47). The clinical benefit and safety profile observed with LUM-IVA in this group of patients with severe lung dysfunction was comparable to the overall population.

4.2.10 Mixed Treatment Comparison results

No indirect comparison or MTC was reported; the ERG agrees that this is not required as the comparator is included in the reported trials.

4.2.11 Summary of adverse events

TEAEs, defined as events from the first dose of study drug until 28 days after the last dose of study drug, occurred in similar rates (approximately 95%) in those treated with LUM-IVA and SoC and those treated with placebo and SoC in the two pivotal RCTs, see Table 19. The rate of any TEAE in the PROGRESS extension study was similar. The majority of adverse events were reported to be mild to moderate in intensity. The CSRs for the three studies report the rates of adverse events considered to be grade 3-4 and

these have been reproduced in Table 19 (for TRAFFIC and TRANSPORT these have been pooled by the ERG). At least one serious adverse event was experienced in 17.3% of participants in the pooled LUM-IVA arm compared with 28.6% in the pooled placebo arm of the TRAFFIC and TRANSPORT trials, and in 29.2% in those treated with LUM-IVA in the extension study over the 48 week period of the interim analysis. For the PROGRESS extension study the CS presented two intervals, week 0-24 and weeks 24-48, see CS Table 28, p65. These include participants in the LUM-IVA to LUM-IVA arm and those in the placebo to LUM-IVA arm. As these are presented as treatment intervals they include double counting of any participants that were followed up for both periods. The CSR reports data for the period 0-48 weeks which is reproduced by the ERG as this includes all participants regardless of the duration of follow-up. Note that as described in section 4.1.3, the reason for sample size of 544 in the PROGRESS study is unclear.

Table 19 Summary of treatment emergent adverse events, safety analysis sets

n (%)	Pooled TRAFFIC and TRANSPORT, 24 weeks		PROGRESS (0-48 weeks), from CSR
	LUM-IVA, n=369	Placebo, n=370	LUM-IVA, n=544
Any adverse event	351 (95.1)	355 (95.9)	532 (97.8)
Any grade 3/4 event	45 (12.2)	59 (15.9)	100 (18.4)
At least one serious adverse event	64 (17.3)	106 (28.6)	159 (29.2)
Adverse events leading to treatment discontinuation[a]	17 (4.6)	6 (1.6)	34 (6.3)

Both treatment groups also had standard of care. CSR: Clinical Study Report, LUM-IVA: Lumacaftor (400mg) – Ivacaftor (250mg) every 12 hours. PROGRESS data include 93% of participants from the TRAFFIC and TRANSPORT trials. [a]of the adverse events leading to discontinuation in 2 or more participants in TRAFFIC and TRANSPORT, 4 participants had elevated creatinine kinases levels, 3 haemoptysis, 2 bronchospasm, 2 dyspnoea, 2 pulmonary exacerbations and 2 rash.

Serious adverse events experienced in at least 3 participants are summarised in Table 20. The most frequently reported serious adverse event was infective pulmonary exacerbation, occurring in 11.1% of the LUM-IVA treated participants in the TRAFFIC and TRANSPORT trials and 24.1% in the placebo treated participants in these trials. In the extension study, up to 48 weeks, the incidence of infective pulmonary exacerbations was 19.5%. Rates of serious haemoptysis and distal intestinal obstruction syndrome were in the region of 1-2% across all groups, as seen in Table 20.

There were no deaths in either TRAFFIC or TRANSPORT. There was 1 death in the PROGRESS study in the 400mg/250mg dose (one other death occurred in the 600mg arm), which was unrelated to the treatment.

Table 20 Summary of serious adverse events, safety analysis sets

n (%)	Pooled TRAFFIC and TRANSPORT,[a] 24 weeks		PROGRESS (0-48 weeks), from CSR[a]
	LUM-IVA, n=369	Placebo, n=370	LUM-IVA, n=544
Infective pulmonary exacerbation of CF	41 (11.1)	89 (24.1)	106 (19.5)
Haemoptysis	5 (1.4)	3 (0.8)	11 (2.0)
Distal intestinal obstruction syndrome	2 (0.5)	5 (1.4)	6 (1.1)

Both treatment groups also had standard of care. CF: Cystic Fibrosis; CSR: Clinical Study Report, LUM-IVA: Lumacaftor (400mg) – Ivacaftor (250mg) every 12 hours. acommonly reported definition in TRAFFIC and TRANSPORT was in at least 3 participants, in PROGRESS the definition was in at least 4 participants.

The Summary of Product Characteristics (SmPC) for LUM-IVA states that liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) are recommended before initiating treatment, every 3 months for year one and annually thereafter. The SmPC also states that in the event of significant elevation of ALT or AST, with or without elevated bilirubin (either ALT or AST >5 x the upper limit of normal [ULN], or ALT or AST >3 x ULN with bilirubin >2 x ULN), dosing should be discontinued and laboratory tests closely followed until the abnormalities resolve. Rates of abnormal elevations of ALT, AST, and ALT or AST and bilirubin can be seen in Table 21. ALT greater than 5 ULN was seen in less than 1% of participants in any study arm, including during the 48 week period of the PROGRESS study. One percent of participants had an AST greater than 5 ULN in the LUM-IVA groups, compared with 1.9% in the placebo groups. During 48 weeks in the PROGRESS trial approximately 2% of participants had raised AST greater than 5 ULN. One participant had ALT or AST >3xULN and total bilirubin >2xULN in the LUM-IVA arm of the TRAFFIC and TRANSPORT trials.

Table 21 Summary of liver function test elevations, safety analysis sets

n (%)	Pooled TRAFFIC and TRANSPORT, 24 weeks		PROGRESS (0-48 weeks), from CSR
	LUM-IVA, n=369	Placebo, n=370	LUM-IVA, n=544
ALT (U/L)			
>3x to ≤5xULN	8 (2.2)	15 (4.1)	17/543 (3.1)
>5x to ≤8xULN	1 (0.3)	1 (0.3)	6/543 (1.1)
>8xULN	1 (0.3)	0 (0.0)	6/543 (1.1)
AST (U/L)			
>3x to ≤5xULN	7 (1.9)	4 (1.1)	17/543 (3.1)
>5x to ≤8xULN	2 (0.5)	5 (1.4)	5/543 (0.9)
>8xULN	2 (0.5)	2 (0.5)	6/543 (1.1)
Total Bilirubin (µmol/L)			
>1.5xULN to ≤2xULN	0 (0.0)	5 (1.4)	0/543
>2xULN	1 (0.3)[a]	1 (0.3)	0/543
ALT or AST >3xULN and Total Bilirubin>2xULN	1 (0.3)[a]	0 (0.0)	0/543

Both treatment groups also had standard of care. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSR: Clinical Study Report; LUM-IVA: Lumacaftor (400mg) – Ivacaftor (250mg) every 12 hours; ULN, upper limits of normal
[a]Elevations for this patient was noted at the local lab and was not captured in the clinical database.

Respiratory symptoms and frequency and severity of acute infections were NICE scoped outcomes, as discussed in section 4.1.6. Adverse events that could be considered of relevance to these outcomes include cough, dypsnoea, sputum increase, haemoptysis, abnormal respiration, and upper respiratory tract infection. Rates of these events can be seen in **Error! Reference source not found.**, which reports adverse events (all grades), reported in at least 10% of participants.

The most frequently reported adverse events in the RCTs were infective pulmonary exacerbation of cystic fibrosis (LUM-IVA 35.8%; placebo 49.2%); cough (LUM-IVA 28.2%; placebo 40%); headache (LUM-IVA 15.7%; placebo 15.7%); and increase in sputum production (LUM-IVA 14.6%; placebo 18.9%). The rate was greater in the placebo groups than the LUM-IVA treated groups for these events with the exception of headache, although this is based on observation of the data only. Other events more frequently reported in the placebo group than the LUM-IVA group included nasal congestion (LUM-IVA 6.5%; placebo 11.9%).

Adverse events experienced in fewer participants in the placebo group than the LUM-IVA group included dyspnoea (LUM-IVA 13%; placebo 7.8%); upper respiratory tract infection (LUM-IVA 10%; placebo 5.4%); diarrhoea (LUM-IVA 12.2%; placebo 8.4%); nausea (LUM-IVA 12.5%; placebo 7.6%).

In the PROGRESS extension study, data for the 48 week interim analysis can be seen in **Error! Reference source not found.** where the most frequently reported adverse events were infective pulmonary exacerbation of cystic fibrosis, cough, increase in sputum production and haemoptysis.

	Pooled TRAFFIC and TRANSPORT[a], 24 weeks		**PROGRESS (0-48 weeks), from CSR[a]**
n (%)	**LUM-IVA, n=369**	**Placebo, n=370**	**LUM-IVA, n=544**
Infective pulmonary exacerbation of CF	132 (35.8)	182 (49.2)	255 (46.9)
Cough	104 (28.2)	148 (40.0)	211 (38.8)
Headache	58 (15.7)	58 (15.7)	88 (16.2)
Increase in sputum production	54 (14.6)	70 (18.9)	116 (21.3)
Dyspnoea	48 (13.0)	29 (7.8)	89 (16.4)
Haemoptysis	50 (13.6)	50 (13.5)	104 (19.1)
Diarrhoea	45 (12.2)	31(8.4)	77 (14.2)
Nausea	46 (12.5)	28 (7.6)	72 (13.2)
Abnormal respiration (chest tightness)	32 (8.7)	22 (5.9)	74 (13.6)
Nasopharyngitis	48 (13.0)	40 (10.8)	81 (14.9)
Oropharyngeal pain	24 (6.5)	30 (8.1)	57 (10.5)
Upper respiratory tract infection	37 (10.0)	20 (5.4)	70 (12.9)
Nasal congestion	24 (6.5)	44 (11.9)	53 (9.7)
Pyrexia	33 (8.9)[b]	34 (9.2)[b]	65 (11.9)
Fatigue	34 (9.2)[b]	29 (7.8)[b]	57 (10.5)
Abdominal pain	33 (8.9)[b]	32 (8.6)[b]	55 (10.1)

Both treatment groups also had standard of care. CF: Cystic Fibrosis; CSR: Clinical Study Report, LUM-IVA: Lumacaftor (400mg) – Ivacaftor (250mg) every 12 hours.

[a]commonly occurring definitions differed in the CS for TRAFFIC and TRANSPORT (at least 10%) and in PROGRESS (at least 5% participants). The ERG has reproduced those occurring in more than 10%.

[b]pooled by the ERG from CSRs for TRAFFIC and TRANSPORT respectively.

The CSR for the PROGRESS extension study presents data for grade 3-4 adverse events experienced by those treated with LUM-IVA up to 48 weeks (at the interim analysis point). Grade 3-4 infections and infestations were experienced in 9.4%; respiratory, thoracic and mediastinal disorders in 3.1%; investigations in 2.9%; gastrointestinal disorders in 2.2% and nervous system disorders in 0.7%. The CSRs for TRAFFIC and TRANSPORT state that specific grade 3-4 adverse events are presented in tabular form, however the tables of events by grade are not available.

4.2.12 Additional work on clinical effectiveness undertaken by the ERG

In view of the limitations with the search strategy in the CS, the ERG conducted searches for completed RCT and non-RCTs relevant to the decision problem. No additional relevant completed studies were identified.

The ERG also undertook searches for ongoing studies of relevance to the decision problem. Four studies were identified (Table 22). Two of these are in children age 6 to 11 years and homozygous for the F508del mutation, with the third study being a follow-up study of these participants. This population is beyond the proposed indication (age 12 years and older), but has been included here for information. The fourth study (VX14-809-106) is a single group open label study in people aged 12 years and over, homozygous for F508del mutation and with advanced disease. This population is relevant to the NICE scope, and is of particular interest as the TRANSPORT and TRAFFIC studies included people with mild to moderate cystic fibrosis. The company confirmed that interim data are not yet available (clarification response A22). The primary outcome of the 24-week study is adverse events, with secondary outcomes listed as absolute change in ppFEV_1, absolute change in FEV_1 in litres, total number of days participants received IV antibiotics for pulmonary exacerbations, number of all cause hospitalisations, absolute change from baseline to average of Day 15 and Week 4 measurements in sweat chloride, and absolute change in CFQ-R respiratory domain score. The estimated enrolment is 200, and the estimated study completion date is January 2016.

Table 22 Ongoing studies identified by ERG

Study ID	Population	Interventions	Study design	Estimated completion date
VX14-809-109 NCT02514473	Age 6-11 years, CF homozygous for F508del	LUM-IVA vs placebo	RCT	April 2016
VX13-809-011 NCT01897233	Age 6-11 years, CF homozygous for F508del	LUM-IVA	Non-RCT single group open label	October 2015
VX15-809-110 NCT02544451	Age 6+ years, CF homozygous for F508del (from Study 109 and 011B)	LUM-IVA	Non-RCT 'rollover study'	April 2018
VX14-809-106 NCT02390219	Age 12+ years, CF and advanced lung disease homozygous for F508del ($ppFEV_1 \geq 30$ to <40 at screening and $ppFEV_1 \geq 30$ on Day1)	LUM-IVA	Non-RCT single group open label	January 2016

4.3 Conclusions of the clinical effectiveness section

The CS presents a systematic review on the effectiveness of LUM-IVA that is of reasonable quality. The two pivotal phase 3 RCTs of LUM-IVA, TRAFFIC and TRANSPORT, were identified and included in the review. In both trials, LUM-IVA with standard of care was compared to placebo with standard of care. This is appropriate given that the NICE scope comparator is standard of care. The summarised evidence of clinical effectiveness and adverse events was also of reasonable quality, has been accurately presented, and is in the main complete. Outcomes of absolute change in $ppFEV_1$, relative change in $ppFEV_1$, rate ratio of pulmonary exacerbations (including those requiring IV antibiotics and those requiring hospitalisations), and change in BMI were presented. The clinical effectiveness evidence generally reflects the scope, though there are concerns about the range of CF severity included in the trials as compared to the scope, and outcomes were not reported completely in line with the scope.

As compared to placebo at 24 weeks of treatment, LUM-IVA produced statistically significantly greater changes on lung function, body mass index and pulmonary exacerbations (including those requiring

hospitalisation and those requiring IV antibiotics), but not HRQoL. However, it is not clear whether the observed benefits are clinically important. While patients in the placebo arm experienced a higher rate of serious adverse events, LUM-IVA patients experienced several adverse events (including dyspnoea and upper respiratory infection) at a greater rate than those in the placebo arm. The CS interpretation of the clinical effectiveness evidence (CS p. 69), that LUM-IVA produces 'consistent improvements in several clinically significant treatment measures', would appear to be borne out by the evidence, although it is not clear whether the magnitude of the improvements is clinically important. The ERG also notes that the relatively short-term nature of the included trials tempers the ability to draw long-term conclusions from these data.

5 ECONOMIC EVALUATION

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The company has provided an appropriate description of the cost-effectiveness systematic review undertaken including the search strategy, inclusion/exclusion criteria and description of included and excluded studies.

The company searched for economic evaluations for the treatment of CF in the following databases: MEDLINE, MEDLINE In-process, Embase (via Embase.com); the Cochrane Library (incorporating Cochrane Database of Systematic Reviews, Database of Abstracts of Review or Effects, NHS Economic Evaluation Database and Health Technology Assessment database); and EconLit and Health Economic Evaluations Databases (via EBSCO). A summary of the eligibility criteria are given in Table 23, below.

Table 23: Eligibility criteria used in the cost-effectiveness systematic review

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	New-born screening
Outcomes	• Cost per QALY • Cost per life year • Other cost-effectiveness outcomes	-
Study type	Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews‡ • Letters • Comment articles • Individual case study reports

‡ To be retained for cross checking purposes

Searches were undertaken on the 22nd September 2015 with no date or language limits applied. A cost-effectiveness filter was applied to the medical databases in the Embase.com search and not to the EBSCO search of economic databases. This was appropriate. The company states (CS p. 73) that the Cochrane Library was searched using terms for the population only, but the related strategy in CS Appendix 6 includes terms for cost-effectiveness, which for NHS Economic Evaluation Database was not appropriate. Search terms and lines appear to have been combined correctly, but it is not always clear whether thesaurus or free text terms were used (see Embase.com cost terms in CS appendix 6). Grey literature was

sought from 20 websites and review papers were checked. Numbers reported in CS appendix 6 (877 + 345 + 207 = 1429) do not match those reported in the PRISMA flow diagram (CS p. 75) (921 + 106 + 34 = 1061).

ERG summary

- Despite the minor concerns raised above concerning a lack of transparency in some aspects of the search strategy reporting, there is no evidence that any important information which would improve the cost-effectiveness analysis has been missed.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (TABLE ONLY)

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for the two populations	The comparator in the decision problem, which is SoC, matches the comparator in the NICE scope. The intervention examined here is intended as an adjunct to SoC, so the comparison is between LUM-IVA with SoC versus SoC alone.
Patient group	As per NICE final scope	People with CF aged 12 years and older who are homozygous for the *F508del* mutation
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime horizon).
Synthesis of evidence on outcomes	Systematic review	Primary clinical evidence from a meta-analysis of relevant trials
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. Health states are evaluated using

		EQ-5D data collected during the clinical effectiveness studies, as well as values from the literature.
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity and scenario analyses are presented.

The cost-effectiveness evidence submitted by the company appears to satisfy the NICE reference case, and the decision problem defined in the scope. To appraise LUM-IVA for CF patients aged 12 and older who are homozygous for the *F508del* mutation in the CFTR gene, the company constructed a de novo Markov model with a lifetime horizon. The model has a cycle length of four weeks for the first two years, to enable replication of data from the studies informing the model, and then cycle lengths are one year from this point on. The model assumed that treatment benefit continues beyond the length of the trials.

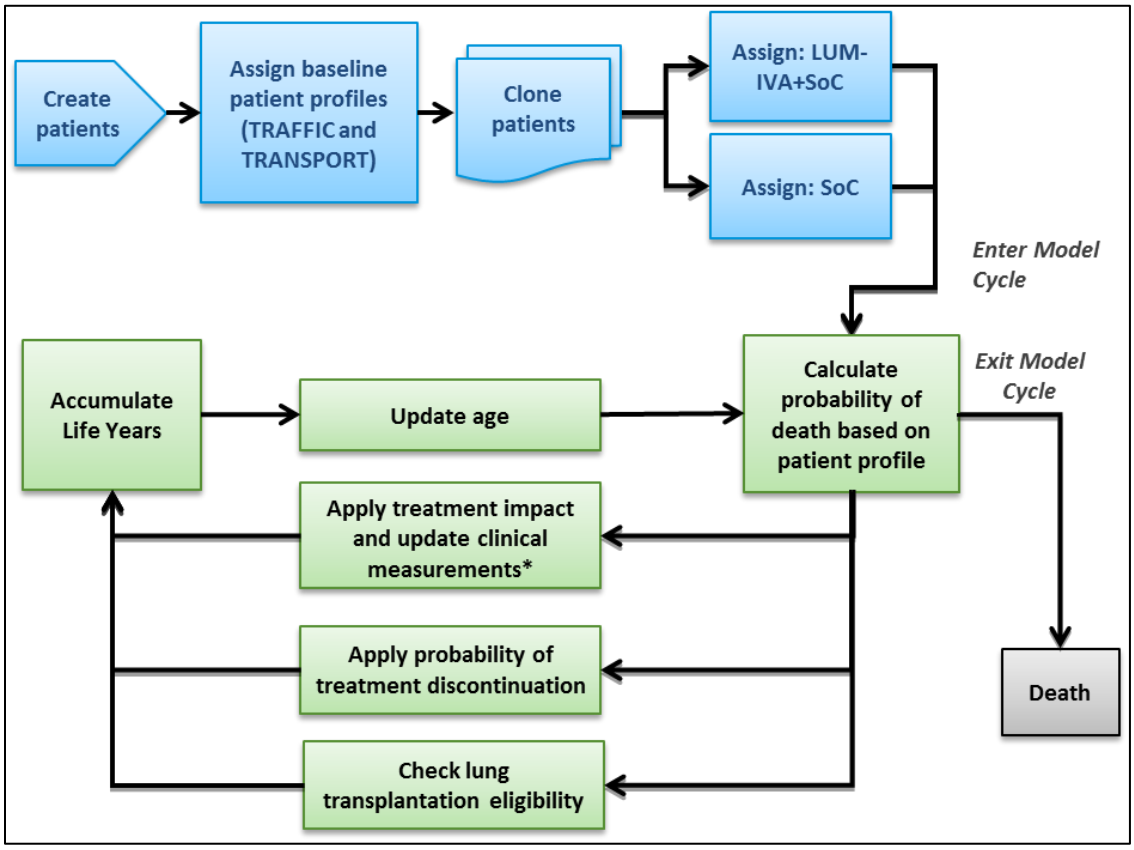
The main data to inform the effectiveness parameters in the model came from the TRAFFIC and TRANSPORT studies, with additional data on CF mortality being included from both the UK CF trust registry, and a paper by Liou et al which looked at factors which predict survival in CF.[1]

5.2.2 Model structure

The model constructed by the company is a discrete time patient-level microsimulation, which follows a similar structure to previous models used in CF evaluations.[7] Identical starting cohorts of patients are run through the model twice, once assuming treatment with LUV-IVA and SoC, the other SoC alone. The baseline characteristics of patients in these runs are derived by randomly sampling from the

characteristics of patients from the TRAFFIC and TRANSPORT studies. The structure of the simulation model is shown below:

Figure 1 Model schematic for the patient-level simulation



The model is run for a lifetime horizon, with a cycle length of 4 weeks for the first two years, and then one year cycles after that. In each cycle of the model, a patient's $ppFEV_1$, weight-for-age z-score, risk of pulmonary exacerbations, age, probability of lung transplantation, probability of adverse events (AEs), diabetes status and probability of treatment discontinuation determine their future progression, and these factors are updated at each cycle of the model to derive the probabilities. Survival, utilities and costs are derived from these factors as follows:

- Survival (section 5.2.6) – Survival combines data on average survival from the UK CF trust registry with a Cox proportional hazards model, taken from Liou et al,[1] which predicts survival for individuals based on relevant clinical factors ($ppFEV_1$, pulmonary exacerbations, weight-for-age z-score, pancreatic sufficiency, diabetes, *B. cepacia*, *S. aureus*, age and sex).
- Utilities (section 5.2.7) – Based on $ppFEV_1$, pulmonary exacerbations and lung transplant status.
- Costs (section 5.2.8) – Based on treatment, $ppFEV_1$ and lung transplant status.

ERG summary

- The model developed appears to capture the main important features of the disease (mortality, $ppFEV_1$ changes, pulmonary exacerbations and lung transplantation, assuming the nine factors included adequately capture the important clinical predictors of survival. The cycle length of one year after the first two years of the model means that particularly rapid changes in patient decline may not be fully captured, but should nonetheless allow sufficiently accurate modelling of patient trajectories.

5.2.3 Population

The patient population included in the model is that from the TRAFFIC and TRANSPORT studies, which is assumed to be sufficiently similar to the UK treatment population as to provide a valid comparison, without the need for any adjustments for differing patient characteristics. Age, sex, weight-for-age z-score and baseline $ppFEV_1$ are sampled directly from the pooled baseline patient cohorts. Baseline diabetes and infection states were estimate from the UK CF registry (averaging across all patients, not just those with the *F508del* mutation), and all patients were assumed to be pancreatic insufficient at baseline. The baseline characteristics of the sample from the TRAFFIC and TRANSPORT studies are shown below:

Table 24 Baseline characteristics for 1,097 patients in TRAFFIC and TRANSPORT

Characteristic	Mean Value – Total Population
Age (years)	25.5
Male	50.6%
Mean BMI	21.2
$ppFEV_1$	60.6%

Abbreviations: $ppFEV_1$: Forced expiratory volume in one second, BMI: Body mass index

Patients from TRAFFIC and TRANSPORT were older than the average individual from the CF registry (25.5 years versus 19.6), and had a lower median $ppFEV_1$ (60.5% versus 75%). However, since it was not possible to compare the trial data to the subset of the patients in the CF registry who would have met the trial inclusion criteria (*F508del* mutation and $ppFEV_1$ between 40 and 90%), it is unclear if these differences are the result of different characteristics between different subtypes of CF or the result of discrepancies between the trial population and the relevant UK CF population.

ERG summary

- All the results presented by the company are based on modelling the population from the TRAFFIC and TRANSPORT studies, with no adjustments made for possible differences between this and the UK clinical population. Therefore, differences between the modelled and real

populations, and the impact this may have on treatment efficacy and thus cost-effectiveness, should be borne in mind when interpreting any of the results in this report.

5.2.4 Interventions and comparators

SoC treatment, as considered in the model, is based on controlling symptoms, maintaining lung function and avoiding disease complications. SoC treatments include prophylactic medications (e.g. pancreatic enzymes), nutritional supplements, antibiotics, nebulised mucolytic agents and physiotherapy. There are no currently available active comparator treatments for patients with CF aged 12 or older who are homozygous for the *F508del* mutation. LUM-IVA is intended as adjuvant to existing SoC, and hence in the TRAFFIC and TRANSPORT studies patients remained on their existing CF medications regimen for the duration of the study. The model assumed patients receiving LUM-IVA continue using SoC treatments.

ERG summary

- The base case analysis incorporates the appropriate intervention and comparator, taken from the NICE final scope.

5.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE 2013 '*Guide to the methods of technology appraisal'*, with benefits from a patient perspective and costs from an NHS/PSS perspective. The model uses a lifetime time horizon and, in the base-case, costs and benefits are discounted at an annual rate of 3.5%.

ERG summary

- The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

5.2.6 Treatment effectiveness

The model follows disease progression over time, considering the following patient characteristics assumed to predict survival in CF: $ppFEV_1$, pulmonary exacerbations, weight-for-age z-score, diabetes, respiratory infections, pancreatic sufficiency and patient age and sex. Additionally, non-survival factors of lung transplantation, adverse events and treatment discontinuation are also tracked. The effect of LUM-IVA is modelled with changes in $ppFEV_1$, rates of pulmonary exacerbations and weight-for-age z-scores, factors where treatment has been shown to have a statistically significant impact. The way each of these predictive factors are included in the model is described below.

Age, sex, pancreatic sufficiency and infection status

Age, sex, pancreatic sufficiency, *S. aureus* infection and *B. cepacia* infection are all assumed to be the same in patients receiving SoC or LUM-IVA. Age updates over the cycles of the model, whilst sex and infection statues are assumed to remain the same over the entire time horizon of the model. All patients in both groups are assumed to be pancreatic insufficient for the whole model (as opposed to 94% from the TRAFFIC and TRANSPORT studies).

Changes in $ppFEV_1$

Progression of $ppFEV_1$ is modelled separately over two time periods, the 24-week time horizon of the TRAFFIC and TRANSPORT studies, and then an extrapolation of changes in $ppFEV_1$ after 24 weeks. The $ppFEV_1$ of patients in the SoC group is assumed to remain constant for the first 24 weeks, and the effect of LUM-IVA is calculated as the absolute increase in $ppFEV_1$ with treatment, taken as the average of the week 16 and week 24 measurements. It should be noted that since the difference between LUM-IVA and SoC is greater at 16 weeks than 24, this method will give results more favourable to LUM-IVA than the more standard approach of matching to only the week 24 measurement. The overall improvement with treatment included in the model is an increase of 2.8 points for LUM-IVA relative to SoC.

Extrapolation for SoC after 24 weeks is based on a large, observational study of US and Canadian CF patients (2,161 adults, 1,359 children).[8, 9] The use of these external cohorts to inform this parameter was necessary as the PROGRESS study had no placebo control group, and the data from the 24-week trials was deemed to be of insufficient duration to estimate long-term rates of decline. However, it should be noted that these data are for the whole CF population, not the subpopulation with *F508del* mutation, and hence any differences between these two groups in $ppFEV_1$ decline will not be taken into account.

Extrapolation for the LUM-IVA arm of the model after 24 weeks is based on 44 weeks of data, made up of the TRAFFIC and TRANSPORT studies (with the first four weeks excluded to remove the impact of the initial, acute change with treatment), and the first 24 weeks of the data from the open-label PROGRESS extension study. This means that, unlike for SoC above the data is drawn from the correct population, but since only short-term follow up data are available, it is not clear the calculated numbers represent the expected long-term decline rates. The decline measured over this initial 48-week period was then assumed to remain unchanged for as long as an individual remained on treatment. The model was correctly constructed to control for multiple $ppFEV_1$ measurements from the same individual. Age-dependent annual changes in $ppFEV_1$, calculated using the methods described, are given below. A lower bound of 15% was set for $ppFEV_1$ values, meaning no individual in the model could drop below that level.

Table 25 Age-dependent annual change in ppFEV1 by treatment

Age	SoC	LUM-IVA
<18 years	-2.34%	-0.68%
18-24 years	-1.92%	-0.68%
25+ years	-1.45%	-0.68%

Abbreviations: $ppFEV_1$: Forced expiratory volume in one second, SoC: Standard of Care

Pulmonary exacerbations

The model makes use of a pre-existing equation, derived by Whiting et al,[7] which links $ppFEV_1$ measurements to pulmonary exacerbation rates, for individuals above and below the age of 18:

$$Annual\ rate\ of\ exacerbation \geq 18\ years = 3.7885e^{-0.026 \times ppFEV_1}$$

$$Annual\ rate\ of\ exacerbation\ < 18\ years = 8.5938e^{-0.035 \times ppFEV_1}$$

This equation, and hence the model, only considers pulmonary exacerbations that require IV antibiotics and/or inpatient stays. Pulmonary exacerbation rates for individuals in the LUM-IVA group are then calculated by multiplying this equation by the relative risk of 0.442 for pulmonary exacerbations requiring IV antibiotics or hospitalisation found in the TRAFFIC and TRANSPORT studies. This risk reduction was greater than that found for all pulmonary exacerbations (56% as opposed to 39%). This treatment benefit is again assumed to persist beyond the duration of the trials, for as long as individuals continue treatment.

A key assumption in this model approach is that the impact of LUM-IVA on $ppFEV_1$ and pulmonary exacerbations are independent, as opposed to LUM-IVA reducing pulmonary exacerbations because of its impact on $ppFEV_1$. This assumption is stated by the company as having been verified as plausible by its clinical experts, but does run the risk of double-counting the benefits of treatment, as rates of pulmonary exacerbation are reduced first by slower declines in $ppFEV_1$, and then the relative risk from the trial is applied in addition to that.

Weight-for-age z-score

Weight-for-age z-score is assumed to remain unchanged for the entire time horizon of the model, but no justification for this (either grounded in data or expert opinion) is provided in the submission. The absolute increase for LUM-IVA (relative to SoC) measured in TRAFFIC and TRANSPORT of 0.068 is applied to patients in the LUM-IVA group at baseline, and is then assumed to be a permanent benefit that persists for the remainder of the model. No long-term data, either from published cohort studies or the PROGRESS extension study, are used to justify the assumption of stable scores after the trial time

horizon. A summary of the three prognostic characteristics (ppFEV1, pulmonary exacerbations and weight-for-age z-scores) that are assumed to differ by treatment is given below in Table 26.

Table 26 Summary of ppFEV1, pulmonary exacerbation and weight-for-age z-score inputs

Parameter		SoC	LUM-IVA + SoC
$ppFEV_1$	First 16 weeks through week 24	Baseline	Baseline + 2.8%
	Annual change after 24 weeks	Age < 18: -2.34% Age 18-24: -1.92% Age ≥ 25: -1.45%	Age < 18: -0.68% Age 18-24: -0.68% Age ≥ 25: -0.68%
Annual rate of pulmonary exacerbation		Predicted conditional on $ppFEV_1$ and age	Predicted conditional on $ppFEV_1$ and age, and multiplied by 0.442
Weight-for-age z-score	First 24 weeks	Baseline	Baseline + 0.068
	After 24 weeks	Remains unchanged	Remains at baseline + 0.068

Diabetes

Diabetes rates are assumed to be the same for individuals treated with LUM-IVA and SoC, with each individual having an age and sex-related risk of developing the condition in each cycle. Data are taken from an analysis of the CF registry, and are not specific to individuals with the *F508del* mutation.[10]

Lung transplant

Individuals are assumed to be eligible for a lung transplant once their $ppFEV_1$ drops below 30% (based on a previous technology assessment in a CF population with a different mutation).[7] In the absence of data linking patient characteristics to the probability of receiving a lung transplant, the model assumes patients have a fixed, one-time probability of receiving a transplant once their $ppFEV_1$ drops below the threshold. The proportion of eligible patients receiving transplants (24.7%) is calculated from the UK CF registry,[3] and is assumed to be the same regardless of patient characteristics or prior treatment. Data on excess mortality post-transplant are calculated from a UK cohort study of 6,766 adult CF patients.[11]

Mortality

Mortality rates in the model are calculated using two components; first age-specific background mortality with CF, and then this hazard is adjusted to account for differing individual patients characteristics.

Survival curves are estimated from data from the UK CF trust registry, with parametric survival curves used to extrapolate beyond where data are available. There are a number of limitations with the data set used for this modelling. Older birth cohorts are subject to selection bias due to not following up

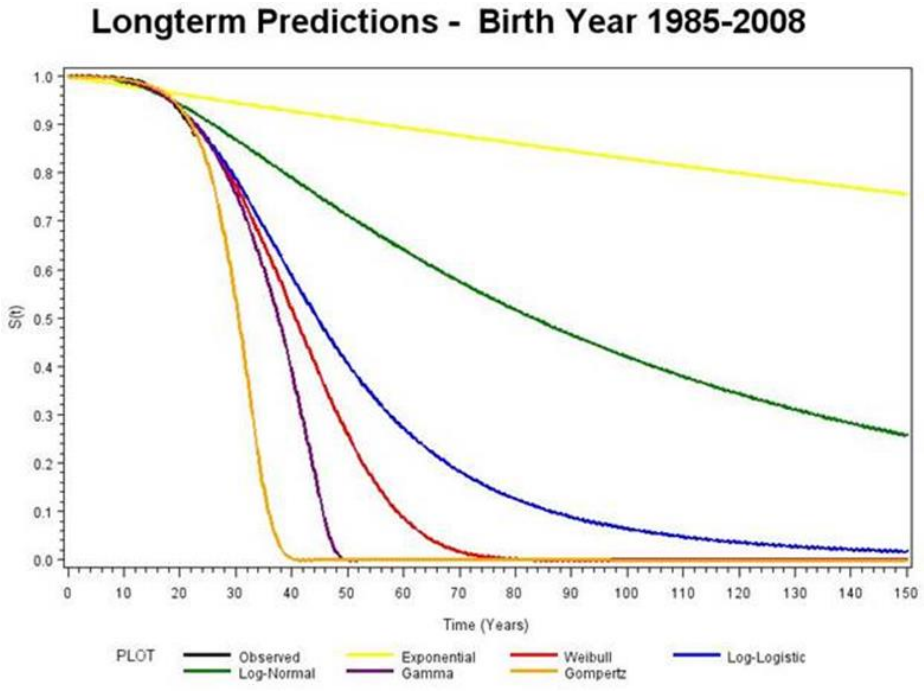
individuals early in their lifetime, which artificially inflates survival rates. More recent cohorts, by contrast, are too immature, with insufficient data to inform reliable long-term extrapolations. The choice of birth years to include in the final analysis (1985-2008) and the choice of distributions was based primarily on which combinations produced results which were deemed to be clinically realistic, rather than any statistical criteria. Model fit statistics and long-tern predictions for each of the functional forms tested are shown below.

Table 27 Projected median survival estimates and fit statistics for fits to UK CF registry population (all genotypes) birth cohort 1985-2008

Distribution	Predicted Median	AIC	BIC
Weibull	40.8	702.626	715.589
Log-normal	83.3	740.975	753.938
Log-logistic	44.6	703.470	716.433
Exponential	372.7	850.475	856.956
Generalized gamma	37.7	703.811	723.256
Gompertz	30.6	702.588	715.551

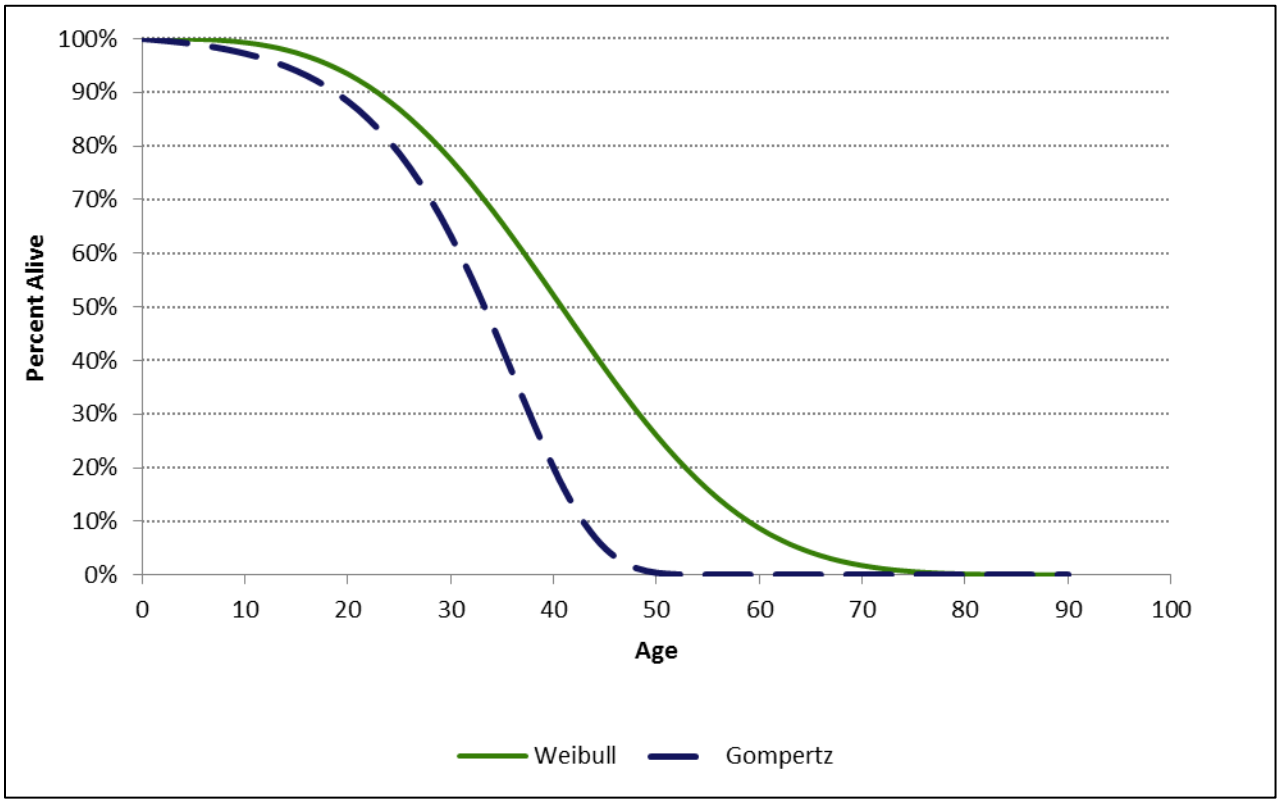
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Figure 2: Long-term projections from the tested parametric curves



The Weibull, log-logistic, generalised gamma and Gompertz distributions all appear to give approximately equally good fits to the data, but the Gamma and Gompertz was rejected as they predict almost all patients to have died by the age of 50, and the log-logistic was rejected as it predicted more than 10% of the CF population would survive past the age of 80. Thus, the Weibull model was selected as being the most appropriate, with the fitted curve (and the Gompertz curve used in sensitivity analyses) shown below in Figure 3.

Figure 3 Survival projections using Weibull and Gompertz distribution – derived from UK CF registry population (all genotypes) birth cohort 1985-2008



Age and sex-specific hazards for simulated patients were constrained that they could not go below those of the UK general population in any cycle of the model.

These baseline hazards were then adjusted for the nine characteristics (age, sex, $ppFEV_1$, weight-for-age z-score, pancreatic insufficiency, diabetes, *S. aureus* infection, *B. cepacia* infection and number of acute pulmonary exacerbations) described above. A previously reported cox-proportional hazards model is used to calculate hazards for each individual in the model,[1] using data from the UK CF registry (where available) to provide reference values for the mean of each parameter. These hazards are updated through

the model as patient characteristics change, giving a per-cycle mortality risk for each individual in the model. The coefficients of the cox model are given below in Table 28.

Table 28 Cox proportional hazards model coefficients and reference values

Covariate	Coefficient*	SE	Reference Value (Mean)	Reference
Age (per year)	0.011	0.0049	19.6	UK CF Registry 2008[12]
$ppFEV_1$ (per percentage point)	-0.042	0.0025	73.2	UK CF Registry 2008[12]
Sex (female = 1)	0.15	0.074	0.467	UK CF Registry 2008[12]
Weight-for-age z-score	-0.28	0.041	-0.85	Liou et al. 2001[1]
Pancreatic sufficiency (yes = 1)	-0.14	0.23	0.126‡	2011 US CFF Registry Estimated based on the % of patients NOT requiring a pancreatic supplement[13]
Diabetes mellitus (yes = 1)	0.44	0.098	0.187†	2012 UK CF Registry[14]
S. aureus (yes = 1)	-0.25	0.09	0.179	UK CF Registry 2008[12]
B cepacia (yes = 1)	1.41	0.19	0.034	UK CF Registry 2008[12]
Annual number of acute exacerbations (max 5)	0.35	0.024	1.1	Liou et al. 2001[1]
Exacerbations × *B. cepacia*	-0.28	0.06	Calculated	Assumed equal to mean *B. cepacia* multiplied by mean annual exacerbations

Abbreviations: *B.cepacia*, Burkholderia cepacia; $ppFEV_{1,}$ percent predicted forced expiratory volume in one second; *S.aureus*, Staphylococcus aureus; SE, standard error

Discontinuations

6.8% of people in the TRAFFIC and TRANSPORT studies had discontinued by week 24, and these numbers are applied directly to the model. The base-case assumes that these levels of continuations would be the same in clinical practice as in a trial, and then that no further individuals discontinue (post 24 weeks) for the entire remaining time horizon of the model. This assumption is then tested in a sensitivity analysis.

ERG summary

- Rates of diabetes and infection are assumed to be the same for this subpopulation as the whole UK CF population, and all individuals are assumed to be pancreatic insufficient
- The difference between the LUM-IVA and SoC groups in $ppFEV_1$, measured in the trials, is averaged across the 16-week and 24-week measurements, which gives results more favourable to LUM-IVA than using the week 24 measurement alone.

- Post-trial declines in $ppFEV_1$ for SoC patients were based on data for the whole CF population, not the subpopulation with the *F508del* mutation.
- Post-trial declines in ppFEV1 for LUM-IVA patients are based on data from weeks 4-48 of the TRAFFIC, TRANSPORT and PROGRESS studies, and the treatment benefit calculated from these short-term studies is then assumed to persist as long as an individual remains on treatment.
- The impact of LUM-IVA on pulmonary exacerbations is assumed to be entirely independent from, rather than partially caused by, its effect on $ppFEV_1$. This treatment benefit is then assumed to persist beyond the time horizon of the trial, for as long as individuals continue to be treated.
- Weight-for-age z-scores are assumed to remain unchanged for both groups after the time horizon of the trial, with the treatment benefit persisting for the remainder of an individual's life.
- There were a number of difficulties in estimating CF survival from the CF registry, including selection bias in older cohorts and immature data in more recent ones.
- The risk factors for CF mortality reported in the Liou study are assumed to remain the same over time and in the UK population, and to be independent of treatment (i.e. reductions in mortality with treatment are entirely mediated through these characteristics).
- It is assumed that discontinuation rates in clinical practice will be the same as those in the trials for the first 24 weeks, and then that no further individuals will discontinue for any reason after this point.

5.2.7 Health related quality of life

A search was undertaken by the company, looking at the same database and grey literature sources as the cost-effectiveness study search described in section 5.1, for studies containing quality of life data for cystic fibrosis. This search, which was comprehensive and well constructed, was undertaken on the 26th May 2015. The eligibility criteria used for this search are given in Table 29.

Table 29: Eligibility criteria used in the utility systematic review

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	Diagnostics New-born screening
Outcomes	• Utility scores in CF • Disutilities	Utility data reported before the year 2000
Study type	• Observational studies • QoL elicitation studies • QoL validation studies • Randomised controlled studies • Economic evaluations: • Cost-utility analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews • Letters • Comment articles • Individual case study reports

In addition, the EQ-5D-3L was administered at each study visit in the TRAFFIC and TRANSPORT studies, with the results converted into UK specific values using the relevant utility tariff. A large number of the respondents gave a value of 1 for their utility, which may be evidence of response shift, where patients become adapted to their condition and begin to report high utility values despite continuing to have clinical symptoms, as their current state has become their "new normal". This can either be viewed as showing a lack of sensitivity in the measurement instruments used, or as accurately reflecting the true adaptation process that individuals with chronic conditions go through.

An analysis was conducted, to estimate the impact of $ppFEV_1$ levels and pulmonary exacerbations on health state utilities. The final model specification chosen (it is not specified how this particular model was chosen over other candidates) included a linear term for having had a pulmonary exacerbation within the current model cycle, and linear and quadratic terms for $ppFEV_1$.

$$U = \beta_0 + \beta_1 \, x \, ppFEV_1 + \beta_2 \, x \, ppFEV_1{}^2 + \beta_3 \, x \, experiencing \, a \, pulmonary \, exacerbation$$

Based on data from the TRAFFIC and TRANSPORT trials, a pulmonary exacerbation is assumed to last for 21.7 days. The parameter estimates for the utility equation estimated are given in Table 30.

Table 30: Parameter Estimates for the Utility Equation

Parameter	Coefficient	Standard Error	p-value
β_0	[redacted]	[redacted]	[redacted]
β_1	[redacted]	[redacted]	[redacted]
β_2	[redacted]	[redacted]	[redacted]
β_3	[redacted]	[redacted]	[redacted]

Following a request for clarification from the ERG, the company ran a new version of the model which included treatment as a covariate, but the coefficient for this was both non-significant and close to 0, once again providing no evidence for short-term differences in utility between the SoC and LUM-IVA groups. No utility decrements were assigned to any adverse events other than pulmonary exacerbations.

Quality of life post-transplant

Post-transplant utilities are taken from a study by Whiting et al, which calculated weighted post-transplant utilities, stratified by time since transplant, and independent of previous treatment or clinical status.[7] These calculations were in turn based on a cross-sectional survey of patients post bilateral lung transplant.[15] The post-transplant utilities used in the model are given in Table 31.

Table 31: Derivation of Post-transplant Utility

Time Post Transplant, Months	Mean Utility	Number of Months	Month Weighted Utility	Weighted Average Post-Transplant Utility for use in model
0-6	0.75	6	0.08	0.81
7-18	0.83	12	0.17	
19-36	0.81	18	0.24	
>36*	0.82	24	0.33	

Source: Whiting et. al.[7]
*Whiting et. al. assumed that >36 category contributes 24 months.

ERG summary

- In the trial, there is no evidence of any differences in utility between the SoC and the LUM-IVA treatment groups.
- In the model, quality of life is assumed to be determined by $ppFEV_1$ status and whether or not an individual has recently experienced a pulmonary exacerbation, with no impact of treatment other than through these values.

- No utility losses were assigned to adverse events other than pulmonary exacerbations, meaning the potential disutilities associated with treatment related adverse events for LUM-IVA will not be included in the model.
- Outcomes post-transplant are assumed to be the same, regardless of pre-transplant status or treatment.

5.2.8 Resources and costs

A search was undertaken by the company, looking at the same database and grey literature sources as the cost-effectiveness study search described in section 5.1, for studies containing data on costs and/or resource use for CF. The Cochrane Library strategy in CS Appendix 11 includes terms for cost-effectiveness, which for NHS Economic Evaluation Database was not appropriate. The ERG also notes that the search was limited by UK country terms. Database records are not reliably indexed by the country where the study was undertaken and abstracts often only include terms for specific regions, cities, institutions, currency, etc. This may have resulted in relevant articles being missed. The eligibility criteria used for screening the results of this search are given in Table 32.

Table 32: **Eligibility criteria used in the cost and resource use systematic review**

Selection criteria	Inclusion	Exclusion
Population	Cystic Fibrosis	-
Intervention/ comparator	Any interventions in the treatment of CF	Diagnostics New-born screening
Outcomes	• Unit or episode costs (direct and indirect) • Resource use (direct and indirect) • End of life costs • Health state costs	Non-UK costs and resource use Cost and resource use reported before the year 2000
Study type	• Costing analysis • Budget impact analysis • Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • Economic evaluation alongside clinical trials (EEACT)	• Reviews‡ • Letters • Comment articles • Individual case study reports

Intervention and comparator treatment costs

The drug price of LUM-IVA is £8,000 per 28-day supply. The annual cost of LUM-IVA (£104,000) was calculated based on a twice-daily dosing schedule assuming a 365-day year. The base-case model assumes that after 12 years a generic alternative to LUM-IVA will become available, which will have a cost of 11% of the current treatment. In response to a request from the ERG for more detail on how these precise numbers were generated, the company gave the following additional justification:

"This assumption has been based on the previous review by Whiting et al. that evaluated ivacaftor as treatment for the G551D mutation.

Similarly to ivacaftor, LUM-IVA is a small molecule and is anticipated to be easy to replicate. Therefore it is realistic to expect there will be generic versions available soon after patent expiry. The 12-year period represents the anticipated residual patent from time of commercialisation."

These comments provide no rationale for the precise level of discount chosen for the putative generic alternative, and hence the impact of different price assumptions will be tested in sensitivity analyses.

The LUM-IVA adherence rate measured in the TRAFFIC and TRANSPORT trials was 96.5%, which is argued to be an unrealistically high rate for clinical practice (although no equivalent argument is made for the discontinuation rates measured in the trial being, similarly, artificially low). Consequently, an adherence rate of 90% is applied for costing purposes instead although the full trial data, based on the 96.5% adherence rate, are still used to estimate clinical data. In response to a request for clarification, the company provided the following justification for this:

"This assumption was driven by real world adherence data for ivacaftor (Kalydeco®) in patients with at least one G551D-CFTR *mutation. It is acknowledged this value is lower than that which produces the treatment effect observed in the TRAFFIC and TRANSPORT trials. However, the 2014 cystic fibrosis registry annual report showed that in practice the efficacy of ivacaftor was consistent with the efficacy observed in the trial while having lower adherence (10.5% increase in ppFEV1 in real world evidence compared to 10.6% in the phase 3 trial). It is assumed that the same efficacy-adherence relationship will be true for LUM-IVA in a homozygous F508del population."*

Health state costs

Disease management costs for SoC in the model were informed by a chart review study conducted in the UK on 200 CF patients with the *G551D* mutation or homozygous for the *F508del* mutation, assuming that costs would be the same for these two different groups (personal communication from Vertex, November

2016). Data for 24 months were extracted for each patient, including patient characteristics, drug treatment costs and healthcare resource use. Costs calculated in this study, stratified by $ppFEV_1$ status, were then inflated to 2014 values. These costs were broken down in to two components, hospitalisation costs and other costs.

Disease management costs for LUM-IVA are derived from these values, assuming that other costs remain the same for patients as for SoC, but hospitalisation costs are reduced by 61%. This reduction is taken from the reduction in pulmonary exacerbation requiring hospitalisation rates in the TRAFFIC and TRANSPORT studies, again assuming this reduction would remain the same after the time horizon of the study, as long as people remain on treatment. There were errors in the initial disease management costs presented in the company submission, which had the impact of overestimating the cost offsets provided by treatment with LUM-IVA. The corrected numbers, provided as a clarification response, are given in Table 33.

Table 33: Disease management direct medical costs (inflated to 2014 GBP)

$ppFEV_1$	**Categories**	**SoC**	**LUM-IVA + SoC†**
$ppFEV_1$ > 70%*	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ 40-69%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]
$ppFEV_1$ < 40%	Total cost	[redacted]	[redacted]
	Hospitalisation cost	[redacted]	[redacted]
	Other cost	[redacted]	[redacted]

Costs associated with lung transplantation are calculated based on 2010 reference costs for an elective in-hospital stay, combined with the costs of excess elective hospital bed days. The costs of follow up care are taken from a study on reported costs up to 15 years post-transplant, with all costs in the model inflated to 2014 values (Table 34). Costs post-transplant are assumed to be the same, regardless of patient status or treatment pre-transplant.

Table 34 Lung transplantation costs (inflated to 2014 GBP)

Parameter	Cost
Procedure	£46,640
Follow-up year 1	£24,014
Follow-up year 2	£14,500
Follow-up year 3	£15,244
Follow-up years 4-10	£9,156
Follow-up years 10+	£5,095

Abbreviations: SoC, standard of care.

Adverse event costs

Adverse events were included in the model if they affected at least 5% more people in the LUM-IVA arms of the studies that the placebo arms. This means that any adverse events which are rare, but potentially costly, will not have been included in the analysis. Each of these events is costed as requiring a GP visit.[16]

Table 35 Adverse event unit costs and resource use

Adverse Event	Cost per event	SoC	LUM-IVA + SoC
Dyspnea	£ 67.50	16.1%	27.9%
Diarrhea	£ 66.00	17.3%	22.3%
Nausea	£ 66.00	15.7%	20.8%
Respiration abnormal	£ 67.50	12.3%	20.0%
Oropharyngeal pain	£ 66.00	16.7%	18.9%

Abbreviations: SoC, standard of care.

Other costs

Treatment with LUM-IVA is associated with an increased number of liver function tests. Patients are assumed to need one additional GP visits (£66) in the first year, and costs are then applied for liver function tests (£1.25 each) prior to the start of therapy, every three months for the first year, and annually thereafter, together with the costs of managing abnormal results. The total costs are calculated as £87.24 in the first year, and £3.64 in each subsequent year, whilst the individual remains on treatment.

ERG summary

- The price of a potential generic alternative to LUM-IVA is assumed to be 11% of the current cost, but no justification is given for the use of this number. It is also assumed that all patients would immediately switch treatment as soon as the generic alternative becomes available.

- The intervention is costed assuming a 90% adherence rate, but the clinical data used in the model are based on the 96.5% adherence rates from the trial.
- Costs of disease management for SoC, stratified by ppFEV$_1$ status, are taken from a CF population including individuals with a different mutation (*G551D*).
- Costs of disease management for LUM-IVA are not based on data, but rather an assumption that hospital costs would be 61% lower than for SoC, and other costs would remain unchanged.

5.2.9 Cost-effectiveness results (updated CS)

For the base-case comparison of LUM-IVA with SoC only, LUM-IVA is predicted to increase median survival by 7.69 years and mean undiscounted life-years by 9.42. Base-case survival results for the two groups are given in Figure 4. Total mean discounted QALYs are 12.38 with LUM-IVA compared with 8.92 for SoC, whilst mean total costs for LUM-IVA are £1,131,202, as opposed to £377,632 for SoC. The results of the base-case analysis are shown in Table 36. The resulting ICER for LUM-IVA versus SoC alone is £218,248 per QALY.

Figure 4 Base case survival

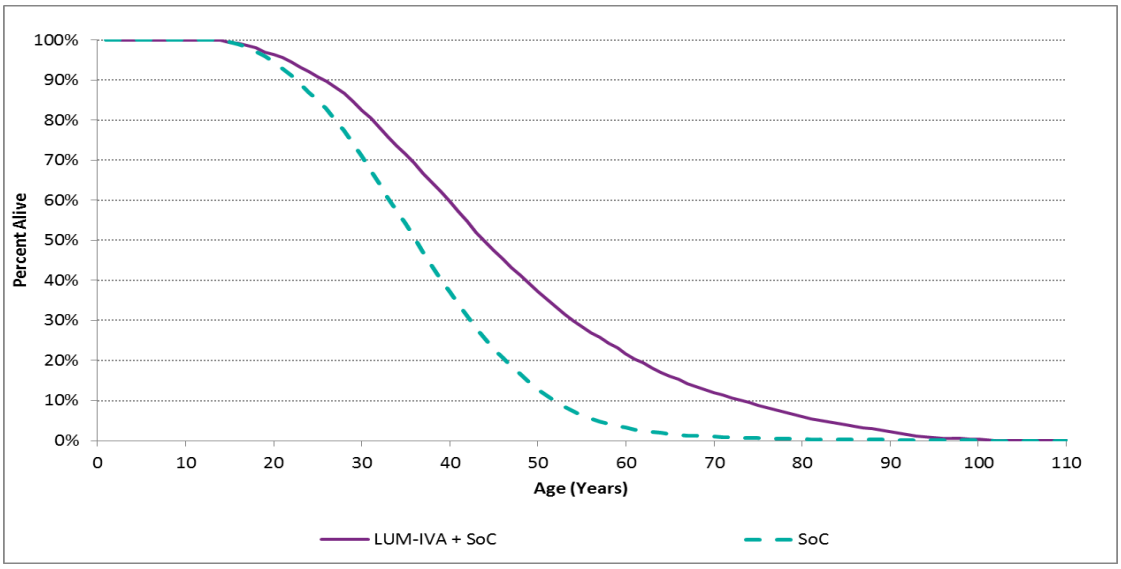


Table 36 Base-case results

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92					
LUM-IVA	£1,131,202	13.78	12.38	£753,570	3.46	3.45	£217,627	£218,248

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness analysis

The company also provides results on other health outcomes for the two groups (Table 37), and costs broken down into different cost categories; LUM-IVA, disease management, lung transplant, adverse event and liver function test (Table 38).

Table 37 Health outcomes

Comparator	LUM-IVA + SoC	SoC	Incremental
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 $ppFEV_1 \geq 70\%$	4.08	1.14	2.94
Mean Years with $ppFEV_1$ between 70% and 40%	17.10	8.84	8.26
Mean Years with $ppFEV_1$ between 40% and 30%	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 Undergoing Lung Transplant	1.82%	6.80%	-4.98%
Mean Years Until Lung Transplant	46.49	19.34	27.14

Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second.

Table 38 Summary of predicted resource use by category of cost

Item	Cost LUM-IVA + SoC	Cost SoC	Increment	Absolute increment	% absolute increment
Drug Cost	£757,776	£0	£757,776	£757,776	98.10%
Disease Management Cost	£371,202	£366,556	£4,647	£4,647	0.60%
Lung Transplant Cost	£1,097	£10,539	-£9,442	£9,442	1.22%
Adverse Event	£995	£537	£458	£458	0.06%
Liver Function Test	£131	£0	£131	£131	0.02%
Total	£1,131,202	£377,632	£753,570	Total absolute increment	100%

Abbreviations: SoC, standard of care

5.2.10 Sensitivity analyses

The company undertook a number of one-way sensitivity analyses, looking at the sensitivity of the model results to changes in particular parameters (Figure 5). The model is most sensitive to the assumed rates of decline in $ppFEV_1$ in the LUM-IVA group, discount rates and disease management costs. The upper limit to the one-way sensitivity analysis for decline in $ppFEV_1$ in the LUM-IVA group is £437,181 per QALY.

The company also conducted a probabilistic sensitivity analysis, where uncertainty in all model parameters is jointly considered (Table 39). Results are presented in the form of a cost-effectiveness plane (Figure 6) and a cost-effectiveness acceptability curve (Figure 7), which plots the probability of LUM-IVA being cost-effective versus SoC at different willingness-to-pay thresholds. At a threshold of £30,000 per QALY, these is a 0% chance of LUM-IVA being cost-effective.

Table 39 Mean Results from the Probabilistic Sensitivity Analysis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,152	10.34	8.94				
LUM-IVA + SoC	£1,125,946	13.82	12.42	£748,794	3.48	3.49	£214,838

Abbreviations: LYG, life years gained; QALY, quality adjusted life year; SoC, standard of care.

Figure 5 One-way sensitivity analysis

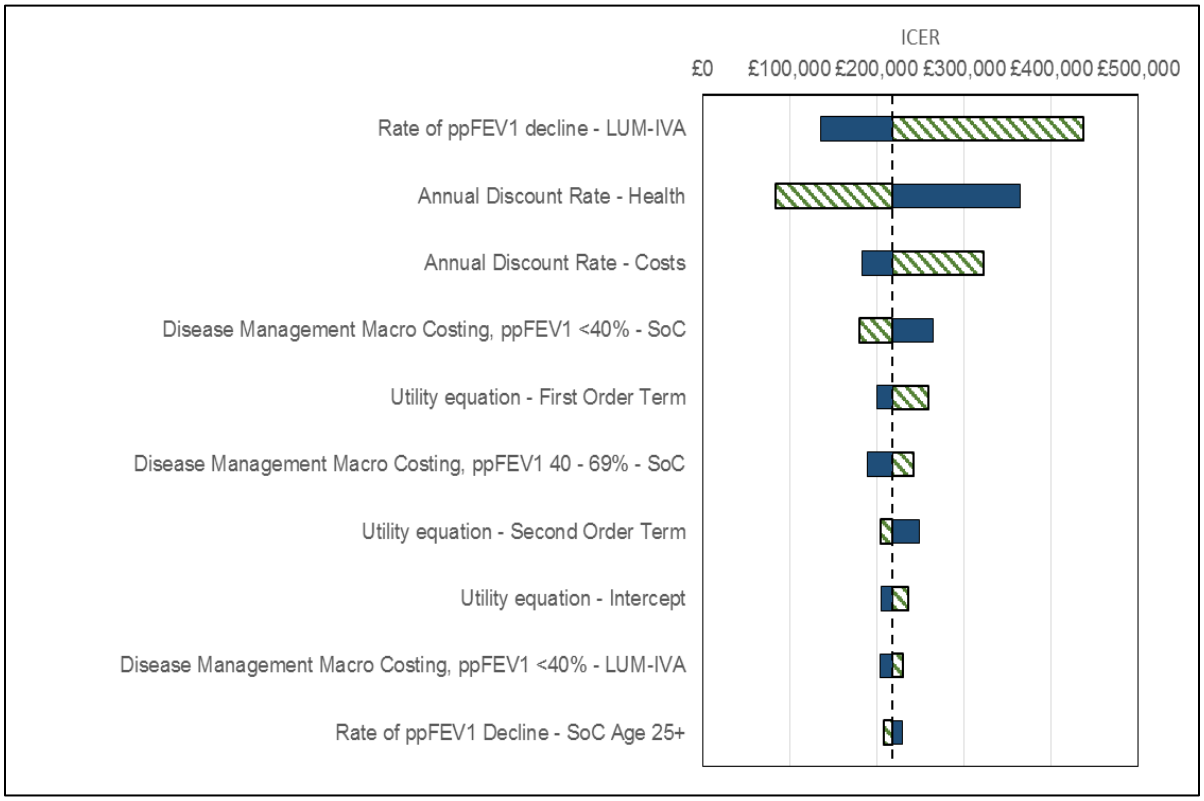
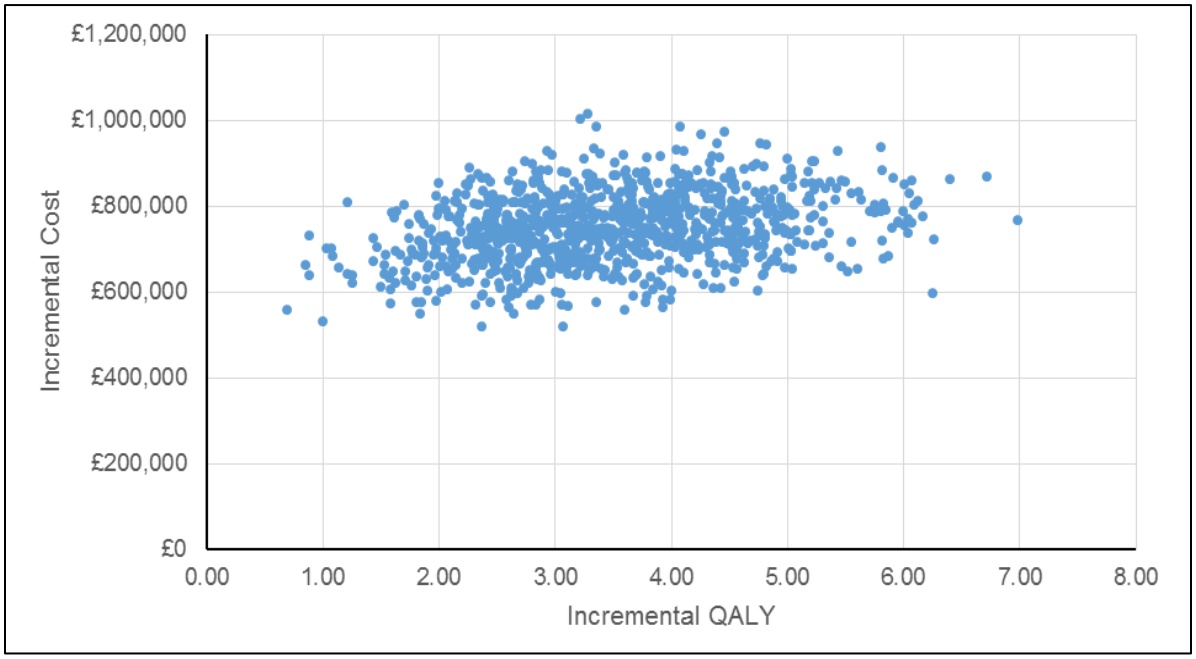
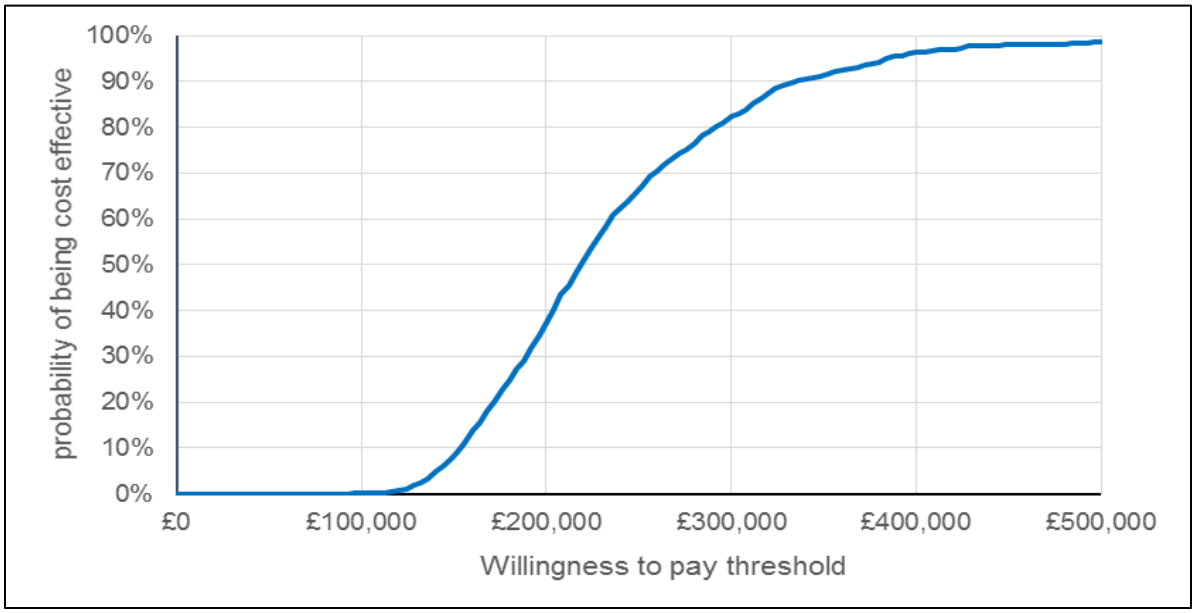


Figure 6 Cost-effectiveness plane



Abbreviations: QALY, quality adjusted life year

Figure 7 Cost-effectiveness acceptability curve



5.2.11 Scenario and subgroup analyses

Discount rates

The company undertook an analysis using discount rates of 1.5%, and justify this with reference to a NICE decision support unit document. The relevant paragraph from the NICE methods guidance states that 1.5% discount rates can be considered in situations where a treatment "restores 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)." It is far from clear that LUM-IVA treatment fulfils these criteria, and therefore the treatment would not be eligible for consideration at 1.5% discount rates.

A summary of the various scenarios analyses undertaken, together with the impact on the ICER for LUM-IVA versus SoC, is given in Table 40.

Table 40 Scenario analyses

Parameter varied	New assumption	ICER (£/QALY)
Base-case	N/A	£218,248
Discount rates	1.5%	£159,678
Rate of $ppFEV_1$ decline (LUM-IVA)	Derived from IVA treatment in a CF population with the *G551D* mutation[17]	£236,284
Rate of $ppFEV_1$ decline (LUM-IVA)	Increased by 20% from baseline	£238,795
Rate of $ppFEV_1$ decline (LUM-IVA)	Decreased by 20% from baseline	£199,003
Rate of $ppFEV_1$ decline (SoC)	Derived from a Canadian CF population[18]	£181,366
Pulmonary exacerbation rate	All pulmonary exacerbations from TRAFFIC and TRANSPORT included, not just those requiring admission to hospital or IV antibiotics	£233,018
Utility values	Tappenden et al.[19]	£241,109
Utility values	Acaster et al.[20]	£283,458
Utility values	Gee et al.[21]	£270,870
Utility values	TRAFFIC and TRANSPORT values stratified by $ppFEV_1$ values	£230,769
Discontinuation rates	Annual rate of 1.9% discontinue annually post 24 weeks	£213,910
Survival curves	Gompertz rather than Weibull distribution used for extrapolation of survival data	£228,830
Disease management costs	Exclude disease management costs for LUM-IVA patients post death of patients treated with SoC	£186,361
Adherence rates	96.5% adherence rate used for costing, rather than 90% in base-case model	£234,000

With the exception of the analysis using 1.5% discount rates for costs and outcomes, the ICERs generated from these analyses all lie within a range of £181,366 per QALY to £283,458 per QALY. Finally, the company presents a number of subgroup analyses, looking at how the cost-effectiveness changes in different patient groups (Table 41). The ICERs for these different subgroups fall within a range of £172,845 per QALY to £300,688 per QALY.

Table 41 Subgroup analyses

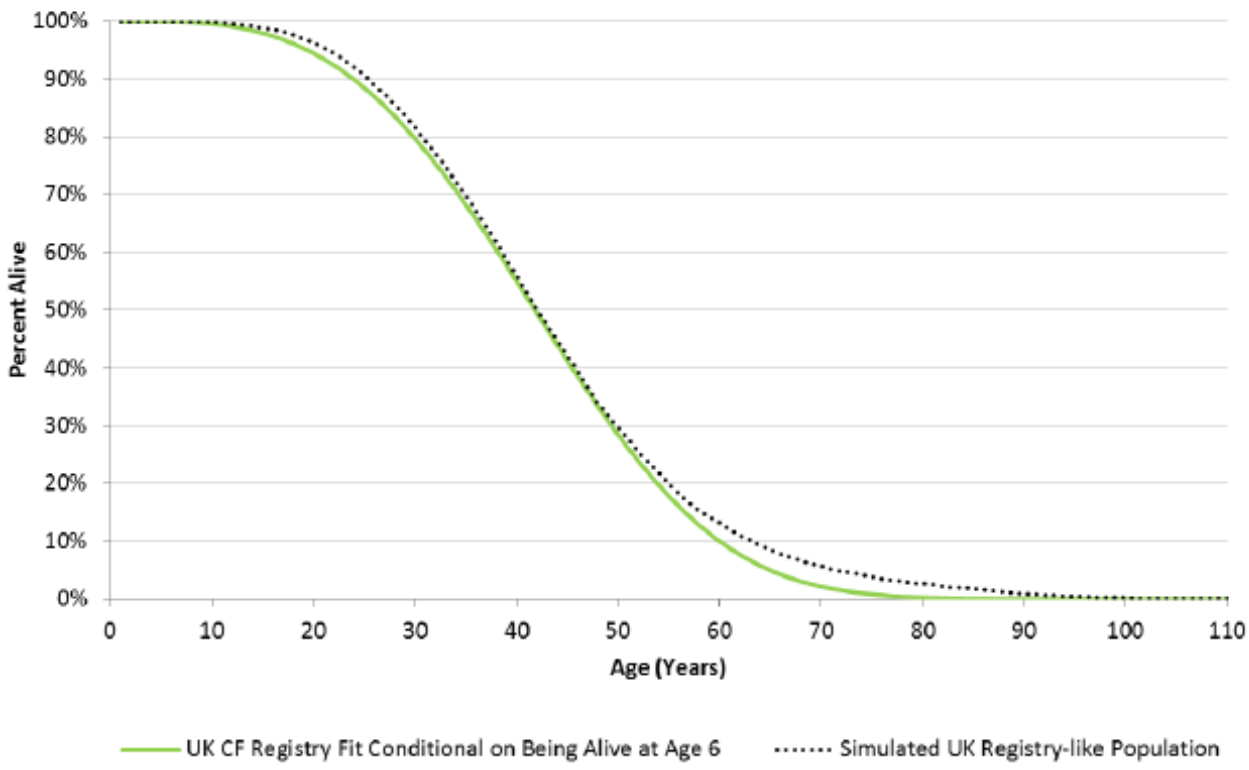
Characteristic varied	Population modelled	ICER (£/QALY)
Base-case	N/A	£218,248
Sex	Male	£212,205
Sex	Female	£220,734
Age at treatment onset	12-18	£172,845
Age at treatment onset	>18	£245,279
Baseline ppFEV$_1$	>40%	£213,366
Baseline ppFEV$_1$	<40%	£300,688
Baseline ppFEV$_1$	>70%	£199,481
Baseline ppFEV$_1$	<70%	£225,907

5.2.12 Model validation

Two errors were identified in the original models supplied by the company. The first, as described above, was an error in the calculation of disease management costs, which had the impact of overestimating the cost offsets afforded by LUM-IVA treatment. The second error was a mistake in one of the distributions included in the PSA, where an error in one of the distribution parameters used led to the construction of a confidence interval that did not contain the mean parameter value. The company supplied a new version of the model that corrected both of these errors, and all results reported in this document are based on this new version of the analysis.

As a validation check for the survival model used, the company simulated a cohort with, as far as possible, the same characteristics as the UK CF registry population, to compare real and predicted survival estimates. There appears to be, over most of the distribution, good agreement between the true and simulated data (Figure 8).

Figure 8 Validation of the Survival Projection Approach



5.3 Additional analyses undertaken by the ERG

The ERG has conducted two new sensitivity analyses, to look at the impact of uncertainty in two model assumptions not addressed in the company submission.

Pulmonary exacerbations

The assumption made in the company's base-case analysis that the effect of LUM-IVA on the pulmonary exacerbation rate is independent of the effect on $ppFEV_1$. Thus, treated individuals rates of pulmonary exacerbations are reduced by both of these factors (indirectly via $ppFEV_1$ differences and directly via the relative risk applied to pulmonary exacerbation rates). An alternative, conservative assumption is that, after the time horizon of the trial, the effect of LUM-IVA treatment on exacerbations is assumed to be mediated entirely via differences in $ppFEV_1$ (i.e. the relative risk for exacerbations is set to 1 after the time horizon of the trial. The results of this analysis are given in Table 42.

Table 42 Sensitivity analysis results (Pulmonary exacerbation relative risk set to 1)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER versus baseline (QALYs)
SoC	£377,632	8.92			
LUM-IVA	£1,082,277	11.51	£704,645	2.59	£272,265

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness analysis

Generic discounting

Table 43 presents the results of a series of sensitivity analyses, looking at the impact on the ICER for LUM-IVA versus SoC, assuming different lengths of time until an alternative generic treatment becomes available, and the price discount provided by that generic treatment.

Table 43 Sensitivity analysis results (generic pricing)

		%price reduction for generic medicine				
		89%	80%	70%[a]	60%[a]	50%[a]
Time until generic alternative becomes available	10 years	£197,790	£213,115	£230,143	£247,171	£264,198
	12 years	£218,248*	£231,504	£246,233	£260,962	£275,691
	15 years	£244,103	£254,745	£266,569	£278,394	£290,218
	20 years	£277,006	£284,321	£292,449	£300,577	£308,704
	Never	£349,337	£349,337	£349,337	£349,337	£349,337

*Company's base-case [a]Costs for these scenarios are calculated by extrapolating costs from the 89% and 80% scenarios.

The ERG has also run a modified version of the company's base-case model, incorporating the following changes:

- Adherence rates to treatment for LUM-IVA are set to 96.5% for costing purposes. This means the same adherence level is used for both effectiveness and cost data.
- The new model makes use of the post-trial discontinuation rates included in a sensitivity analysis by company, where 30% of patients are assumed to have discontinued after 15 years of treatment (1.9% annually).
- The placebo-adjusted mean change from baseline in $ppFEV_1$ is calculated using data from the 24-week time point, rather than the average of the 16-week and 24-week follow ups. This replaces the 2.8% absolute increase in the company's base-case model with a 2.45% absolute increase.

Results, comparable to those reported in section 5.2.9 for the company's base-case model are given below.

Table 44 ERG base-case results

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92					
LUM-IVA	£1,092,269	13.56	12.14	£714,637	3.24	3.22	£220,405	£221,992

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness analysis

Table 45 Health outcomes (ERG model)

Comparator	LUM-IVA + SoC	SoC	Incremental
Projected Median Survival (Years)	43.27	36.15	7.13
Undiscounted Life Years	23.84	15.05	8.78
Mean $ppFEV_1$ Cumulative Change	-13.40	-21.89	8.49
Mean Years with $ppFEV_1 \geq 70\%$	3.92	1.14	2.78
Mean Years with $ppFEV_1$ between 70% and 40%	16.73	8.84	7.89
Mean Years with $ppFEV_1$ between 40% and 30%	2.48	2.66	-0.18
Mean Years with $ppFEV_1 < 30\%$	0.71	2.42	-1.71
Annual Rate of pulmonary exacerbation	0.55	1.24	-0.69
Percent Undergoing Lung Transplant	1.55%	6.80%	-5.25%
Mean Years Until Lung Transplant	44.40	19.34	25.06

Abbreviations: SoC, standard of care; ppFEV1, Percent predicted forced expiratory volume in 1 second.

Table 46 Summary of predicted resource use by category of cost (ERG model)

Item	Cost LUM-IVA + SoC	Cost SoC	Increment	Absolute increment	% absolute increment
Drug Cost	£724,234	£0	£724,234	£724,234	98.55%
Disease Management Cost	£365,835	£366,556	-£721	£721	0.10%
Lung Transplant Cost	£1,143	£10,539	-£9,396	£9,396	1.28%
Adverse Event	£935	£537	£398	£398	0.05%
Liver Function Test	£122	£0	£122	£122	0.02%
Total	£1,092,269	£377,632	£714,637	Total absolute increment	100%

Abbreviations: SoC, standard of care

Generic discounting

Table 47 presents sensitivity analyses looking at the impact of differing assumptions about the level of generic price discounts and the length of time until a generic alternative becomes available, using the ERG's model.

Table 47 Sensitivity analysis results (generic pricing)

		% price reduction for generic medicine				
		89%	80%	70%[a]	60%[a]	50%[a]
Time until generic alternative becomes available	10 years	£203,100	£215,971	£230,272	£244,573	£258,874
	12 years	£221,992*	£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	£330,385	£330,385	£330,385	£330,385

*ERG's base-case [a]Costs for these scenarios are calculated by extrapolating costs from the 89% and 80% scenarios.

ERG summary

- The changes made by the ERG to the company's base-case assumptions increased the ICER for LUM-IVA versus SoC from £218,248 per QALY to £221,992 per QALY.
- Uncertainty in the availability of generic alternatives to LUM-IVA can make a significant difference to the ICER.

5.4 Conclusions of the cost-effectiveness section

The company submission is based around an economic analysis of LUM-IVA with SoC versus SoC alone in a CF population homozygous for the *F508del* mutation, with the key clinical data informing differences between patient outcomes between these two groups coming from the TRAFFIC and TRANSPORT RCTs, as well as the open-label PROGRESS study. The population modelled was that from the TRAFFIC and TRANSPORT studies, and this was assumed to be sufficiently similar to the relevant UK treatment population that no adjustments to the modelled population were necessary. Additional clinical data were taken from the UK CF clinical registry, and in a number of places in the submission an assumption was made that the long-term outcomes for individuals with the *F508del* mutation would be the same as those for the whole CF population included in the registry.

There are a number of potentially important sources of uncertainty which are not fully discussed or justified in the company submission. First, the model estimates improvements in $ppFEV_1$ with treatment by averaging values from the 16- and 24-week measurements, which gives a greater improvement over SoC than using the 24-week measurement alone. Post-trial declines for the treated group are then

estimated from 48 week data, with these same short-term decline rates assumed to remain the same over time. The treatment benefit with LUM-IVA is then assumed to persist for the entire duration of the model, as long as people remain on treatment. The importance of these assumptions is shown in the one-way sensitivity analysis of declines in $ppFEV_1$ with LUM-IVA, with the upper end of the sensitivity analysis giving an ICER of £437,181, more than twice that in the base-case analysis.

There are also assumptions made in several of the other modelled clinical characteristics. The effect of LUM-IVA on pulmonary exacerbations is assumed to be independent from, rather than caused by, its effect on $ppFEV_1$. This means treated individuals gain a benefit from reduces pulmonary exacerbations from the slower decline in $ppFEV_1$, and then an additional benefit when the relative risk is directly applied. Weight-for-age z-scores are assumed to remain unchanged for both groups after the time horizon of the trial, meaning the benefit of treatment with LUM-IVA is assumed to be permanent, persisting both beyond the trial time horizon and beyond treatment discontinuation. Finally, whilst discontinuation rates for the first 24 weeks are taken from trial data, it is assumed in the base-case that no individuals would discontinue from treatment after that point (despite evidence from the PROGRESS study that discontinuations do continue past this point).

The model assumed that, after 12 years, a generic drug would become available costing 11% of the current list price. Whilst an explanation is given for including such a price discount, no robust justification is given for why this particular value was chosen. The intervention was also costed assuming a lower adherence rate than that measured in the trial, but the clinical effectiveness results based on the higher trial level of adherence were used without adjustment. Disease management costs were based on a CF population with a different mutation (*G551D*), and the measured reduction in incidence of pulmonary exacerbations requiring hospitalisation from the trial (61%) was applied as a reduction to all hospital costs in the LUM-IVA arm of the model.

Quality of life data (stratified by $ppFEV_1$ status and recent pulmonary exacerbation) are taken from the TRAFFIC and TRANSPORT data and appear to be appropriately used. However, no justification is given for the specific model specification chosen to link quality of life to clinical outcomes, and the model does not consider the impact of treatment related adverse events.

Whilst the impact of some of these assumptions was tested in sensitivity or scenario analyses (e.g. rate of long-term decline in $ppFEV_1$ with LUM-IVA, discontinuation rates, alternative sources of utility data) there are a number of important assumptions where no such sensitivity analyses were conducted (e.g. duration of post-trial treatment benefit with LUM-IVA, costs of generic alternatives and length of time

until they become available). This means that considerable uncertainties remain in the overall cost-effectiveness of treatment, although all relevant sensitivity and scenario analyses appear to lie within a range of £135,377 per QALY and £437,181 per QALY.

5.5 Impact on the ICER of additional analyses undertaken by the ERG

Alterations to the base-case assumptions made by the ERG increased the ICER for LUM-IVA versus SoC from £218,248 per QALY to £221,992 per QALY. Consistent with the results from the probabilistic sensitivity analysis of the company's base-case model, there remains a 0% chance of LUM-IVA being cost-effective versus SoC at willingness-to-pay thresholds of £30,000 per QALY and £50,000 per QALY. Additional sensitivity analyses conducted the ERG showed that the ICER is sensitive to different assumptions made about the availability and price of generic alternatives to LUM-IVA, in particular the length of time until a generic alternative becomes available.

Key sources of uncertainty in these estimates, together with the current assumptions utilised in the model and the likely impact of varying those assumptions, are summarised in the table below (see Table 48). There remain considerable sources of structural uncertainty in the model that it has not been possible to quantitatively assess, and these additional uncertainties should be borne in mind when interpreting the ICERs given above.

Table 48: Key sources of uncertainty in ICERs

Parameter/model feature	Current assumption	Likely impact of varying assumption
Patient population	The population modelled is that from the TRAFFIC and TRANSPORT studies, which is assumed to be sufficiently similar to the UK treatment population that results can be extrapolated to this group.	If the treatment benefit of LUM-IVA is less in the UK clinical population than in the TRAFFIC and TRANSPORT populations, LUM-IVA would become less cost-effective than it currently appears.
CF natural history data	Several parameter values are informed by data from the whole CF population, not that with the mutation of interest: • $ppFEV_1$ extrapolations for SoC • Survival data • Relationship between survival and patient characteristics.	Varying this assumption would only affect the ICERs produced if there are systematic differences in outcomes between the whole CF population and the *F508del* mutation subpopulation.
Long-term extrapolation of treatment benefit with LUM-IVA	Data taken from the TRAFFIC, TRANSPORT and PROGRESS studies are used to extrapolate long-term outcomes.	If the long-term treatment benefits with LUM-IVA are less than those measured in the comparatively short-term studies used to inform these parameters, LUM-IVA will becomes less cost-effective than it currently appears.
Long-term extrapolations of $ppFEV_1$ values	The extrapolations for LUM-IVA and SoC are undertaken separately, based on different, non-randomised studies.	It is unclear if this introduces bias in any particular direction into the model, but all the standard caveats around interpreting observational data apply when interpreting these results.
Duration of treatment benefit with LUM-IVA	Benefits in slower $ppFEV_1$ decline and reduced rates of pulmonary exacerbations are assumed to last for	Any assumption that the treatment benefit with LUM-IVA may decline after the time horizon of the trial

	as long as an individual remains on treatment. Improvements in weight-for-age z-score are assumed to last the remained of the individual's life.	will result in it appearing less cost-effective, versus SoC, than it currently does.
Quality of life	Quality of life, pre-transplant, is assumed to depend only on $ppFEV_1$ and recent pulmonary exacerbations, with no other treatment-related effects.	This assumption will not be justified if there are other treatment-related factors which affect quality of life (e.g. adverse events with LUM-IVA)
Disease management costs	Disease management costs are estimated from a population including individuals with the *G551D* mutation, and the measured reduction in pulmonary exacerbation hospitalisations from TRAFFIC and TRANSPORT is applied to all hospital costs whilst patients remain on treatment.	Different costing assumptions are likely to lead to smaller hospital cost offset with LUM-IVA

6 END OF LIFE

Not applicable.

7 INNOVATION

The CS notes on p. 22 and on pp. 24-25 that LUM-IVA combination therapy represents a 'step change' in management of CF, and describes it as 'a highly innovative transformative medicine in an area of severe unmet medical need'. Current management of CF is supportive only; that is, it aims to control inevitable decline of lung function and improve nutritional status, and requires aggressive specialist management across the lifespan. Improvements in supportive care have been successful in extending the life span of people living with CF. However, as noted in the CS (p 23), the chronic nature of CF means that the treatment burden is high on patients and their carers. Frequent hospitalisations and treatments have negative impacts on their lives. Thus, a treatment to slow progressive decline and reduce the burden of illness could be a breakthrough in CF treatment. The CS (p 22) notes that LUM-IVA combination therapy is the first therapy to address the underlying defects in protein formation and function that lead to CF symptoms. While LUM-IVA has the potential to improve quality of life and slow progressive lung function decline in CF patients, effects may not be as clinically significant as with similar drugs in other CF genotype populations. The ERG clinical advisor noted that the results obtained in the TRAFFIC and TRANSPORT trials were 'disappointing' compared with reductions in $ppFEV_1$ seen with ivacaftor in people with the G551D mutation.

8 OVERALL CONCLUSIONS

8.1 Clinical effectiveness evidence

The ERG considers that the evidence presented in the CS meets the decision problem. Despite several issues that were not resolved through clarification, the presentation of evidence from TRAFFIC and TRANSPORT (and, where relevant, PROGRESS) was mostly accurate. The ERG regarded the systematic review and included trials as being of reasonable quality, and the trial populations were considered to be reflective of the UK population. While LUM-IVA had statistically significant effects on key outcomes from the NICE scope, it was unclear how clinically significant these outcomes were and, given the length of the two key trials, what their long-term durability would be.

8.2 Cost-effectiveness evidence

Judging both from the model submitted by the manufacturer and the ERG's modified model, which includes more conservative assumptions, LUM-IVA appears to provide long-term benefits over SoC in the TRAFFIC and TRANSPORT study populations. However, it is also associated with considerably higher costs, mostly as a result of both the high cost and long duration of LUM-IVA therapy, and these increased costs are consistent across all different scenarios modelled.

There are several difficulties in extrapolating the results from these analyses to the relevant decision problem in the UK. Specifically:

- The treatments benefits of LUM-IVA on both $ppFEV_1$ and pulmonary exacerbations are assumed to continue as long as the individual remains on treatment, and on weight-for-age z-scores are assumed to continue for the entire time horizon of the model, even though no sufficiently long-term studies have been conducted to verify this assumption.
- Data from a 48-week open-label follow up study have been used to estimate long-term progression with treatment, even though this follow-up period may not be long enough to establish a consistent long-term trend.
- A number of assumptions (e.g. extrapolation of reduced pulmonary exacerbation hospitalisations in the trial to long-term reductions in all hospitalisations with treatment, independence of effect of LUM-IVA on $ppFEV_1$ and pulmonary exacerbations) are based on expert opinion rather than data.

In the absence of data to test the impact of these assumptions, the uncertainty generated should be borne in mind when considering the cost-effectiveness of LUM-IVA in the UK.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 5 February 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 9 – "Details of Standard of Care (SoC) were not reported in the company submission (CS)."	"SoC is reported in the submission as patients' usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated)."	Vertex considers this statement to be factually incorrect. We have stated the treatments that are considered SoC in the CS. In Section 1.1, Table 1 of the CS, SoC is cited in the following statement: 'Submission presents data for LUM-IVA in conjunction with patients' usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), referred to as standard of care [SoC] throughout the submission, vs. SoC alone.' This is further mentioned in section 1.3 of the CS: 'In the LUM-IVA and placebo arms of the Phase 3 studies, TRAFFIC (Study 103 – 24 weeks) and TRANSPORT (Study 104 – 24 weeks), patients continued with their usual CF management (e.g. dornase alfa, pancreatin, inhaled hypertonic saline, bronchodilators and antibiotics, as clinically indicated), for the duration of the studies.'	Not a factual inaccuracy, no change required.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 11 – "Mortality is also not directly	"No deaths were reported in either TRAFFIC or TRANSPORT; one death	Vertex considers this statement to be factually incorrect. In Section 4.12.1.1 of	Page 11 amended to: '"Mortality is also not directly

addressed, though only one death occurred in the relevant arms of TRAFFIC and TRANSPORT, and this was judged to be unrelated to the study."	was reported in PROGRESS"	the CS, it is stated that no deaths were reported in either TRAFFIC or TRANSPORT. In Section 4.12.2.2, it is stated that one death has been reported from respiratory failure following a pulmonary exacerbation at day 344 (>48 weeks), in the extension study PROGRESS. This was judged to be unrelated to the study."	addressed, though only one death occurred among the relevant dose arms of the trials (during PROGRESS extension study), and this was judged to be unrelated to the study."

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 16 – "The ERG clinical advisor notes that median survival has improved over the last 20 years with improved standards of care, and that the median age of death does not reflect this."	"Although the median survival has increased, this has not had a significant effect on the median age of death." In fact it has stayed very stable in the last 5 years, with the figure listed in the registry of 29 in 2010.	Vertex considers that the median age of death of 28 years among CF patients is considerably shorter than the life expectancy of the general population in the UK. Therefore current SoC does not address this unmet need.	Not a factual inaccuracy, no change required.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 "Of those living with CF in the UK, approximately 50% match the genotype for which this drug is indicated (CS p.23), and that this corresponds to approximately 2,748 patients (CS p. 22). However, the submission for the Cystic Fibrosis Clinical	"Based on data from the 2015 CF registry, the number of CF patients over 12 years of age, having the genotype for which the drug is indicated, is estimated to be 2,748 patients. "	Vertex considers that the submission for the CF Clinical Reference Group for NHS England may have included a larger population than that indicated for this drug. It is not clear how the number of 3,500 was derived, and whether this was restricted to those older than 12 years or included a wider population.	Not a factual inaccuracy, no change required.

Reference Group, for NHS England, suggests that the number of eligible patients would be closer to 3,500."			

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 56 "Primary clinical evidence from a meta-analysis of relevant trials"	"Primary clinical evidence from a pre-planned pooled analysis of relevant phase 3 trials"	The similarity of the TRAFFIC and TRANSPORT protocols for key outcome assessments allowed for a pre-specified pooled analysis of results from both studies, providing a robust dataset to evaluate the totality of the data. Results of the pooled analysis are reported within this submission.	Not a factual inaccuracy, no change required.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 "the company constructed a de novo Markov model with a lifetime horizon"	"the company constructed a de novo patient-level microsimulation model with a lifetime horizon"	The model submitted is a discrete time patient-level microsimulation as referred to elsewhere in the ERG report.	Page 57 amended as suggested.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 59 "However, since it was not possible to compare the trial data to the subset of the patients in	"However, since it was not possible to compare the trial data to the subset of the patients in the CF registry who would have met the trial inclusion criteria (F508del	All inclusion criteria made a comparison between the CF registry and trial data difficult, not just ppFEV1 and genotype.	Not a factual inaccuracy, no change required.

the CF registry who would have met the trial inclusion criteria (F508del mutation and ppFEV1 between 40 and 90%)“	mutation, ppFEV1 between 40 and 90% and age 12 or greater along with other inclusion criteria)“		

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 62 “This assumption is stated by the company as having been verified as plausible by its clinical experts , but does run the risk of double-counting the benefits of treatment , as rates of pulmonary exacerbation are reduced first by slower declines in ppFEV1, and then the relative risk from the trial is applied in addition to that.”	“This assumption is stated by the company as having been verified as plausible by its clinical experts and by a repeated measures analysis of trial data.”	This assumption was also tested by isolating the impact of LUM-IVA on the rate of pulmonary exacerbations requiring IV antibiotics or hospitalization from $ppFEV_1$ changes, a repeated measures binomial regression model was conducted estimating the rate of exacerbations based on a number of variables, predominantly previous $ppFEV_1$ and a dummy variable to represent the treatment effect of LUM-IVA. This analysis estimated LUM-IVA to be associated with a rate ratio of 0.2941 (confidence interval 0.2054 – 0.4211), implying that treatment with LUM-IVA confers a large benefit on	Not a factual inaccuracy, no change required.

		exacerbations even when accounting for ppFEV1 changes and in fact the base case assumption may be conservative. Discussed in section 5.3.3 of the CS	

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 64 "The choice of birth years to include in the final analysis (1985-2008) and the choice of distributions was based primarily on which combinations produced results which were deemed to be clinically realistic, rather than any statistical criteria."	"The choice of birth years to include in the final analysis (1985-2008) and the choice of distributions was based on which combinations produced results which were deemed to be clinically realistic, in addition to statistical criteria."	Clinical plausibility alongside statistic criteria were considered when deciding which parametric curve to use. Results from statistical analysis was used initially to rule out potential curves, then when comparing the curves with the best statistical scores clinical plausibility was considered.	Not a factual inaccuracy, no change required.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 66 "The difference between the LUM-IVA and SoC groups in ppFEV1, measured in the trials, is averaged across the 16-week and 24-week measurements, which gives results more favourable to LUM-IVA than using the week 24 measurement alone."	"Averaging the mean absolute change at week 16 and week 24 is an acceptable approach in CF clinical trials to reduce known variability. "	On page 31 of the ERG report, the following statement is provided: The absolute change from baseline ppFEV1 at week 24 was calculated by averaging the mean absolute change at week 16 and week 24 to reduce known variability. The ERG clinical expert advised that this approach is becoming common in cystic fibrosis trials and is acceptable. The average of weeks	Not a factual inaccuracy, no change required.

		16 and 24 weeks was also used for the relative change from baseline ppFEV$_1$. Vertex would like to clarify that the analysis to assess the primary endpoint was chosen to provide a better estimate of the treatment difference at the end of the treatment period. The rationale and simulations for how Vertex chose the method to assess the primary endpoint are provided below and this approach was accepted by the EMA for licencing purposes. Rationale and Simulations Subjects in Studies 103 and 104 received 24 weeks of LUM/IVA combination therapy or placebo. Vertex anticipated that the treatment difference for the 2 active groups (LUM 400 and LUM 600 group) compared with the placebo group would be stable during the last 8 weeks of treatment (Week 16 through Week 24). Because of the inherent variability in ppFEV1, an analysis using the average change from baseline in ppFEV1 at Week 16 and at Week 24 (the last 2 scheduled visits in the studies) was assumed to have reduced variability compared with the point estimate at Week 24 alone, as 2 measurements are likely to provide a better	

		estimate of the treatment difference than either time point alone. Based on this assumption, Vertex chose to assess the primary endpoint by conducting an analysis which was anticipated to provide a better estimate of the true treatment effect at the end of treatment. Recent data from Study 105 IA 2 further support the durability of response through 48 weeks and support the use of this analysis to estimate the true treatment effect despite the inherent variability in ppFEV1 (Figure 1). Despite the combination of biological variability and the variability in $ppFEV_1$ observed at each scheduled visit, the absolute change in $ppFEV_1$ was within the same 'range' at all visits.	

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 69 "Following a request for clarification from the ERG, the company ran a new version of the model which included treatment as a covariate, but the coefficient for this was both non-significant and close to 0, once again	"Following a request for clarification from the ERG, the company ran a new version of the model which included treatment as a covariate in addition to pulmonary exacerbation status and $ppFEV_1$, but the coefficient for this was both non-significant and close to 0, once again providing no evidence for short-term differences in utility between the SoC and LUM-IVA groups	The inclusion of treatment arm as a covariate in the regression, in addition to other criteria, showed that the equation was not improved by the inclusion of treatment arm as a covariate. Importantly this means that short-term differences are captured by $ppFEV_1$ and pulmonary	Not a factual inaccuracy, no change required.

providing no evidence for short-term differences in utility between the SoC and LUM-IVA groups."	that wasn't captured by ppFEV1 and pulmonary exacerbation status."	exacerbation.	

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 70 "No utility losses were assigned to adverse events other than pulmonary exacerbations, meaning the potential disutilities associated with treatment related adverse events for LUM-IVA will not be included in the model."	"No utility losses were assigned to adverse events explicitly other than pulmonary exacerbations, meaning the potential disutilities associated with treatment related adverse events implicitly captured"	Treatment arm was included in the regression predicting utility score. The coefficient associated with treatment arm was close to 0 and non-significant. This means that differences in adverse events did not have a significant impact on the regression and when considered was did not cause a difference between treatment arms.	Not a factual inaccuracy, no change required.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 74 "Costs of disease management for LUM-IVA are not based on data, but rather an assumption that hospital costs would be 61% lower than for SoC, and other costs would remain unchanged."	"Costs of disease management for SoC are based on data. Costs of disease management for LUM-IVA are the same, but the hospital costs are 61% lower than for SoC based on data from the TRAFFIC and TRANSPORT trials (discussed in section 1.4)."	Disease management costs for LUM-IVA are not based on assumptions. The disease management costs are based on the same costs as SoC and reduction in hospitalisations based on trial data.	Not a factual inaccuracy, no change required.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 90 "A number of assumptions (e.g. extrapolation of reduced pulmonary exacerbation hospitalisations in the trial to long-term reductions in all hospitalisations with treatment, independence of effect of LUM-IVA on ppFEV1 and pulmonary exacerbations) are based on expert opinion rather than data."	"A number of assumptions (e.g. extrapolation of reduced pulmonary exacerbation hospitalisations in the trial to long-term reductions in all hospitalisations with treatment, independence of effect of LUM-IVA on ppFEV1 and pulmonary exacerbations) are validated by expert opinion."	The assumptions were tested empirically with outcomes from the analysis validated by experts. These assumptions were not based entirely on expert opinion.	Not a factual inaccuracy, no change required.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 89 – "The ERG clinical advisor noted that the results obtained in the TRAFFIC and TRANSPORT trials were 'disappointing' compared with reductions in ppFEV1 seen with ivacaftor in people with the	"Comparison cannot be made of improvements in $ppFEV_1$ for LUM-IVA combination therapy in CF patients with the F508del mutation against $ppFEV_1$ improvements with ivacaftor in those with the G551D mutation because of the added disease complexity in F508del patients arising from defects in both CFTR quantity and also	Vertex considers that such comparison is not justified or accurate for the following reasons. CFTR bearing the G551D variant is found at normal levels in the cell membrane but cannot be activated. The F508del variant causes a	Not a factual inaccuracy, no change required.

G551D mutation.”	CFTR chloride ion channel gating function. F508del is usually therefore a more severe form of CF than G551D due to impairment of both CFTR quantity and function	defect in protein folding, which greatly diminishes CFTR quantity at the plasma membrane and reduces both membrane residency and channel activity. Thus different theratype strategies are required for CF patients with these respective distinct mutations. The CFTR potentiator ivacaftor increases the activity of the CFTR protein, thereby increasing chloride transport in airway epithelia. In patients with the G551D mutation, the action of ivacaftor alone is sufficient to produce a clinical response in the lungs. The CFTR corrector lumacaftor enhances stability and function of the CFTR protein, and improves quantity at the plasma membrane by increasing processing and trafficking. The complementary mechanisms of action of both molecules is required to address both protein defects in patients with the F508del mutation as F508del is usually therefore a more severe form of CF than G551D due to impairment of both CFTR quantity and function It should be further noted that ppFEV$_1$ is not the only parameter of efficacy in CF treatment closely linked to mortality.	

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

ERRATUM

Replacement pages following the factual accuracy check

10th February 2016

Produced by ERG: Warwick Evidence

patients receiving LUM-IVA, whereas patients receiving LUM-IVA reported dyspnoea, diarrhoea, nausea and upper respiratory infection in greater numbers.

The frequency and severity of NICE scoped outcomes of acute infections, and respiratory symptoms, are not discussed directly in the CS. Some acute infections and respiratory symptoms are reported in the adverse events, but these do not record the severity of the events. Mortality is also not directly addressed, though only one death occurred among the relevant dose arms of the trials (during PROGRESS extension study), and this was judged to be unrelated to the study.

1.3 Summary of the ERG's critique of submitted clinical evidence

The ERG appraisal of TRAFFIC and TRANSPORT, the pivotal phase 3 trials in the CS, substantially agreed with the CS appraisal, and the ERG agreed that the trials were of generally good quality. However, the ERG noted some evidence of selective reporting bias. The CS approach to pooling the phase 3 trials appeared reasonable, and the analytic methods used within both phase 3 trials also appeared to be appropriate.

The ERG noted several issues with the submitted clinical evidence:

- First, though the NICE scope did not specify severity of disease, both trials included only CF patients with mild to moderate CF (that is, with ppFEV$_1$ between 90% and 40% at screening). This means that clinical evidence may not generalise to those with 'end-stage' CF or those at the beginning of the disease course. The CS does not discuss this issue.
- Second, several outcomes addressed in the NICE scope were not adequately reflected in the included clinical evidence. Specifically, mortality was not directly addressed in the CS except as an adverse event; respiratory symptoms were only considered as adverse events; frequency of acute infections was only considered under adverse events, and severity of acute infections was not discussed; and results for EQ-5D-3L, a measure of health-related quality of life (HRQoL), were mentioned but not presented in the CS.
- Third, some outcomes were not adequately reported in the CS. Clarifications for these outcomes were requested and responses were generally useful, with some exceptions. Specifically, data presented on rates of pulmonary exacerbations were not clear regarding the unit of analysis, and numbers did not appear (based on the ERG's reading) to reconcile between different tables.

1.3.1 Strengths

This CS had several strengths:

- In the main, quality of the systematic review was reasonable, and assessment of study quality was appropriate.

Table 4 Key baseline characteristics from included studies

	TRAFFIC		TRANSPORT		Pooled		PROGRESS (Part A), from point of first randomisation	
	LUM-IVA 400/250mg BD N=182	**Placebo N=184**	**LUM-IVA 400/250mg BD N=187**	**Placebo N=187**	**LUM–IVA 400/250mg BD N=369**	**Placebo N=371**	**LUM–IVA 400/250mg BD N=340**	**Placebo to LUM–IVA 400/250mg BD N=176**
Mean Age (SD)	25.5 (10.09)	25.0 (10.80)	25.0 (9.03)	25.7 (10.02)	25.3 (9.56)	25.4 (10.41)	25.1 (9.33)	24.9 (10.10)
Age groups, years, n (%)								
12 to <18	52 (28.6)	53 (28.8)	46 (24.6)	43 (23.0)	98 (26.6)	96 (25.9)	94 (27.6)	47 (26.7)
≥18	130 (71.4)	131 (71.2)	141 (75.4)	144 (77.0)	271 (73.4)	275 (74.1)	246 (72.4)	129 (73.3)
Female (%)	46.2	45.7	52.4	51.9	49.3	48.8	48.2	48.9
Mean (SD) BMI (kg/m^2)	21.68 (3.17)	21.03 (2.96)	21.32 (2.89)	21.02 (2.89)	21.5 (3.03)	21.0 (2.92)	21.4 (2.94)	20.86 (2.76)
$ppFEV_1$ Mean (range)	60.5 (34.8, 94.0)	60.5 (34.0, 88.0)	60.6 (31.3, 96.5)	60.4 (33.9, 99.8)	60.5 (31.3, 96.5)	60.4 (33.9, 99.8)	60.4 (SD 14.20)[a]	60.2 (SD 13.78)[a]

BD: Twice daily (every 12 hours); [a]from CSR

		EQ-5D data collected during the clinical effectiveness studies, as well as values from the literature.
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity and scenario analyses are presented.

The cost-effectiveness evidence submitted by the company appears to satisfy the NICE reference case, and the decision problem defined in the scope. To appraise LUM-IVA for CF patients aged 12 and older who are homozygous for the *F508del* mutation in the CFTR gene, the company constructed a de novo patient-level microsimulation model with a lifetime horizon. The model has a cycle length of four weeks for the first two years, to enable replication of data from the studies informing the model, and then cycle lengths are one year from this point on. The model assumed that treatment benefit continues beyond the length of the trials.

The main data to inform the effectiveness parameters in the model came from the TRAFFIC and TRANSPORT studies, with additional data on CF mortality being included from both the UK CF trust registry, and a paper by Liou et al which looked at factors which predict survival in CF.[1]

5.2.2 Model structure

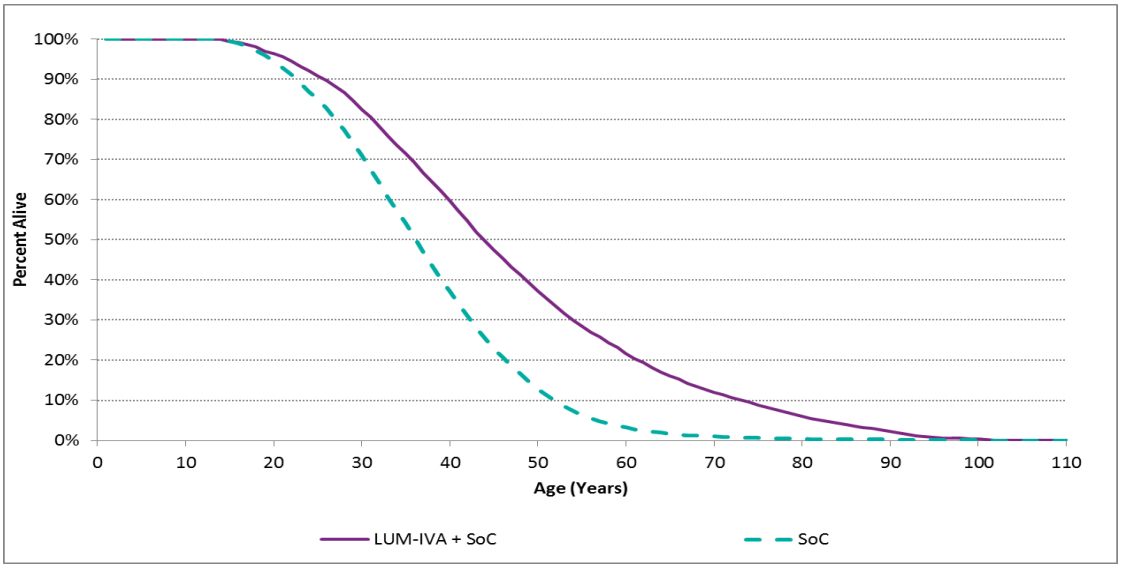
The model constructed by the company is a discrete time patient-level microsimulation, which follows a similar structure to previous models used in CF evaluations.[7] Identical starting cohorts of patients are run through the model twice, once assuming treatment with LUV-IVA and SoC, the other SoC alone. The baseline characteristics of patients in these runs are derived by randomly sampling from the

- The intervention is costed assuming a 90% adherence rate, but the clinical data used in the model are based on the 96.5% adherence rates from the trial.
- Costs of disease management for SoC, stratified by ppFEV$_1$ status, are taken from a CF population including individuals with a different mutation (*G551D*).
- Costs of disease management for LUM-IVA are not based on data, but rather an assumption that hospital costs would be 61% lower than for SoC, and other costs would remain unchanged.

5.2.9 Cost-effectiveness results (company's response to clarification letter)

For the base-case comparison of LUM-IVA with SoC only, LUM-IVA is predicted to increase median survival by 7.69 years and mean undiscounted life-years by 9.42. Base-case survival results for the two groups are given in Figure . Total mean discounted QALYs are 12.38 with LUM-IVA compared with 8.92 for SoC, whilst mean total costs for LUM-IVA are £1,131,202, as opposed to £377,632 for SoC. The results of the base-case analysis are shown in **Error! Reference source not found.**. The resulting ICER for LUM-IVA versus SoC alone is £218,248 per QALY.

Figure 4 Base case survival



Lumacaftor STA – additional analyses

1) The rate of $ppFEV_1$ decline in the LUM-IVA group was set to 1.58% annually post 24-weeks, the lower bound of the 95% confidence interval from the PROGRESS study.

Results – 1.58% $ppFEV_1$ decline in LUM-IVA group post 24-weeks

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92					
LUM-IVA	£1,061,163	11.80	10.41	£683,532	1.48	1.49	£461,816	£459,045

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost effectiveness analysis

2) The rate of $ppFEV_1$ decline in the LUM-IVA group was set to -0.16% annually post 24-weeks (i.e. a slight improvement), the upper bound of the 95% confidence interval from the PROGRESS study.

Results – -0.16% $ppFEV_1$ decline in LUM-IVA group post 24-weeks

	Total costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER versus baseline (LYs)	ICER versus baseline (QALYs)
SoC	£377,632	10.32	8.92					
LUM-IVA	£1,164,047	16.07	14.73	£786,415	5.76	5.81	£136,598	£135,464

Abbreviations: LYG, life years gained; QALYs, quality adjusted life years; ICER, incremental cost effectiveness analysis