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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Vertex Pharmaceuticals
   - The Cystic Fibrosis Trust
   - The British Thoracic Society
   - NHS England

   The Royal College of Nursing and Department of Health both submitted a 'no comments' response.

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Iolo Doull - Guideline Development Group representative, nominated by the National Collaborating Centre for Women's and Children's Health
   - Ms Lynsey Beswick - Patient Expert, nominated by The Cystic Fibrosis Trust

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of the company's ACD comments** prepared by Warwick Evidence

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

Single Technology Appraisal

Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Vertex	Thank you for the opportunity to comment. In reviewing the report, Vertex found a number of inaccurate interpretations of the evidence base supporting the use of lumacaftor–ivacaftor in the treatment of cystic fibrosis patients with the F508del homozygous mutation. Vertex has sought to address each of these inaccuracies in turn, as they go to the heart of this evaluation of lumacaftor-ivacaftor and make these provisional recommendations an unsuitable basis for guidance to the NHS. These inaccuracies can be summarised in three key themes and then followed in more detail by 11 key issues; **1. It is felt that the 2.8% improvement in ppFEV1 seen with lumacaftor–ivacaftor is clinically meaningful, especially in the context of a rapidly progressive disease like cystic fibrosis.** The rapid progressive nature of Cystic Fibrosis means that any preservation of lung function as measured by ppFEV1 is clinically relevant and significantly reduces the risk of death. A decrease in ppFEV1 of just 1% per annum increases the risk of death over 5 years by 4%. Therefore the 2.8% increase in ppFEV1 observed over 48 weeks, is a clinically meaningful improvement that in the long term is expected to translate into reduction in mortality. **2. The comparisons of improvements in ppFEV1 seen with lumacaftor–ivacaftor in F508del CF patients to ivacaftor in G551D is inappropriate and does not align with the final scope.** The final scope, which was agreed upon with clinical experts, patient groups, NICE and other relevant stakeholders does not include ivacaftor monotherapy as a comparator. Ivacaftor monotherapy is neither indicated, nor is it used in clinical	Comments noted. The committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition. A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. The committee noted that the absence of an agreed minimum clinically important difference would not prevent it from being able to make a recommendation for lumacaftor–ivacaftor. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The committee was aware that ivacaftor monotherapy is used for treating cystic fibrosis in

Consultee	Comment [sic]	Response
	practice for the treatment of cystic fibrosis in patients with the F508del mutation. In fact, evidence from the DISCOVER clinical trial confirms that ivacaftor monotherapy does not work in this F508del population. The complementary mechanisms of action of both lumacaftor–ivacaftor molecules are required to address both protein defects CF is a huge umbrella term encompassing all mutations and it would be like comparing two different types of chemotherapy in two different types of cancer. **3. The totality of the evidence package for lumacaftor-ivacaftor has not been taken into consideration by the committee in their assessment.** The evidence from the pivotal phase 3 clinical trials (the largest interventional trials ever conducted in CF) have shown that treatment with lumacaftor-ivacaftor led to sustained improvements in ppFEV1 and BMI as well as reductions in pulmonary exacerbations over a 48 week period. All of these improvements were statistically and clinically significant. Over time improvements in these three key areas have been shown to be the most important beneficial modifiers of mortality risk and disease progression. Given the multi-systemic and heterogeneous nature of the disease, one endpoint will be insufficient to capture all the benefits of treatment with lumacaftor-ivacaftor, as such the focus should be on the totality of the evidence. **Issue 1 ppFEV1 modest response** *Description of problem* Summary p43 - The committee concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant. Summary p46 - The acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant. *Description of proposed amendment* Rewording required for p43 - 46: The committee concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor "can be considered as clinically significant in light of the progressive nature of CF, but that a sustained	people with the G551D mutation and this was not a comparator for this appraisal. The committee heard from the clinical experts that the general size of the effect seen for lumacaftor–ivacaftor was lower than the absolute acute improvement in ppFEV1 seen with other treatments for cystic fibrosis directed against mutations conferring a similar severity of disease. Please see section 4.6 of the FAD. The committee understood from the company's response to consultation that the company considered that all the evidence for lumacaftor–ivacaftor had not been taken into account. However, the committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had not been captured in its economic modelling. Please see section 4.27 of the FAD. Comments noted. Section 4.6 of the FAD has been updated: The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for

Consultee	Comment [sic]	Response
	benefit requires further real world evidence". *Description of justification for amendment / agreement* This is not a reasonable interpretation of the evidence as acute (short-term) changes in ppFEV1 and the ppFEV1 benefits of a chronic medication for CF should always be considered in the context of the progressive nature of CF and the inevitable FEV1 decline. As noted by the committee "longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis." The treatment effect on ppFEV1 is clinically relevant as the chronic nature of CF means that it is not only the acute (short-term) change in ppFEV1, but essentially disease progression, i.e. ppFEV1 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 ppFEV1 increases the risk of death over 5 years by 4% (4).Therefore a 2.8% positive increase is not only statistically significant, but is also clinically significant for patients and treating physicians. **Issue 2 - Patient expert statement correction around clinical significance** *Description of problem* P27 – 4.6 - A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be clinically significant, but from a patient perspective any improvement in lung function is welcomed. *Description of proposed amendment* Rewording required: A patient expert stated that "although the committee may not view an absolute increase of 2.8% in ppFEV1 as clinically significant, from a patient perspective any improvement in lung function is welcomed". *Description of justification for amendment / agreement*	patients. The committee concluded that longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis, and both the observed and extrapolated benefits of lumacaftor–ivacaftor on ppFEV1 were taken into account in the company's cost-effectiveness analysis. Comments noted. The committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition. A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. No changes to the FAD required.

Consultee	Comment [sic]	Response
	This has been misinterpreted as the patient expert did not state exactly “it may not be clinically significant” and this seem to have been misinterpreted. The proposed amendment more accurately reflects what was said and intended. **Issue 3 - Inappropriate comparison to Ivacaftor** *Description of problem* P27 – 4.6 - However, the clinical experts agreed with the committee that the size of the effect seen for lumacaftor–ivacaftor was lower than the 10–12% absolute improvement in ppFEV1 seen with ivacaftor monotherapy in people with cystic fibrosis who have the G551D mutation. *Description of proposed amendment* Requested removal of this summary, however at the least a suggested addition at the end: <u>However the committee accept that a direct comparison is not appropriate as each targeted medicine treats a different mutation of CF.</u> *Description of justification for amendment / agreement* The clinical experts also stated it is not appropriate to directly compare between the 2 different genetic mutations. This needs to be reflected in the summary statement. This was also stated at the NICE scoping meeting when raised by NHSE as a potential comparator. Ivacaftor alone does not work in the F508del population and the comparison is medically inappropriate. CF is a huge umbrella term encompassing all mutations and it would be like comparing two different types of chemotherapy in two different types of cancer. 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	Comments noted. It is important to clarify that this naïve comparison did not affect assessing the clinical and cost-effectiveness of lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. The committee was aware that ivacaftor monotherapy is used for treating cystic fibrosis in people with the G551D mutation and this was not a comparator for this appraisal. The committee heard from the clinical experts that the general size of the effect seen for lumacaftor–ivacaftor was lower than the absolute acute improvement in ppFEV1 seen with other treatments for cystic fibrosis directed against mutations conferring a similar severity of disease. Please see section 4.6 of the FAD.

Consultee	Comment [sic]	Response
	chloride ion transport. The net result is increased quantity and quality of CFTR at the cell surface. F508del is usually therefore a more severe form of CF than G551D due to impairment of both CFTR quantity and function. 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. **Issue 4 – MCID interpretation of ppFEV1** *Description of problem* P19 – 3.22 - The ERG's clinical adviser stated that absolute changes in ppFEV1 were more clinically relevant than relative changes, and that an absolute change in ppFEV1 of 5% or more would be considered clinically important. Proposed addition: *Description of proposed amendment* P27 – 4.6 <u>However, the committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition.</u> *Description of justification for amendment / agreement* This addition from the clinical experts and committee conclusions will make the statement and interpretation more clinically accurate and balanced for the reader. **Issue 5 – Failure to recognise the importance of BMI** *Description of problem* The reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for the management of cystic fibrosis. *Description of proposed amendment*	Comments noted. This is not a factual inaccuracy. A review of the company submission is undertaken by an external group to NICE (the 'evidence review group [ERG]'). Section 4.6 of the FAD clearly states: The committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition. Comments noted. This is not a factual inaccuracy. No changes to the FAD required.

Consultee	Comment [sic]	Response
	Addition of wording - The reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment and the significant improvements in BMI were clinically significant and important for the management of cystic fibrosis. *Description of justification for amendment / agreement* It is important to note that because CF is a multi-organ, systemic disease that the three main goals of CF treatment (i.e. ppFEV1, pulmonary exacerbations and weight gain, which are independent risk factors for mortality), will vary between patients – i.e. ppFEV1 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. **Issue 6 - Generalisability of results** *Description of problem* Trial results may not be generalisable to people with mild or very severe cystic fibrosis because the inclusion criteria required people to have a percent predicted forced expiratory volume in 1 second (ppFEV1) of 40–90%. *Description of proposed amendment* We request that this is removed entirely as it is not appropriate. *Description of justification for amendment / agreement* LUM-IVA is indicated for all F508 patients >12 years old and sub group analysis has demonstrated that all patients including those under 40% benefit. As in virtually all clinical studies in CF, it was a regulatory requirement to work within upper and lower limits of percent predicted FEV1 as inclusion criteria in order to standardise the patient population (ppFEV1 ≥40 and ≤90). Indeed, subpopulation analyses confirmed that in both pivotal studies, and in the pooled analysis, LUM-IVA combination therapy resulted in improvements in ppFEV1, reductions in pulmonary exacerbations and increases in BMI vs. placebo	Comments noted. This is not a factual inaccuracy. No changes to the FAD required. The committee noted that a key issue highlighted by the ERG was that the trial results may not be generalisable to people with mild or very severe cystic fibrosis because the inclusion criteria required people to have a percent predicted forced expiratory volume in 1 second (ppFEV1) of 40–90%. The clinical experts and commissioning representative stated that it would be inappropriate to restrict treatment in clinical practice until a person's lung function declined to a ppFEV1 of 90%. This was because they considered that these patients would have substantial capacity to benefit from treatment. The committee concluded that the results from TRAFFIC and TRANSPORT were

Consultee	Comment [sic]	Response
	regardless of baseline spirometry measurements. A substantial number of patients had ppFEV1 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 ppFEV1 <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. **Issue 7 – Appropriateness of the STA process for evaluation of LUM-IVA** *Description of problem* P49 - The committee acknowledged that when the company's arbitrary price reduction (assuming the introduction of a future low cost generic for lumacaftor–ivacaftor) was removed, the company's base-case ICER increased from £218,000 to £349,000 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including all of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. *Description of proposed amendment* Proposed addition: "A NICE STA process in its current form is not an adequate mechanism to assess precision medicines for small patient populations / orphan diseases." *Description of justification for amendment / agreement* 1. Vertex believes LUM-IVA should be subject to an appropriate Health Technology Appraisal for its use within the NHS such as a HST appraisal which would allow recognition of the value of the medicine outside of the constrained STA ICER criteria. - This is supported by the fact that another CFTR medicine, Kalydeco, originally received a positive decision and was funded for all eligble patients in England by the North of England Specialised Commissioning Group with a predicted	generalisable to most patients in routine clinical practice in England. Please see section 4.4 of the FAD. Comments noted. Lumacaftor-ivacaftor was referred to NICE by the Department of Health as an appropriate topic for the single technology appraisal process. The committee's recommendation is in line with NICE's guide to the processes of technology appraisal (2014) and guide to the methods of technology appraisal (2013).

Consultee	Comment [sic]	Response
	ICER between £411,000 – £1,160,000 per QALY (median £789,000). A subsequent analysis (March 2014) by the NHS NIHR put the ICER at between £335,000 and £1,274,000 per QALY. 2. Vertex is of the opinion that an STA process evaluation would result in a negative decision on a cost basis, ignoring the huge positive impact this innovative precision medicine could have on CF patients and their carers' lives. 3. The NICE STA process is not an adequate mechanism to assess precision medicines for small patient populations / orphan diseases because: • NICE STA cost effectiveness thresholds are not appropriate to accurately incorporate the wider societal benefits of the medicines that treat CF patient populations especially as precision medicines like LUM-IVA represent a step change in the treatment of CF by treating the underlying cause of the disease • The NICE STA process considers absolute health gains rather than relative health gains, which is challenging for rare diseases with short life expectancy • For CF, demonstrating gains in QALYs is challenging because CF is a genetic disorder with manifestations from birth, so patients score very high in terms of their quality of life on standard of care (SOC) despite having a condition like CF, leaving little room to significantly improve these scores with the addition of new therapies • Treatments which have a significant impact on life-expectancy, as LUM-IVA is projected to do, naturally incur additional costs compared to SOC. This often means that greater clinical benefits and associated significant improvements in survival, do not results in lower ICERS and thus it is difficult for any chronic treatment that considerably increases survival far in the future to be considered cost-effective. Moreover the survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms. **Issue 8 – Rate ratios for all pulmonary exacerbations** *Description of problem* P34: The committee discussed the company's methods for estimating the treatment effect of lumacaftor–ivacaftor on pulmonary exacerbations. The committee stated that it would have been more appropriate for the company to apply the rate ratio for	Comments noted. Section 4/14 of the FAD has

Consultee	Comment [sic]	Response
	all pulmonary exacerbations rather the rate ratio specifically for pulmonary exacerbations needing intravenous antibiotics or hospitalisation. *Description of proposed amendment* Delete this statement as it is factually incorrect. *Description of justification for amendment / agreement* No alternative sources of data were available that include all types of exacerbations (i.e., including those treated exclusively with outpatient oral treatment) and captures the relationship between disease progression and pulmonary exacerbations. The model tracks the subset of pulmonary exacerbations treated with IV antibiotics and/or hospitalization. The reason for including only this subset of events was because the data source used to predict pulmonary exacerbations in the model defined pulmonary exacerbations as requiring treatment with IV and/or hospitalization. We thus applied the rate ratio from the trials that was consistent with the definition used in the model. Choosing the rate ratio on all exacerbations and applying it to the exacerbation risk in the model would not be appropriate. **Issue 9 - Double-counting of pulmonary exacerbation costs** *Description of problem* P38 - The committee commented that the company had also double-counted any cost savings from lumacaftor–ivacaftor treatment. It explained that this was a result of the company applying a rate ratio to the number of pulmonary exacerbations (treatment effect), and another reduction to the cost of hospitalisation by 61%, for people having lumacaftor–ivacaftor plus standard of care. *Description of proposed amendment* Delete this statement as it is factually incorrect.	been updated: The committee acknowledged that the model chosen by the company from the literature to relate ppFEV1 to the number of pulmonary exacerbations was based on pulmonary exacerbations needing hospitalisation or intravenous antibiotics. However, the committee was aware that the company had used the number of pulmonary exacerbations needing hospitalisation or intravenous antibiotics from the Liou et al. (2001) survival model. The committee understood from the ERG that the Liou model was estimated from data relating to all pulmonary exacerbations. Therefore the company including only pulmonary exacerbations needing hospitalisation or intravenous antibiotics may have overestimated the survival benefit for lumacaftor–ivacaftor. However, the committee considered that the company had been selective in the approaches it used to model the pulmonary exacerbation data from its trials. The committee also agreed that there was considerable uncertainty around the effect of using data for pulmonary exacerbations needing hospitalisation or intravenous antibiotics in the modelling rather than for all pulmonary exacerbations. The committee concluded that the treatment effect of lumacaftor–ivacaftor on pulmonary exacerbations used in the company's base-case analysis underestimated the ICER. Please see sections 4.14 and 4.24 of the FAD. Comments noted. Section 4.21 of the FAD has

Consultee	Comment [sic]	Response
	Description of justification for amendment / agreement We are not double counting as the model does not assign costs explicitly to exacerbations. Costs are stratified by ppFEV1 and applied annually in the model regardless of exact number of exacerbations in that year. Thus to account for reductions in hospitalized pulmonary exacerbations observed with LUM-IVA the hospitalization costs within each ppFEV1 strata were adjusted. The number of pulmonary exacerbations impacts the patient's risk of mortality and quality of life. **Issue 10 - Treatment effects after discontinuation** *Description of problem* P37 - However, the committee emphasised that it remained concerned about the company's modelling and how the treatment effect on ppFEV1 and pulmonary exacerbations was maintained until week 24 in people who stopped lumacaftor–ivacaftor early. *Description of proposed amendment* Delete this statement as it is factually incorrect. *Description of justification for amendment / agreement* This was an appropriate assumption to make since the treatment effects were calculated using an intention to treat (ITT) analysis and therefore included patients who discontinued LUM-IVA in the LUM-IVA group within the first 24 weeks. **Issue 11 - The clarification of Oral Treatments named as LUM-IVA** *Description of problem* The below descriptions of the technology does not accurately represent all of the benefits offered by LUM – IVA: P25 – 4.2 - The committee concluded that oral	been updated. The committee commented that it appeared that the company had also overestimated any cost savings from lumacaftor–ivacaftor treatment. It explained that this was a result of the company applying a rate ratio to the number of pulmonary exacerbations (treatment effect), and another reduction to the cost of hospitalisation by 61%, for people having lumacaftor–ivacaftor plus standard of care. Comments noted. Section 4.20 of the FAD has been updated. The committee emphasised that it remained concerned about the company's modelling and how the treatment effect was maintained indefinitely for BMI.

Consultee	Comment [sic]	Response
	treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers. P44 - Oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers. P44 Lumacaftor–ivacaftor offered people an oral treatment option that has potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. *Description of proposed amendment* Proposed change: <u>LUM – IVA offers people an oral treatment option that addresses the cause of the disease and that has the potential to slow progression</u> and reduce complications associated with cystic fibrosis. This would be beneficial to patients and their carers with the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. *Description of justification for amendment / agreement* This important clarification allows for a more accurate representation of the value LUM-IVA brings to patients in slowing the progression of disease, which has been demonstrated in the evidence submission.	Comments noted. This is not a factual inaccuracy. No changes to the FAD required.
British Thoracic Society	Lumacaftor-ivacaftor is a highly innovative treatment which shows significant promise in the treatment of cystic fibrosis. After the success of ivacaftor in the G551D mutation, patients with F508del/F508del mutations have been eagerly awaiting this treatment and will be disappointed that NICE is not recommending this treatment. The statistically significant improvement in FEV1 demonstrated in the clinical trials may well also be clinically significant in the context of a disease which is	Comments noted. Please see sections 4.6 and 4.25 of the FAD. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the

Consultee	Comment [sic]	Response
	characterized by a progressive decline in lung function. Regarding 5% improvement in FEV1 as clinically significant is a rather arbitrary cut-off point. Although the improvement in FEV1 is modest, when combined with the improvement in rates of exacerbations, the clinical trials provides preliminary evidence that this treatment may significantly improve the long term outcome for these patients. CF is a progressive disease that ends in transplantation or death and the stability of FEV1 may be an indicator of important long term benefit. This could form the basis for a different approach to this treatment. CF Clinicians and patients would favour conditional approval of ivacaftor-lumacaftor under a reduced cost patient access scheme whilst further long term outcome data is collected via the CF Registry and CF Centres.	improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal.
Cystic Fibrosis Trust	**Overview** The Cystic Fibrosis Trust (the Trust) is profoundly disappointed that NICE proposes not to recommend lumacaftor-ivacaftor therapy (Orkambi®) for routine use in the NHS in England. This is a distressing announcement for the thousands of families who could benefit from the therapy that NICE's Appraisal Consultation Document (ACD) concludes is a valuable new therapy for managing cystic fibrosis that has wider benefits to society, for people with cystic fibrosis, and carers of people with cystic fibrosis.	Comments noted. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.

Consultee	Comment [sic]	Response
	Orkambi® may have a significant protective effect against future health deterioration for eligible individuals with cystic fibrosis. However, the evidence from the clinical trials and rollover studies to see if the therapy slows disease progression and facilitates compound health improvement is immature and, naturally, a confident assessment of the ultimate value it could bring is uncertain. The ACD centres on concerns relating to: • Uncertainty regarding longitudinal effects • Uncertainty regarding clinical significance of acute effects • Uncertainty regarding elements of economic modelling • Uncertainty regarding transferability of clinical trial results to routine use The Trust accepts that the NHS must use its resources carefully to deliver high-quality care for all. However, it is imperative that it is now recognised that risk associated with making life-changing decisions on the use of new rare-disease medicines in the NHS where such degrees of uncertainty exist is unacceptable. In the case of Orkambi®, this uncertainty persists in spite of the fact that the data used to assess the therapy was drawn from the largest ever clinical trial of a new cystic fibrosis medicine. NICE and the Government must now accept that actively engaging to address uncertainty in modelling the long-term impact of medicines for chronic, rare diseases is the only viable option if a future of disease-modifying and more personalised interventions is to be realised. Throughout the NICE scoping and appraisal process for this therapy, the Cystic Fibrosis Trust has highlighted the potential of the UK Cystic Fibrosis (CF) Registry to	

Consultee	Comment [sic]	Response
	support reimbursement decision- making for new cystic fibrosis therapies that are proven to be safe and effective, and boost the NHS's ability to confidently invest in new technologies. In the Trust's submission to the NICE STA process, it was stated that: "[Orkambi®] 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." A copy of the principles of for using UK CF Registry data to support reimbursement decision-making, co-designed and agreed in principle by members of the CF specialist clinical community, representatives of the company, and representatives of CF services for NHS England, has been submitted alongside this response. **Solution** The UK CF Registry is a national, centralised web-based database that collects demographic, health and treatment data from consenting people with cystic fibrosis	The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a

Consultee	Comment [sic]	Response
	from every CF care centre in England, Wales, Scotland and Northern Ireland. The UK CF Registry is sponsored and managed by the Cystic Fibrosis Trust. The infrastructure to undertake an assessment of the therapy's real-world impact across the whole eligible population in the UK already exists and, by embracing such a solution, the NHS would be able to develop its own extended and novel evidence base via the UK CF Registry's patient records, to confidently address uncertainty in the data set currently at its disposal and make a more confident valuation of the clinical and cost-effectiveness of the therapy. The Trust firmly believes this solution is a progressive model for all new technologies for people with cystic fibrosis enabling access to safe, effective and innovative products faster, whilst providing the NHS with the robust, real world data to confidently support investment opportunities. For Orkambi®, we have witnessed the inevitable and agonising delay in access that is a consequence of the current approach to health technology appraisal for cystic fibrosis technologies. It has been nearly a year since Orkambi® received marketing authorisation in Europe. People with cystic fibrosis who are eligible for the treatment within its marketing authorisation have now waited for over 22 months since the publication of the pivotal Phase III trials that demonstrated the treatment's clinical efficacy. **Critique of the Appraisal Consultation Document (ACD)** • *Disease severity* The Trust is concerned that, despite the input of consultees, stakeholders and expert opinion the ACD presents a view of cystic fibrosis which is not consistent with the reality of the condition, its progressive nature, and its geno- and phenotypic expression. **Section ACD extract**	commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.

Consultee	Comment [sic]	Response
	3.19 The ERG stated that because both trials included people with mild to moderate cystic fibrosis (that is, ppFEV1 of 40–90% at screening), the clinical evidence may not be generalisable to people with severe cystic fibrosis, or people with very mild cystic fibrosis. Section 3.19 of the ACD refers to testimony from the Evidence Review group that describes mild, moderate and severe cystic fibrosis as definable by the measure of an individual's ppFEV1. It should be made clear that, ultimately, cystic fibrosis disease severity depends on the type of mutations present and well as other modifying environmental and physiological factors. It is important that disease severity is not confused with acute health status. • *Long term data uncertainty* **Section** **ACD extract** 3.23 The ERG noted that because the company's trials were short, the long-term effects of lumacaftor–ivacaftor were uncertain. 4.6 The committee recognised that longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis. However, it concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant. 4.7 The committee heard from the clinical experts that pulmonary exacerbations are associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant.	Comments noted. A review of the company submission is undertaken by an external group to NICE (the 'evidence review group [ERG]'). Section 4.4 of the FAD has been updated: The committee noted that a key issue highlighted by the evidence review group (ERG) was that the trial results may not be generalisable to people with very mild or severe cystic fibrosis because the inclusion criteria required people to have a percent predicted forced expiratory volume in 1 second (ppFEV1) of 40–90%. The committee noted a consultation comment that stated that the severity of cystic fibrosis was not defined by ppFEV1, but depended on the type of mutation present and other modifying environmental and physiological factors.

Consultee	Comment [sic]	Response
	Section 3.23 of the ACD acknowledges the ERG's conclusion that all long-term effects of the therapy are uncertain. Section 4.6 demonstrates the committee's acknowledgement of the primacy of the importance of longitudinal change over acute change in ppFEV1. However, it must be more clearly recognised that cystic fibrosis is a progressive condition, where long-term maintenance of ppFEV1 is an important clinical achievement, given the measure's well-established relationship with long-term survivorship. The conclusion associated with Section 4.6 – that acute improvements in ppFEV1 are modest and unlikely to be clinically significant – appears to dismiss the concept of ppFEV1 maintenance as a positive clinical outcome, and appears to disregard the evidence provided by clinical and patient experts, recorded in Section 4.13, that, in converse, an annual decline in ppFEV1 of ≥2% is treated as a reflection of rapidly declining lung function. The Trust seeks the committee's comment on these points. In Section 4.7 the committee acknowledges the significance of the therapy's impact on hospitalisation. This fundamental aspect of the positive benefit described by trial data, with reduction in pulmonary exacerbations, indicates the potential for this treatment to slow the disease's progression versus Standard of Care in the long-term. This data is given disproportionately low standing in the ACD and the Trust seeks the committee's reassurance that its relationship to health maintenance is well represented in the documentation. **Section** **ACD extract** 4.11 The committee concluded that, overall, the company's methods for estimating survival seemed valid but there was uncertainty about how the differences in outcomes between the whole cystic fibrosis population and the population with the F508del mutation would affect the cost-effectiveness results. 4.12 The committee highlighted that there was also considerable uncertainty associated with how the company modelled the decline in ppFEV1	Comments noted. Section 4.6 of the FAD has been updated. The committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition. A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. The committee noted that the absence of an agreed minimum clinically important difference would not prevent it from being able to make a recommendation for lumacaftor–ivacaftor. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The committee concluded that longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis, and both the observed and extrapolated benefits of lumacaftor–ivacaftor on ppFEV1 were taken into account in the company's cost-effectiveness analysis.

Consultee	Comment [sic]	Response
	after 24 weeks. 4.12 The committee commented that because extrapolations for ppFEV1 decline were based on different, non-randomised studies for each treatment group, it would have been appropriate for the company to explore the impact on the ICER using the ppFEV1 decline for standard of care alone based on the 24-week trial data. The committee concluded that the company's methods for estimating changes in ppFEV1 were associated with considerable uncertainty and were likely to have overestimated the benefits of lumacaftor–ivacaftor treatment. 4.15 Therefore, it concluded that there was uncertainty associated with the treatment effect on BMI in the company's model 4.20 The committee concluded that people could discontinue lumacaftor–ivacaftor after 24 weeks, but the rate of discontinuation was uncertain. Addressing the comment in Section 4.11, in order to confidently estimate survival in the relevant population, supportive data is available to both NICE and the company upon request from the UK CF Registry. Sections 4.12, 4.15 and 4.20 highlight the difficulty of estimating performance beyond the 24-week trial period and the Trust, again, indicates the potential of the UK CF Registry to explore and overcome this uncertainty using real-world evidence. 4.24 The committee acknowledged that the company had used the data from its trials when available, which were recognised as the largest trials in cystic fibrosis to date. 4.24 The committee also agreed that there was considerable uncertainty around: • the estimates of relative effectiveness for ppFEV1 decline • the rapid rate of ppFEV1 decline in the standard of care group	Please see NICE's response below in relation to the Cystic Fibrosis Trusts 'Concluding remarks'.

Consultee	Comment [sic]	Response
	• how the treatment effect was modelled when people came off treatment and over the longer term (that is, no waning effect of treatment over time) • how independent the effects of lumacaftor–ivacaftor on ppFEV1 and on pulmonary exacerbations were • potential double counting of cost savings associated with hospitalisations and • The company's utility estimates. Section 4.24 outlines areas of considerable uncertainty whilst simultaneously acknowledging the scale of the trials used to source the novel data used to describe this treatment effect. It must be acknowledged that the Single Technology Appraisal of Orkambi® has failed to produce an unequivocal recommendation, in the respect that, with or without the committee's preferred assumptions, the inherent uncertainty regarding the therapy's long-term performance leave the committee's conclusions begging more questions than are answered. **Concluding remarks** In Section 6.1 of the ACD, NICE proposes to review the guidance issued 3 years from the publication of this guidance. This timescale in unconscionable, whilst an alternative option exists. The Trust firmly believes that NICE, the NHS and Government must work cooperatively, alongside the company to address the challenge of The Trust welcomes the committee's comment on the Trust's document describing the principles of using the data collected by the UK CF Registry to collect real world evidence supporting clinical- and cost-effectiveness assessments.	The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal.

Consultee	Comment [sic]	Response
		Please see section 4.25 of the FAD.
Department of Health	No comments.	Comments noted. No action required.
NHS England	**Has all of the relevant evidence been taken into account?** Yes we believe all the relevant evidence has been taken into account. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes with respect to the clinical evidence. With respect to the cost effectiveness analysis, although we do not have the specific expertise to interpret this data, we believe the NICE conclusion that this intervention is not cost effective is also correct. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes. NHS England agree that the recommendations are a suitable guidance to the NHS and commissioners. **Any other comments** We understand that were the drug offered at a much lower price to the NHS that was deemed cost effective by NICE, clinicians would wish to have access to this drug.	Comments noted. No action required. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Royal College of Nursing	No comments.	Comments noted. No action required.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Guideline Development Group representative, nominated by the National Collaborating Centre for Women's and Children's Health	We would agree with the majority of the conclusions of the appraisal consultation document (ACD), and they are much as might have been predicted from both the submission documentation and the discussion on the day. We believe that all the relevant evidence been taken into account. We believe the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Specifically we would support the ACD view that only the 24 week change in FEV1% should be considered, which results in a revised figure of only 2.49% absolute improvement in FEV1%. We are unclear on the clinical significance of this change in FEV1%. Furthermore the company's economic modelling was always going to be challenging with the submitted ICERs, and the ACD has unpicked some contentious assumptions in the model. We believe that the revised ICERs are likely to be a more accurate representation. We are of the opinion that the review is comprehensive and its conclusions appropriate, and thus the provisional recommendations are sound and a suitable basis for guidance to the NHS.	Comments noted. No action required.
Patient Expert, nominated by The Cystic Fibrosis Trust	• **Has all of the relevant evidence been taken into account?** The only evidence available is the immediate/short term benefits from the trial itself which is frustrating as the longer term effects of the treatment are not reflected within this appraisal, which is a great shame. Whilst all the clinical outcomes such as FEV1 and BMI are relevant, I need to re-emphasize that they are not a real life reflection of the patient	Comments noted. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had

Nominating organisation	Comment [sic]	Response
	experience such as daily symptoms, mental wellbeing and the longer term impact on health decline and treatment burden. I would have like to have heard further patient representation (or at the very least a written statement) from a person with CF who had perhaps experience of taking Orkambi so that the panel could understand the impact of drug and the difference it had made. • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I am frustrated that the potential long term benefits of the drug are not captured or taken into account. I feel this is a significant failing of the appraisal process. I feel there is too much emphasis on the immediate clinical benefits such as lung function or BMI, rather than the impact on the longer term health benefits such as improving quality of life, reduction of symptoms, stabilisation of health and life expectancy. CF is a progressive disease that does not improve, it is in a condition that is in decline. The document does not perhaps reflect that lung function tends to generally go downwards and not upwards. The only exception would be during an exacerbation when lung function may dip lower but then recovers following treatment. Therefore any increase in lung function, no matter how small, is a perceived benefit to patients. On this basis I do feel that the FEV1 increase is downplayed. The reduction in exacerbations and IV treatment is perhaps understated in the document and yet it is a significant outcome of this treatment for patients living with the condition. Both are of significant benefit because a reduction in exacerbations is a reduction in lung damage and less time spent on IV's is a huge reduction of treatment burden. It also limits disruption to education, work, family and social life. A reminder that CF is still very much a young person's illness, as this is perhaps not very clear in the document. Around half the patients are actually	not been captured in its economic modelling. Please see section 4.27 of the FAD. Clinical experts, commissioning experts and patient experts are selected by the appraisal committee chair from nominations provided by consultees and commentators. Please note that the long term benefits of the drug were taken into account in the company's cost effectiveness analysis, and therefore taken into consideration in the committee's decision making. The committee considered a broad range of evidence submissions. These included submissions from the company, clinical experts, commissioning experts, patient experts and an external review group (that is, an ERG). Section 4.6 of the FAD states: A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Section 4.7 of the FAD states that: The committee concluded that the reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important

Nominating organisation	Comment [sic]	Response
	children or young people and the median age of death is just 28 years old. Most of these patients are people who are just starting, developing or in the prime of their life with goals, dreams and aspirations. Please remember this. Orkambi is a pill which is taken twice a day and relatively low burden in comparison to multiple IV therapies which are not just disruptive, but have a physical and mental impact too. The document in section 4.1 onwards plays down the impact on everyday life for patients – there is no mention of the day to day symptoms, for example. Where treatment burden is stated – please note that this is not just tablets; but nebulisers, inhalers and physiotherapy as well as a high fat, high calorie diet. There is no mention of the length of time taken each and every day to take treatments, impact on family planning or the psychological impact of a life expectancy which is nearly half that of a non-CF person. Continuous reference and comparisons made to Kalydeco (Ivacaftor) seems excessive, given that the treatment is for a completely separate class of mutation with a different level of CFTR function. On this basis not sure how comparable to two are. Orkambi may not be deemed as clinically effective as Kalydeco, but please do at least acknowledge within the document that the list price is actually significantly lower than the list price for Kalydeco. • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. I am extremely disappointed and heartbroken at this decision. As stated at the meeting, many of us living with the condition have waited a lifetime for drugs like this to become available that can for the first time treat the underlying cause, whereas current medication only treats the symptoms. I do believe Orkambi should be recommended for use in England on the basis that NICE have stated that this drug is clinically effective and this drug is the only treatment for this mutation group available now.	for the management of cystic fibrosis. The appraisal committee will also take into account the Institute's guidance on social value judgements described in the Institute's document, Social value judgements: principles for the development of NICE guidance. The appraisal committee takes into account advice from the Institute on the appropriate approach to making scientific and social value judgements. Advice on social value judgements is informed by the work of the Citizens Council, NICE's advisory bodies, and NICE's Board, as well as legislation on human rights, discrimination and equality as reflected in NICE's equality scheme. Section 4.2 of the FAD has been updated: The patient experts highlighted that managing cystic fibrosis is relentless and can take up 2 or more hours of the person's time each day. The person may have to take up to 50 tablets every day and may need frequent hospital admission. It is important to clarify that the naïve comparison of lumacaftor–ivacaftor with ivacaftor monotherapy did not affect assessing the clinical and cost-effectiveness of lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. The committee was aware that ivacaftor monotherapy is used for treating cystic fibrosis in people with the G551D mutation and this was not a comparator for this appraisal. The committee heard from the clinical experts that the general size of the effect seen for lumacaftor–ivacaftor was lower than the absolute acute improvement in ppFEV1 seen with other treatments for cystic fibrosis directed

Nominating organisation	Comment [sic]	Response
	If the drug is clinically effective then cost should not be a barrier. There should be no cost placed on a patient's life. Please consider that in the meantime if Orkambi is not recommend, that patient's like me will continue to decline and develop irreversible lung damage increasing our dependence on the NHS and need for transplantation. This treatment has the potential to reduce the cost and burden on the NHS and I am disappointed more evidence was not presented and explored on this aspect. I also wish to emphasise that Orkambi could help to address pressures around the increasing patient capacity on CF centres – particularly in adult care where access to inpatient and even home IV antibiotic care is becoming increasingly difficult with long waiting lists just to access basic and necessary care. The decision may create a level of worry and uncertainty for patients like me that as more treatments like Orkambi are developed and become available, that this may set a prescient for access to future treatments. So despite all the fantastic research and exciting scientific breakthroughs in precision medicine for CF, the treatment is not able to reach the front line and patients like me may never actually get to try or ever benefit from these treatments. This seems cruel and unfair. • **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** This is a treatment specifically for homozygous delF508 and is the only precision medication if its kind available to those with this mutation. Another drug Kalydeco (referenced) is already available for 5% of the population with a class three mutation. Concern that refusing access will divide with the CF community – those mutations who can access precision medicines and	against mutations conferring a similar severity of disease. Please see section 4.6 of the FAD. The appraisal committee makes recommendations to the Institute regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the appraisal committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee understood from a patient expert that reducing pulmonary exacerbations is the most important aspect of managing their condition. Please see section 4.7 of the FAD. Comments noted. The committee noted a comment from the company that there is potential for inequality of access based on the subtype of a person's cystic fibrosis, if lumacaftor-ivacaftor was not recommended for treating cystic fibrosis

Nominating organisation	Comment [sic]	Response
	those who cannot. The overall impact of not recommending Orkambi on patients and their families' needs to be carefully considered. Patients who are not able to access a precision medicine whilst other groups with CF can, both in the UK and elsewhere globally may cause significant distress to patients and their families. General comment that cost is cited as the most significant factor in not recommending this treatment. I wonder if those with the homozygous delF508 are perhaps at an unfair disadvantage from the offset, purely because of the sheer number of patients within the mutation group and how common the mutation is?	homozygous for the F508del mutation. The committee considered that this did not constitute an equality issue for any group protected by the equality legislation and that its recommendation was in line with NICE's guide to the processes of technology appraisal (2014) and guide to the methods of technology appraisal (2013). The committee concluded that its recommendation was fair and did not discriminate against any protected groups, and therefore no changes were needed. Please see section 4.26 of the FAD. The appraisal committee takes into account the cost effectiveness of a technology, which assesses how well a technology works in relation to how much it costs compared with current practice. The potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision. The committee does take account of how its advice may enable the more efficient use of available healthcare resources. Please see sections 6.2.13–19 of NICE's guide to the methods of technology appraisal (2013).

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Carer	General	You are discriminating against humans with a terminal illness ,how can any of you human beings on that committee possible deprive these people	Comments noted. The Institute has to make decisions across different technologies and

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		of a life transforming drug regardless of how transforming and costly it is, just the cost saving of hospitalisations and for someone to breathe easy is more than enough evidence, be human all of you.	disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013). In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance. This document, developed by NICE's Board, describes the principles NICE should follow when designing the processes used to develop its guidance. In particular, it outlines the social value judgements that NICE and its advisory bodies, including appraisal committees, should apply when making decisions about the effectiveness and cost effectiveness of interventions.
Carer (2)	General	My 21 year old daughter has Cystic Fibrosis and as such attends hospital every 4 weeks throughout the year. In addition, on average she requires three hospital admissions each year for the duration of two weeks. Without Orkami, it is predicted that her disease will progress and she will require even more hospital admissions for longer periods of time. This is just one patient. We all agree that Orkabmi will reduce the necessity for	Comments noted. The committee acknowledged that lumacaftor–ivacaftor was a valuable new therapy for managing cystic fibrosis. The committee also agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis.

Role*	Section	Comment [sic]	Response
		hospital admissions, therefore it will be cost effective for the NHS to prescribe this drug. There is no argument. Cystic Fibrosis is still the most common genetic condition for the caucasian population, with 1 in 25 carriers. The disease has undeniably devastating consequences for the patient and their families but also financially on the state by way of benefits, medication, a plethera of professionals and additional complications as a result of Cystic Fibrosis. When all of these factors are taken into consideration, the actual cost of one patient to the NHS with Cystic Fibrosis is immense. To provide a treatment such as Orkambi which will benefit the patient by alleviating some of their ailments will in turn, benefit the financial strain on the NHS.	The appraisal committee makes recommendations to the Institute regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the appraisal committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.
Carer (3)	3.3	There is a cost to patients ,parents , informal carers and employers Loss of income due to reduced working which can be planned because of awareness of reduced health and stamina or unplanned time off due to exacerbations and admissions. Care has to be found to support children when their siblings or parents are in hospital .Family members reduce working days or give up work to support patients or their children. Over all the worry of management and long term outcomes take their toll for patients and their family.	Comments noted. The committee heard from the patient experts that cystic fibrosis can impair a person's social life and ability to work, and significantly affects the lives of their families and carers. The committee concluded that cystic fibrosis has a major impact on the quality of life of patients and their carers. The committee also agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis (for example, maintaining employment and improved family life). Please see sections 4.1 and 4.27 of the FAD.

Role*	Section	Comment [sic]	Response
Carer (3)	4.10	Tiredness, lack of energy, shortness of breath on exertion and increased respiratory rate and heart rate to compensate are taken as normal for someone who has grown up with CF. They also have to put effort into physio if they feel like it or not . Depression and anger affect their motivation as it affects the motivation of those who support and encourage them on a day today basis .This will have an affect on their function and can lead to an exacerbation . Deprivation of known treatment also will have a negative effect .i am aware of this from your recent publication re Orkambi .	Comments noted.
Carer (3)	5.22	See response to section 4.10 please.	Comments noted. Please see NICE's response above.
Carer (3)	Appendix A	Decrease in pulmonary exacerbations when treating with Orkambi This is such a positive outcome in every way. Surely over time medication will be refined .there is no encouragement to firms to spend on this if treatment is not started and evaluated on a larger scale tha the trials. I refer to comments made in Comment 1 again .there is an ongoing acost to CF pts and their employers as well as to their families in the short term and in the long term reduction in working hours and retirement benefits .	Comments noted. The committee concluded that the reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for the management of cystic fibrosis. The committee heard from the patient experts that cystic fibrosis can impair a person's social life and ability to work, and significantly affects the lives of their families and carers. The committee concluded that cystic fibrosis has a major impact on the quality of life of patients and their carers. The committee also agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis (for example, maintaining employment and improved family life). Please see sections 4.1, 4.7 and 4.27 of the FAD.
Carer (4)	General	The appraisal committee did not give sufficient consideration or weight to the reduction in exacerbations requiring hospital treatment apparent in the	Comments noted. The committee heard from the clinical experts that pulmonary exacerbations are

Role*	Section	Comment [sic]	Response
		treatment arms of TRAFFIC and TRANSPORT: such a reduction is not merely "clinically significant" (as per para 4.7 of the ACD): 1. A reduced need for admissions is vital for people with cystic fibrosis in order to allow them to live normal lives and to reduce interference with both education and employment. 2. There is a major issue in England with respect to the capacity of adult CF centres to admit patients for inpatient treatment; most - if not all - centres are routinely unable to meet target admission times laid down by the NHS England Service Specification. Anything which reduces the need for patients homozygous for F508del to be admitted will benefit not just those patients, but also patients with other mutations who will gain speedier access to an inpatient bed than would otherwise have been the case. Timely treatment of exacerbations is key to delaying disease progression, but these benefits (some of which would be to a part of the CF population who would not receive Orkambi) have not been taken into account at all by the appraisal committee. Further, the adoption of an ICER based on "all pulmonary exacerbations" (per para. 4.24) is likely to understate the benefits of Orkambi even when those benefits are assessed in the target population alone. The comment by the ERG that "because the companyâ€™s trials were short, the long-term effects of lumacaftorâ€“ivacaftor were uncertain" is concerning. Thr trials undertaken by the company were of standard length and it would be unreasonable to expect longer Phase 3 trials to be undertaken. If endorsed (as it appears to be at p.47 of the ACD in the comment that "There was uncertainty ... over the longer term (that is, no waning effect of treatment over time)", the ERG's approach would make it very difficult for any innovative treatments to gain reimbursement.	associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee understood from the clinical experts that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. Comments noted. When the evidence on key parameters used to estimate cost effectiveness (for example, clinical effectiveness and effect on health-related quality of life) has serious limitations and/or when a variety of assumptions have been necessary in the cost-effectiveness modelling, the additional uncertainty this generates is a key factor in underpinning the judgements of the Committee. The appraisal committee is likely to consider more favourably technologies for which evidence on cost effectiveness is underpinned by the best-quality clinical data than those for which supporting evidence is dependent to a large extent on theoretical modelling alone. However, the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very

Role*	Section	Comment [sic]	Response
		The appraisal committee has taken no account of the potential adverse impact which its decision may have upon clinical research activity into innovative, gene-specific treatments: 1. In the field of cystic fibrosis generally. 2. In England in particular. As to the second of these points, if the NHS in England is not willing to reimburse the cost of such treatments, questions may be asked as to the ethics of English patients participating in trials for treatments from which they will not benefit; drug manufacturers may also see no point in enlisting participation from centres in England. Accordingly, the Appraisal Committee's provisional recommendation has (again) failed to take a key issue into account and, if maintained in the final recommendation, would be likely over time to diminish the research base in England, to the detriment of patients.	rare diseases. Please see section 6.2.16 of NICE's guide to the methods of technology appraisal (2013). The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (5)	General	As a parent of a child with Cystic Fibrosis, drugs such as Orakambi offer hope and a substantial difference to people lives. Cystic Fibrosis can be an all consuming disability and anything that helps sufferers with their daily lives should be made a priority!	Comments noted. The committee recognised that oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers.
Carer (6)	General	I have just finished another course of 3 monthly iv antibiotics, this was for three weeks due to the first medication my child was given she had a reaction to. I can not imagine, how much this one course of treatment must have cost, just for the medication alone. As I do them for her at home we did not take up the space of an NHS hospital bed, but this	Comments noted. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account

Role*	Section	Comment [sic]	Response
		expense must come into it for other children, not to mention the the other 15 different types of medication she takes everyday. This is just one CF. When I think of the millions that is being spent on the EU leaflet, as a mum of a cf little girl I know where I would rather spend my money, and I am sure a lot of people would feel the same.	the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
Carer (7)	General	The evidence about quality of life seems flawed. It seems to be saying that people with CF are used to feeling ill most of the time and see this as normal and so any improvement is negligible. I would also robustly question the lifestyle questionnaire itself: - who designed it? - was it co-designed with people with CF? - does it include questions about things which are important to people with CF rather than the general population? If it has been designed for a general population, this could potentially be discriminatory for people with CF, as the appraisal has admitted that the baseline for people with CF is skewed. The patient expert highlighted the huge negative impact that CF has on people's lives. This kind of evidence is hard to quantify and seems to have been given far less consideration than all the other numerical scientific evidence in the appraisal. If you asked people with CF which aspects of their lives are most important to them, you may need that these psycho-social aspects are more important to them than figures about BMI, FEV, etc. This appraisal seems to see people with CF as machines which can be measured, rather than human beings whose fears and feelings cannot be quantified and are therefore ignored. I actually cannot finish reading this appraisal as it's language and presentation is inaccessible and exhausting. I am currently exhausted from being a carer for my son, and the impact of that role means I don't have the energy to plough through this non-user friendly gobbledygook. I do think the appraisal should have included statements from people coping with CF - written statements about their everyday lives. This document is biased towards statistics and clinical language - I know you will argue that	Comments noted. The committee recognised the difficulty of valuing health states in chronic conditions of an unpredictable nature because a person's health-related quality of life is generally their current health on the day of assessment rather than at the time of an event (for example, during a pulmonary exacerbation), and it was not always assessed over the longer term. However, the committee highlighted that the company had not provided qualitative empirical evidence to support that the EQ-5D was inappropriate, as recommended in NICE's guide to the methods of technology appraisal (2013). The committee also understood from the clinical experts that they considered that the 5 dimensions of the EQ-5D questionnaire generally captured most of the important effects of cystic fibrosis. Please see section 4.8 of the FAD. Comments noted. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence

Role*	Section	Comment [sic]	Response
		is a scientific necessity but I wish to argue that you are ignoring the psycho-social aspects at your peril. If people with CF cannot work full-time because of the unpredictability of their condition, what financial impact does that have on their lives and the country's economy? The appraisal does not include enough evidence about the complex psycho-social aspects of people's everyday lives and therefore discriminates against people with CF, as you are using scientific methods of assessment which ignore the complexity of CF. I wonder how many people with CF have actually contributed to your evidence? This consultation is inaccessible and will exclude a lot of people who will find this document linguistically biased towards clinicians and scientists. How can you say you have truly consulted with people with CF, when these documents are so hard to understand and don't reflect people's everyday lives and difficulties?	to support that important health-related quality of life effects had not been captured in its economic modelling. Please see section 4.27 of the FAD. The committee considered a broad range of evidence submissions. These included submissions from the company, clinical experts, commissioning experts, patient experts and an external review group (that is, an ERG).
Carer (8)	General	Lumacaftor-ivacaftor is a highly innovative treatment for people with Cystic Fibrosis who are homozygous for the F508del mutation in the CFTR gene. It is the first treatment that targets the underlying gene deficiency, rather than merely managing the symptoms of the condition and as such should be considered as a significant breakthrough in the treatment of those with the F508del mutation. It is stated in the appraisal consultation document that the increase seen in ppFEV1 â€œmay not be clinically significantâ€□, however it is important to realise that for a patient with Cystic Fibrosis even a stabilisation in ppFEV1 would be highly beneficial. Meaning that the condition would not progressively worsen over time. Current, highly invasive and time-consuming, treatments for the symptoms of Cystic Fibrosis (including intravenous antibiotics) may temporarily increase ppFEV1 by more than lumacafotr-ivacaftor, however these	Comments noted. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD.

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		increases are short lived and the ppFEV1 of patients soon start to decrease again once intravenous antibiotics are stopped, requiring more hospitalisations and more time away from everyday life. Intravenous antibiotics, by their nature, are designed to be drugs that are used for finite periods of time, with their efficacy also waning over time in a patient population that needs to use them frequently. This means they are only ever provide a temporary increase in ppFEV1, by reducing infection levels in the Cystic Fibrosis lung, with this benefit being quickly lost as infection levels start to rise again. This means that the benefit of the ppFEV1 increase seen with these drugs should not really be compared with that seen from lumacaftor-ivacaftor, which due to the mechanism of the effect â€“ with the drug treating the underlying cause of the condition and designed to be taken continuously â€“ mean that this increase will provide a long-term increase/stabilisation of lung function rather than a temporary increase which is quickly lost. As the partner of a patient with Cystic Fibrosis I would also ask that the reduction in hospitalisations is recognised as clinically significant â€“ as is noted in the appraisal consulation document â€“ and that more weight is given to this when NICE make their final decision. My fiancÃ© is 34 years old and has a full time job working as an education researcher, with an active life outside of work. However, over this past year she has been in hospital for 12 out of 52 weeks, with her condition worsening, as she ages. This has taken a significant toll on her and my mental health and quality of life, with the uncertainty making it very difficult to plan events. A reduction in the number of hospitalisations, along the lines of the effects seen in the lumacaftor-ivacaftor trial would therefore drastically improve our quality of life. As the consultation notes, due to the long-term nature of Cystic Fibrosis it is often hard for patients to assess their own quality of life compared to people without the condition and I therefore think the benefits of reduced hospitalisations may have been under-estimated.	The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the clinical and cost-effectiveness evidence. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. Please see sections 6.2.1–4 of NICE's guide to the methods of technology appraisal (2013). The committee heard from the clinical experts that pulmonary exacerbations are associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee agreed that lumacaftor–ivacaftor offered people an oral treatment option that has the

Role*	Section	Comment [sic]	Response
		The fact that lumacaftor-ivacaftor is an oral tablet is also important. As a patient with Cystic Fibrosis, my fiancÃ© complete 3 hours of physiotherapy each day, 30 minutes of nebulized therapies and take 48 tablets. All of these treatments only slow her ppFEV1 decline and none of them result in an increase. The low treatment burden of lumacaftor-ivacaftor when compared with traditional treatments is therefore very important when considering whether it should be funded. While the preliminary recommendation is that this treatment is not cost effective, I do think that it is worth exploring if there is a way it can be made available to NHS patients. The Cystic Fibrosis Trust has suggested an interim arrangement between Vertex pharmaceuticals and the NHS, allowing for evidence about its long-term clinical impact to be collected by using the UK Cystic Fibrosis Data Registry. The long-term impact of the drug is likely to make it cost-effective, reducing the need for hospitalisations, other treatments and preventing lung transplantations in the long-term. It is therefore vitally important that this longitudinal data can be collected and that the long-term benefit can be assessed, as it is only through collecting this data that a fair assessment of its cost-effectiveness can be undertaken. In summary, having access to an effective treatment, which targets the underlying cause of Cystic Fibrosis, stabilises ppFEV1 and has a low treatment burden would be life-changing for my finance, our family and all other patients in the UK with the F508del mutation. I therefore ask that NICE reconsiders their draft guidance and that the drug is approved so that people with Cystic Fibrosis have the same opportunity as those without the disease to reach their full potential.	potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. Please see section 4.27 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (9)	General	As a scientist and father of a 19yr old boy who is homozygous Delta F508 I feel the committee has underestimated the importance of the benefits shown by Orkambi.	Comments noted. The committee heard from the clinical experts that

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		Firstly the benefits of the major reduction in pulmonary exacerbations seen cannot be overestimated. These events can be major health threatening incidents that can be described as a â€˜lung attackâ€™ in much the same way as people suffer heart attacks. The cause of these attacks is usually microbial infection which even if cured, often leads to permanent lung damage and a reduction in FEV. In the appraisal document it is stated that hospital admission from such attacks are on average 21.7days and treatment is 12-14 days. While the 12-14 treatment days may refer to the length of time the person is on intravenous antibiotics in hospital the actual treatment for these infections usually goes on for months not days, typically three to six months of nebulised antibiotics and DNase and/or heavy doses of oral antibiotics etc. It is successive pulmonary exacerbations that lead to the major loss of lung function and any treatment that can significantly reduce them will have a much greater impact over the long term than is currently been accounted for in the drug appraisal. Secondly I would like to suggest that the committee has underestimated the value of Orkambi on the rest of the body. One of the other systems significantly affected in CF is the digestive tract and while dietary enzymes may deal with pancreatic insufficiency they do not tackle the thick mucus which lines the intestines. This mucus not only reduces uptake of nutrients leading to low BMIâ€™s and susceptibility to infection but can also clog the intestine. Many people with CF suffer with chronic constipation for which there is no treatment other than powerful laxatives, while others have to have feeding tubes inserted to try and increase their weight. CF related constipation can result in debilitating abdominal pain for days, unrelieved by pain killers while waiting for the strong laxatives to work. Anything that helps the digestive system work better would be a miracle. The increase in BMI observed by those taking Orkambi during the relatively short trial shows that the drug is functional in the digestive tract	pulmonary exacerbations are associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The health-related quality of life impact from pulmonary exacerbations were captured in the company's cost-effectiveness analysis. The committee understood from the clinical experts that an average course of treatment (hospitalisation) for a pulmonary exacerbation episode was 12–14 days. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had not been captured in its economic modelling. Please see section 4.27 of the FAD.

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		and should be a real asset in this department. Finally most people fail to understand the amount of work that is required by those inflicted with CF just to try and stay healthy, adherence to treatment is a significant problem in CF. The large treatment burden of multiple bouts of nebuliser treatment with all the associated washing and cleaning , bouts of physio, multiple tablets , dietary considerations etc. All this is expected of young people who just want to get on with life and be normal, young people trying to study at school or university, heading out to work, exploring the world. Many of the treatments currently associated with CF just get in the way of â€˜normalâ€™ life. That is why Orkambi, which is just a couple of pills twice a day, has 96.5% adherence rate, so even though itâ€™s currently observed benefit over conventional treatment in the trials has not met all the hopes of those involved, I would suggest that in the â€˜real worldâ€™ where not everyone is as motivated to do their treatment as those volunteering for trials, it would still be a real asset in the treatment of CF. Even the most recalcitrant teenager can manage some pills! It seems clear that Orkambi could be life changing if not life saving for some with CF if given the chance. It may offer them the chance to stay strong and healthy enough to benefit from the other new treatments that may come along in time, but they are in the future while Orkambi is now. If a better/cheaper drug comes along great, but it is of no benefit to you if you are dead. We are talking about the life and future of a group of young people who just want to be like the rest of us and we should help achieve that goal.	The committee agreed that lumacaftor–ivacaftor offered people an oral treatment option that has the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. Please see section 4.27 of the FAD. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
Carer (10)	General	As the parent of a 19 year old and being his carer for 17 years I have much experience to draw on. The implications of lung exacerbations seem to have been poorly	Comments noted. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of

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		understood by NICE. They have two separate effects. The first is the amount of time and cost of treatment dealing with the exacerbation itself and the second is the consequent lung damage caused by the exacerbation. Firstly, an exacerbation does not just last for 2 weeks. The exacerbation manifests as an increase in physical symptoms and suffering of the patient and worsening of lung function. Because of the sticky mucus in the lungs there can be a prolonged period of time in which the cause of the exacerbation cannot be determined. In the case of my sonâ€™s last exacerbation, this period was 4 months. During this time there were many visits to hospital, with breathing difficulties, sometimes on a weekly basis, not only to try and alleviate the symptoms but also to try and determine the cause. Treatments do not always work, which can lead to chronic infection and more rapid deterioration on lung function. Treatments themselves have side effects and can damage the liver and kidneys. CF related liver disease can preclude intravenous Tobramycin for that reason. Even when IVâ€™s are done at home, there can be problems with the lines meaning stays in hospital and cost of nurses have to checking blood levels during the course. An exacerbation also makes it more likely for other pathogens to colonise the lungs e.g. my son was growing Aspergillus and Mycobacterium avium initially, causing damage and lung disease, then was colonised by Pseudomonas aeruginosa and Stenotrophomonas maltophilia. The exacerbation lasted for years causing lung disease and a permanent cough which were not there before the event. In terms of financial cost it has meant increased hospitalisations, cost of	exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The health-related quality of life impact from pulmonary exacerbations were captured in the company's cost-effectiveness analysis. The committee understood from the clinical experts that an average course of treatment (hospitalisation) for a pulmonary exacerbation episode was 12–14 days. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is

Role*	Section	Comment [sic]	Response
		drugs to try and treat them, increased clinic visits in hospitals, lost days at work for myself and my husband, inability of myself to work in a full time well paid job (I had to give up a job in senior management to take a low paid part time job), lost days at school and then university, associated stress and anxiety, loss of sleep by the patient and other family members due to coughing, increased expense due to many trips to hospital, some a long way off when at university and increased food costs as he tries to replace calories that are being consumed by his body trying to fight the infection. The second consequence of an exacerbation is lung damage. Lung damage cannot be reversed. If the person recovers from the exacerbation, they are starting from a lower baseline because their lungs do not work as effectively and this happens time and again with each new episode, until the lungs are destroyed and the person drowns in their own mucus. Reducing exacerbations is therefore of critical importance when treating Cystic Fibrosis and Orkambi has been shown to do this. I have seen the refusal of NICE to recommend Orkambi being referred to as a disappointment. A disappointment is when you cannot go on holiday, or when you do not get the job that you want, or when your exam results are worse then you hoped. Disappointments are things that people with Cystic Fibrosis have to deal with every single day of their short lives and we are talking about thousands of people. Research and treatments for this group of people have consistently fallen short of that needed for decades and when a drug is finally developed which NICE have agreed is beneficial and which is available for people in other countries is refused, it is an utter travesty and a disgrace. Orkambi is not designed to be a cure for Cystic Fibrosis, but it is the only	normally considered a cost-effective use of NHS resources. Please see section 4.24 of the FAD. The committee agreed that lumacaftor–ivacaftor has wider benefits to society for people with cystic fibrosis and carers of people with cystic fibrosis (for example, maintaining employment and improved family life). Please see section 4.27 of the FAD. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had not been captured in its economic modelling. Please see section 4.27 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company

Role*	Section	Comment [sic]	Response
		medicine which works towards correcting the flaw that causes the disease. There are no other medicines available that do this, all the others do is to try and stave off the inevitable early death. Orkambi buys time for people while research continues. By refusing to fund Orkambi you are writing off a whole section of our society of young people, with so much to offer and deeming that they are not worth saving. Your decision is ethically, morally and clinically unjustifiable.	that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (11)	General	I urge you to consider the cost benefits of 'holding back the tide' of Cystic Fibrosis. My son was born nearly 6 years ago when substantial benefits had been made in antibiotic treatment and pancreatic treatment (with enzymes) so that patients no longer died in childhood with CF. However, this prolonged life is one of huge expense to the NHS as the patients become progressively ill, with frequent hospitalisations, development of CF related diabetes and in some cases transplant. My son, [redacted], had a lung function of 110+% until his first hospitalisation following a severe chest infection. It now is never more than 93%. He had to have a Bronchoscopy, IV antibiotics and 14 days stay up at Kings College Hospital with amazing around the clock, multi-disciplinary care. That was his first major set-back. He now has to have daily DNase (Â£500+ a month) twice daily Promixin (another expensive drug) Domperidone and Omeprazole, that he did not require before. I know that the next hospitalisation will be just as costly to his health and to the NHS. Since birth [redacted] has seen Specialists, physiotherapists and dieticians every month. He has had too many courses of antibiotics to count and this is all before he's 6 years old. I know worse is to come, if we cannot access new drugs that 'hold back the tide' of CF while a better and more decisive treatment - or even cure - comes along. [redacted] and all other patients are loosing lung function after every hospitalisation, so the next one comes sooner and the effects are worse and the spiral continues. As a drain on	Comments noted. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had not been captured in its economic modelling. Please see sections 4.6 and 4.27 of the FAD. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The

Role*	Section	Comment [sic]	Response
		the NHS they become more and more so as they age. I am aware that my son is using up probably 1000+ patients allocation of funds within the NHS and is still getting progressively more ill, so progressively using more funds. If a drug that can slow this progression is expensive it needs to be balanced against what it is saving in future cost and that is not only in hospitalisations. If more people with CF can be fit enough to work at age 18/21 they can contribute to society and pay back some of the funds they've had in NI payments. They will not be a future drain on public funds. Most people with CF are so grateful for their life, that given any opportunity for increased wellness they will use it positively. This is all aside from how much mentally more healthy a person can be when their general health is better and they have a full potential for a lot longer. I urge you to consider the medical, emotional and societal benefits that slowing the onset of CF has. While short term gains in lung function might appear moderate on the face of it, the effect that small percentage has on the frequency of hospitalisations is huge., saving every patient, the NHS and society from a large amount of money and detriment to health and wellbeing.	committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013) and section 4.24 of the FAD. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
Carer (12)	General	I feel that this drug is very important and even as a non medical person it will help to keep overall costs of hospital stays/transplants down. Surely if	Comments noted. All direct costs to the NHS were considered in the company's cost effectiveness

Role*	Section	Comment [sic]	Response
		this drug can extend lives and also give better quality of life to C F sufferers it is essential. It would also be important in helping parents and sufferers themselves to be in full time employment and live a normal life. My granddaughter of 1 years old and is a CF sufferer would benefit greatly as she has the F508 mutation.	analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.
Carer (13)	General	By not approving ORKAMBI, you are helping people to die. I believe that American CFers are not different from British CFers. If they are getting benefitted how can you say that the impact of the drug is not significant. Let every CFer decide how ORKAMBI affects him or her. The one who is suffering should be the judge and not the one who is treating....It is simply unacceptable that some people decide on how long others should live, just to save the money ...	Comments noted. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013) and section 4.24 of the FAD. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.

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Carer (14)	General	I write this from the point of view of a grandfather of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical	Comments noted. The remit of 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. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties

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		effectiveness is evaluated.	could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (15)	General	I write this from the point of view of a auntie of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a	Comments noted. The remit of 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. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD.

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		longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.	The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (16)	General	I love my little grandson so much and desperately want some new treatments to come out that can help him. I understand from my daughter, who keeps me updated with information on CF drugs, that Orkambi could help slow down the progression of CF and reduce the amount of time people with CF have to spend in Hospital. [redacted] is a wonderful, intelligent little boy, doing well at school. He loves Sports and does so well with his Mum taking all his medications and treatments. Please re-consider your advice on Orkambi because anything that helps [redacted] and others like him would be a blessing. Thank you	Comments noted. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the

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			committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (17)	General	I write this from the point of view of a grandmother of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and	Comments noted. The remit of 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. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a

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		report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.	commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (18)	General	I'm very disappointed with the initial recommendation... My son has a lung function of just over 30% and even a very small percentage improvement makes him feel considerably better. As you say yourselves, Orkambi reduces hospital admissions which must almost mean that it would pay for itself. I fully accept that the cost of new drugs to the NHS must be considered carefully but genuinely feel this recommendation is wrong. Probably none of you have a child with Cystic Fibrosis.	Comments noted. A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. Please see section 4.6 of the FAD. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is

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			normally considered a cost-effective use of NHS resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013) and section 4.24 of the FAD. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
Carer (19)	General	As parents of a little boy with F508del Cystic Fibrosis, the results showing Orkambi to increase lung function and reduce infection and hospital stays are very significant, extremely important and give us (our son and us as parents and carers) hope for the first time since he was born. That's why we are asking NICE to recommend Orkambi maybe with the solution put forward by the CF Trust to provide Orkambi to patients while further evidence is collected on its long-term clinical impact using the UK Cystic Fibrosis Data Registry. Please give us the chance to see if this medicine will give us the benefits we desperately need. Thank you, from tired, sad, unhappy and depressed but hopeful parents.	The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (20)	General	I write this from the point of view of a mother, my son is 3 years old and has Cystic Fibrosis. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent	Comments noted. The remit of this appraisal was to appraise the clinical and cost effectiveness of lumacaftor in combination with ivacaftor within its

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		analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF, if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, as they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased to receive the medication and report on its effectiveness or otherwise, I know we as a family certainly would be. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.	marketing authorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible

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		Thank you for your time. [redacted]	potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Carer (21)	General	My name is [redacted]. My son [redacted] was born on the 12th June 2010. 3 weeks later we had the horrifying news that he had the condition (Cystic fibrosis) Our life's have been turned upside down, but we manage to cope as you have to. Let's talk about [redacted]. He's already been in hospital for 2 weeks on course of I v's & many other children with CF have been hospitalized many times. All [redacted] family from my side & his mums are & have always been get up & goers, hard workers & always paid our way in this life. [redacted] is the same, he is a determined Young boy & I will want take the bull by the horns everyday of his working life, please don't hold him back from this by not funding drugs that could help him stay well & get out of bed in the morning & go to work to earn a honest living & contribute to the N I, Or are you saying you can't afford to fund these drugs? Let CF suffers be unwell & be in hospital & cost NHS more money.	Comments noted. The committee recognised that cystic fibrosis has a major impact on the quality of life of patients and their carers. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013) and section 4.24 of the FAD. In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social

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		There are many people out there who have good health & able bodied & drain the system. Please fund the new drugs that people are spending brain taxing time researching these new life changing drugs to change the life's of people, then you won't fund them. With tears [redacted]	value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
Carer (22)	General	Vertex have made significant steps towards the revolutionary treatment of people with Cystic Fibrosis. Unfortunately it would seem that the analysis made by NICE of Orkambi appears short termed in its views. Cystic Fibrosis is a gradual disease - with relatively small reductions in lung function each year culminating to a point when the patient is typically 30-40 and their lungs eventually can cope no more. Therefore a drug like Orkambi does not need to see dramatic effects but merely reduce or even stop this gradual decline. The sooner Orkambi can ben taken, the sooner this decline can be reduced, with the hope that patients could have a near normal life expectancy. My daughter is 4 years old, she is healthy and her lungs have very good function - I have done everything I possibly can to keep her this way - encouraging her to be active, ensuring she is nt in higher risk environments, giving her percussion 2-3 times per day. All of this has been in the hope I can keep her as well as possible until a revolutionary new drug can come along. Well it would appear that revolutionary drug has come along, but the analysis taken by Nice has nt addressed the bigger picture of the fact that CF is a gradual disease. Yes it would be great if it could take a person with CF with a 40% lung function and improve it	Comments noted. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The committee highlighted that the company's economic modelling had captured the impact of lumacaftor–ivacaftor across multiple end points and over the longer term. The committee stated that the company had not presented any qualitative or quantitative evidence to support that important health-related quality of life effects had not been captured in its economic modelling. Please see sections 4.6 and 4.27 of the FAD. The remit of this appraisal was to appraise the clinical and cost effectiveness of lumacaftor in

Role*	Section	Comment [sic]	Response
		drastically. But for my daughter, 1000's of others and every future generation Orkambi could be enough - please don't rob my daughter of her future when it appears modern science does nt need it to be this way. I would also point out that Vertex has a pipeline of future drugs for cystic fibrosis, and in particular the most common DD508 mutation that Orkambi treats. Clinical trials on these "second generation correctors" are showing to be 3 times as effective as Orkambi which would obviously be fantastic and could be in clinic within two years. Could Nice, NHS, and Vertex not come to agreement where Orkambi can be agreed upon for now, knowing that it would help stop lung function declines until these second generation correctors are available, and which given their results, Nice would have to recommend.	combination with ivacaftor within its marketing authorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013) and section 4.24 of the FAD.
General public (1)	General	I have no formal knowledge of this debilitating disease but would urge serious consideration in the use of Orkambi in its use to relieve the condition. I do understand, however that these children and young adults are intelligent human beings who struggle through regardless. They are serious contenders to become successful adults who will contribute to the future of our society. If the drug Orkambi is a valuable tool, please consider strongly the benefits to help those afflicted by Cystic Fibroses.	Comments noted. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the appraisal committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. Please see section 5 of NICE's guide to the methods of technology appraisal (2013).

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			In formulating its recommendations, the appraisal committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The appraisal committee will also take into account the Institute's guidance on social value judgements described in NICE's Social value judgements: principles for the development of NICE guidance.
General public (2)	General	I think there is enough evidence that Orkambi has a healing effect on people suffering from Cystic Fibrosis and that should be enough when people pay a lot in taxes and work hard in this country for a health system that is being taken away from them. I think we need to put health before wealth and if you personally were a sufferer and there was a possibility you could be on less pain and get better you would expect that this was offered by a service which puts people before profit. I think as a tax payer it is our right to have this drug and I appreciate it's not a quick decision but I feel the evidence is enough proof this drug should be available on the NHS	Comments noted. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. The appraisal committee makes recommendations to the Institute regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the appraisal committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources. The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. Please see section 5

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			of NICE's guide to the methods of technology appraisal (2013).
General public (3)	General	Orkambi and its use in the treatment of cystic fibrosis. Cystic fibrosis is a life limiting condition that has a huge impact on sufferers and their families. Many families affected by cystic fibrosis have placed a great deal of hope in this drug and believe particular care should be taken to assess its effectiveness. Although I understand that the preliminary recommendation is that this treatment is not cost effective, I do think that it is worth exploring if there is a way it can be made available to NHS patients.	Comments noted. The committee noted the consultation comments suggesting that to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through data collection, nor had the company offered a commercial access agreement that demonstrated plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee agreed that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal.
General public (4)	General	Please take into account the Cystic Fibrosis Trust's proposal on making Orkambi available to certain people through an interim arrangement between the drug's manufacturer and the NHS. It is accepted that Orkambi helps with the management of the condition and reducing the number of hospitalisations, therefore this saving needs to be balanced out against the cost of the drug.	Comments noted. The committee noted the consultation comments suggesting that to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through data collection, nor had the company offered a commercial access agreement that demonstrated plausible potential for the ICER to fall within the range usually considered to be a cost-effective use

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			of NHS resources. Therefore, the committee agreed that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.
General public (5)	General	That the reduction in sudden hospitalisations alone should be considered as a great improvement to those with this condition	Comments noted. The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee concluded that the reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for the management of cystic fibrosis. Please see section 4.7 of the FAD.
General public (6)	General	I hope the committee will consider carefully the compromise suggestion put forward by the Cystic Fibrosis Trust. And also take into account the extra costs of withholding this treatment, in terms of the foregone costs of reducing sudden hospitalisations and the stress illnesses caused to CF sufferers and their carers if they are left feeling that NICE is not sympathetic to their situation.	Comments noted. The committee noted the consultation comments suggesting that to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through

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			data collection, nor had the company offered a commercial access agreement that demonstrated plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee agreed that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. All direct costs to the NHS were considered in the company's cost effectiveness analysis of lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including any of its preferred assumptions, the estimated ICERs were considerably higher than what is normally considered a cost-effective use of NHS resources.
General public (7)	General	I write this from the point of view of an uncle of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers	Comments noted. The remit of 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. The committee noted the comments from a consultee on the appraisal consultation document indicating that although the acute improvement in ppFEV1 was modest, when combined with the improvement in rates of exacerbations, the clinical trials provide evidence that lumacaftor–ivacaftor may significantly improve the long-term outcome for patients. Please see section 4.6 of the FAD.

Role*	Section	Comment [sic]	Response
		spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,000 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.	The clinical experts highlighted that if the observed effect on hospitalisation could be replicated in clinical practice, it would also help ease the current pressures on the capacity of the specialist cystic fibrosis centres. The committee noted that the consequences of this reduction were accounted for in the company's cost-effectiveness analysis. Please see section 4.7 of the FAD. The committee noted the consultation comments suggesting that, to reduce uncertainty, lumacaftor–ivacaftor should be made available with a commercial access agreement while data were collected for up to 2 years in the Cystic Fibrosis Registry. However, the committee highlighted that it had not received any proposal from the company that identified how the longer-term uncertainties could be addressed through the data collection. Given that no commercial arrangement had been offered by the company there was no plausible potential for the ICER to fall within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend the use of lumacaftor–ivacaftor with data collection for this appraisal. Please see section 4.25 of the FAD.
Patient (1)	General	I am 32 and suffer from CF. My lung function is 32% (FEV1) and I notice every single percent, I'm able to predict what my lung function will be before I take the test. Anything that can give me even a few extra percent would be literally life changing as it'd mean I could jog and do more exercise, which is currently difficult. Also, the main thing I struggle with is numerous exacerbations following one after the other. This often requires	Comments noted. A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be viewed as clinically significant, but from a patient perspective any improvement in lung function is welcomed. The committee agreed that lumacaftor–ivacaftor

Role*	Section	Comment [sic]	Response
		IV or oral antibiotics which can be a big practical distraction to every day life. Anything that can help keep me stable and reduce the ups and downs would be worth its weight in gold to me and make my life more predictable and help me plan better for the future.	offered people an oral treatment option that has the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. It recognised that this was particularly important to people with cystic fibrosis. Please see sections 4.6 and 4.27 of the FAD.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma ACD Response

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

Thank you for the opportunity to comment. In reviewing the report, Vertex found a number of inaccurate interpretations of the evidence base supporting the use of lumacaftor–ivacaftor in the treatment of cystic fibrosis patients with the F508del homozygous mutation. Vertex has sought to address each of these inaccuracies in turn, as they go to the heart of this evaluation of lumacaftor-ivacaftor and make these provisional recommendations an unsuitable basis for guidance to the NHS. These inaccuracies can be summarised in three key themes and then followed in more detail by 11 key issues;

1. **It is felt that the 2.8% improvement in ppFEV1 seen with lumacaftor–ivacaftor is clinically meaningful, especially in the context of a rapidly progressive disease like cystic fibrosis.**

   The rapid progressive nature of Cystic Fibrosis means that any preservation of lung function as measured by ppFEV1 is clinically relevant and significantly reduces the risk of death. A decrease in ppFEV1 of just 1% per annum increases the risk of death over 5 years by 4%. Therefore the 2.8% increase in ppFEV1 observed over 48 weeks, is a clinically meaningful improvement that in the long term is expected to translate into reduction in mortality.

2. **The comparisons of improvements in ppFEV1 seen with lumacaftor–ivacaftor in F508del CF patients to ivacaftor in G551D is inappropriate and does not align with the final scope.**

   The final scope, which was agreed upon with clinical experts, patient groups, NICE and other relevant stakeholders does not include ivacaftor monotherapy as a comparator. Ivacaftor monotherapy is neither indicated, nor is it used in clinical practice for the treatment of cystic fibrosis in patients with the F508del mutation. In fact, evidence from the DISCOVER clinical trial confirms that ivacaftor monotherapy does not work in this F508del population. The complementary mechanisms of action of both lumacaftor–ivacaftor molecules are required to address both protein defects CF is a huge umbrella term encompassing all mutations and it would be like comparing two different types of chemotherapy in two different types of cancer.

3. **The totality of the evidence package for lumacaftor-ivacaftor has not been taken into consideration by the committee in their assessment.**

   The evidence from the pivotal phase 3 clinical trials (the largest interventional trials ever conducted in CF) have shown that treatment with lumacaftor-ivacaftor led to sustained improvements in ppFEV1 and BMI as well as reductions in pulmonary exacerbations over a 48 week period. All of these improvements were statistically and clinically significant. Over time improvements in these three key areas have been shown to be the most important beneficial modifiers of mortality risk and disease progression. Given the multi-systemic and heterogeneous nature of the disease, one endpoint will be insufficient to capture all the benefits of treatment with lumacaftor-ivacaftor, as such the focus should be on the totality of the evidence.

Issue 1 ppFEV1 modest response

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
Summary p43 - The committee concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant. Summary p46 - The acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant.	Rewording required for p43 - 46: The committee concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor "can be considered as clinically significant in light of the progressive nature of CF, but that a sustained benefit requires further real world evidence".	This is not a reasonable interpretation of the evidence as acute (short-term) changes in ppFEV1 and the ppFEV1 benefits of a chronic medication for CF should always be considered in the context of the progressive nature of CF and the inevitable FEV1 decline. As noted by the committee "longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis." The treatment effect on $ppFEV_1$ is clinically relevant as the chronic nature of CF means that it is not only the acute (short-term) change in ppFEV1, but essentially disease progression, i.e. ppFEV1 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 ppFEV1 increases the risk of death over 5 years by 4% (4).Therefore a 2.8% positive increase is not only statistically significant, but is also clinically significant for patients and treating physicians.

Issue 2 - Patient expert statement correction around clinical significance

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P27 – 4.6 - A patient expert stated that an absolute increase of 2.8% in ppFEV1 may not be clinically significant, but from a patient perspective any improvement in lung function is welcomed.	Rewording required: A patient expert stated that "*although the committee may not view an absolute increase of 2.8% in ppFEV1 as clinically significant*, from a patient perspective any improvement in lung function is welcomed".	This has been misinterpreted as the patient expert did not state exactly "it may not be clinically significant" and this seem to have been misinterpreted. The proposed amendment more accurately reflects what was said and intended.

Issue 3 - Inappropriate comparison to Ivacaftor

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P27 – 4.6 - However, the clinical experts agreed with the committee that the size of the effect seen for lumacaftor–ivacaftor was lower than the 10–12% absolute improvement in ppFEV1 seen with ivacaftor monotherapy in people with cystic fibrosis who have the G551D mutation	Requested removal of this summary, however at the least a suggested addition at the end: However the committee accept that a direct comparison is not appropriate as each targeted medicine treats a different mutation of CF.	The clinical experts also stated it is not appropriate to directly compare between the 2 different genetic mutations. This needs to be reflected in the summary statement. This was also stated at the NICE scoping meeting when raised by NHSE as a potential comparator. Ivacaftor alone does not work in the F508del population and the comparison is medically inappropriate. CF is a huge umbrella term encompassing all mutations and it would be like comparing two different types of chemotherapy in two different types of cancer. 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. The net result is increased quantity and quality of CFTR at the cell surface. F508del is usually therefore a more severe form of CF than G551D due to impairment of both CFTR quantity and function. 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

Issue 4 – MCID interpretation of ppFEV1

Description of problem	**Description of proposed amendment**	**Description of justification for amendment / agreement**
P19 – 3.22 - The ERG's clinical adviser stated that absolute changes in ppFEV1 were more clinically relevant than relative changes, and that an absolute change in ppFEV1 of 5% or more would be considered clinically important.	Proposed addition: P27 – 4.6 However, the committee understood from the clinical experts that there was no agreed minimum clinically important difference for absolute and relative changes in ppFEV1 because of the heterogeneous nature of the condition.	This addition from the clinical experts and committee conclusions will make the statement and interpretation more clinically accurate and balanced for the reader.

Issue 5 – Failure to recognise the importance of BMI

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
The reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment were clinically significant and important for the management of cystic fibrosis.	Addition of wording - The reductions in pulmonary exacerbations seen with lumacaftor–ivacaftor treatment and the significant improvements in BMI were clinically significant and important for the management of cystic fibrosis.	It is important to note that because CF is a multi-organ, systemic disease that the three main goals of CF treatment (i.e. ppFEV1, pulmonary exacerbations and weight gain, which are independent risk factors for mortality), will vary between patients – i.e. ppFEV1 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.

Issue 6 - Generalisability of results

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement Description of justification for amendment / agreement
Trial results may not be generalisable to people with mild or very severe cystic fibrosis because the inclusion criteria required people to have a percent predicted forced expiratory volume in 1 second (ppFEV1) of 40–90%.	We request that this is removed entirely as it is not appropriate.	LUM-IVA is indicated for all F508 patients >12 years old and sub group analysis has demonstrated that all patients including those under 40% benefit. As in virtually all clinical studies in CF, it was a regulatory requirement to work within upper and lower limits of percent predicted FEV1 as inclusion criteria in order to standardise the patient population (ppFEV1 ≥40 and ≤90). Indeed, subpopulation analyses confirmed that in both pivotal studies, and in the pooled analysis, LUM-IVA combination therapy resulted in improvements in

		ppFEV1, reductions in pulmonary exacerbations and increases in BMI vs. placebo regardless of baseline spirometry measurements. A substantial number of patients had ppFEV1 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 ppFEV1 <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.

Issue 7 – Appropriateness of the STA process for evaluation of LUM-IVA

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P49 - The committee acknowledged that when the company's arbitrary price reduction (assuming the introduction of a future low cost generic for lumacaftor–ivacaftor) was removed, the company's base-case ICER increased from £218,000 to £349,000 per QALY gained for lumacaftor–ivacaftor plus standard of care compared with standard of care alone. The committee concluded that, even without including all of its preferred assumptions, the estimated ICERs were considerably higher than what is normally	Proposed addition: "A NICE STA process in its current form is not an adequate mechanism to assess precision medicines for small patient populations / orphan diseases."	1. Vertex believes LUM-IVA should be subject to an appropriate Health Technology Appraisal for its use within the NHS such as a HST appraisal which would allow recognition of the value of the medicine outside of the constrained STA ICER criteria. - This is supported by the fact that another CFTR medicine, Kalydeco, originally received a positive decision and was funded for all eligble patients in England by the North of England Specialised Commissioning Group with a predicted ICER between £411,000 - £1,160,000 per QALY (median £789,000). A subsequent analysis (March 2014) by the NHS NIHR put the ICER at between £335,000 and £1,274,000 per QALY. 2. Vertex is of the opinion that an STA process evaluation would result in a negative decision on a cost

considered a cost-effective use of NHS resources.		basis, ignoring the huge positive impact this innovative precision medicine could have on CF patients and their carers' lives 3. The NICE STA process is not an adequate mechanism to assess precision medicines for small patient populations / orphan diseases because: • NICE STA cost effectiveness thresholds are not appropriate to accurately incorporate the wider societal benefits of the medicines that treat CF patient populations especially as precision medicines like LUM-IVA represent a step change in the treatment of CF by treating the underlying cause of the disease • The NICE STA process considers absolute health gains rather than relative health gains, which is challenging for rare diseases with short life expectancy • For CF, demonstrating gains in QALYs is challenging because CF is a genetic disorder with manifestations from birth, so patients score very high in terms of their quality of life on standard of care (SOC) despite having a condition like CF, leaving little room to significantly improve these scores with the addition of new therapies • Treatments which have a significant impact on life-expectancy, as LUM-IVA is projected to do, naturally incur additional costs compared to SOC. This often means that greater clinical benefits and associated significant improvements in survival, do not results in lower ICERS and thus it is difficult for any chronic treatment that considerably increases survival far in the future to be considered cost-effective. Moreover the survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms

Issue 8 – Rate ratios for all pulmonary exacerbations

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P34: The committee discussed the company's methods for estimating the treatment effect of lumacaftor–ivacaftor on pulmonary exacerbations. The committee stated that it would have been more appropriate for the company to apply the rate ratio for all pulmonary exacerbations rather the rate ratio specifically for pulmonary exacerbations needing intravenous antibiotics or hospitalisation.	Delete this statement as it is factually incorrect.	No alternative sources of data were available that include all types of exacerbations (i.e., including those treated exclusively with outpatient oral treatment) and captures the relationship between disease progression and pulmonary exacerbations. The model tracks the subset of pulmonary exacerbations treated with IV antibiotics and/or hospitalization. The reason for including only this subset of events was because the data source used to predict pulmonary exacerbations in the model defined pulmonary exacerbations as requiring treatment with IV and/or hospitalization. We thus applied the rate ratio from the trials that was consistent with the definition used in the model. Choosing the rate ratio on all exacerbations and applying it to the exacerbation risk in the model would not be appropriate.

Issue 9 - Double-counting of pulmonary exacerbation costs

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P38 - The committee commented that the company had also double-counted any cost savings from lumacaftor–ivacaftor treatment. It explained that this was a result of the company applying a rate ratio to the number of pulmonary exacerbations (treatment effect), and another reduction to the cost of hospitalisation by 61%, for people having lumacaftor–ivacaftor plus standard of care.	Delete this statement as it is factually incorrect.	We are not double counting as the model does not assign costs explicitly to exacerbations. Costs are stratified by $ppFEV_1$ and applied annually in the model regardless of exact number of exacerbations in that year. Thus to account for reductions in hospitalized pulmonary exacerbations observed with LUM-IVA the hospitalization costs within each $ppFEV_1$ strata were adjusted. The number of pulmonary exacerbations impacts the patient's risk of mortality and quality of life.

Issue 10 - Treatment effects after discontinuation

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
P37 - However, the committee emphasised that it remained concerned about the company's modelling and how the treatment effect on ppFEV1 and pulmonary exacerbations was maintained until week 24 in people who stopped lumacaftor–ivacaftor early.	Delete this statement as it is factually incorrect.	This was an appropriate assumption to make since the treatment effects were calculated using an intention to treat (ITT) analysis and therefore included patients who discontinued LUM-IVA in the LUM-IVA group within the first 24 weeks.

Issue 11 - The clarification of Oral Treatments named as LUM-IVA

Description of problem	Description of proposed amendment	Description of justification for amendment / agreement
The below descriptions of the technology does not accurately represent all of the benefits offered by LUM – IVA: P25 – 4.2 - The committee concluded that oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers. P44 - Oral treatments that address the cause of the disease and that have potential to slow progression and reduce complications associated with cystic fibrosis would be beneficial to patients and their carers. P44 Lumacaftor–ivacaftor offered people an oral treatment option that has potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation.	Proposed change: LUM – IVA offers people an oral treatment option that addresses the cause of the disease and that has the potential to slow progression and reduce complications associated with cystic fibrosis. This would be beneficial to patients and their carers with the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation.	This important clarification allows for a more accurate representation of the value LUM-IVA brings to patients in slowing the progression of disease, which has been demonstrated in the evidence submission.

NICE Appraisal Consultation Document (ACD) - Cystic fibrosis - lumacaftor and ivacaftor [ID786]

Cystic Fibrosis Trust consultation response – April 2016

Overview

The Cystic Fibrosis Trust (the Trust) is profoundly disappointed that NICE proposes not to recommend lumacaftor-ivacaftor therapy (Orkambi®) for routine use in the NHS in England.

This is a distressing announcement for the thousands of families who could benefit from the therapy that NICE's Appraisal Consultation Document (ACD) concludes is **a valuable new therapy for managing cystic fibrosis that has wider benefits to society, for people with cystic fibrosis, and carers of people with cystic fibrosis**.

Orkambi® may have a significant protective effect against future health deterioration for eligible individuals with cystic fibrosis. However, the evidence from the clinical trials and rollover studies to see if the therapy slows disease progression and facilitates compound health improvement is immature and, naturally, a confident assessment of the ultimate value it could bring is uncertain.

The ACD centres on concerns relating to:

- **Uncertainty** regarding longitudinal effects
- **Uncertainty** regarding clinical significance of acute effects
- **Uncertainty** regarding elements of economic modelling
- **Uncertainty** regarding transferability of clinical trial results to routine use

The Trust accepts that the NHS must use its resources carefully to deliver high-quality care for all.

However, it is imperative that it is now recognised that risk associated with making life-changing decisions on the use of new rare-disease medicines in the NHS where such degrees of uncertainty exist is unacceptable.

In the case of Orkambi®, this uncertainty persists in spite of the fact that the data used to assess the therapy was drawn from the largest ever clinical trial of a new cystic fibrosis medicine.

NICE and the Government must now accept that actively engaging to address uncertainty in modelling the long-term impact of medicines for chronic, rare diseases is the only viable option if a future of disease-modifying and more personalised interventions is to be realised.

Throughout the NICE scoping and appraisal process for this therapy, the Cystic Fibrosis Trust has highlighted the potential of the UK Cystic Fibrosis (CF) Registry to support reimbursement decision-

making for new cystic fibrosis therapies that are proven to be safe and effective, and boost the NHS's ability to confidently invest in new technologies.

In the Trust's submission to the NICE STA process, it was stated that:

> [Orkambi®] 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.

A copy of the principles of for using UK CF Registry data to support reimbursement decision-making, co-designed and agreed in principle by members of the CF specialist clinical community, representatives of the company, and representatives of CF services for NHS England, has been submitted alongside this response.

Solution

The UK CF Registry is a national, centralised web-based database that collects demographic, health and treatment data from consenting people with cystic fibrosis from every CF care centre in England, Wales, Scotland and Northern Ireland. The UK CF Registry is sponsored and managed by the Cystic Fibrosis Trust.

The infrastructure to undertake an assessment of the therapy's real-world impact across the whole eligible population in the UK already exists and, by embracing such a solution, the NHS would be able to develop its own extended and novel evidence base via the UK CF Registry's patient records, to confidently address uncertainty in the data set currently at its disposal and make a more confident valuation of the clinical and cost-effectiveness of the therapy.

The Trust firmly believes this solution is a progressive model for all new technologies for people with cystic fibrosis enabling access to safe, effective and innovative products faster, whilst providing the NHS with the robust, real world data to confidently support investment opportunities. For Orkambi®, we have witnessed the inevitable and agonising delay in access that is a consequence of the current approach to health technology appraisal for cystic fibrosis technologies.

It has been nearly a year since Orkambi® received marketing authorisation in Europe. People with cystic fibrosis who are eligible for the treatment within its marketing authorisation have now waited for over 22 months since the publication of the pivotal Phase III trials that demonstrated the treatment's clinical efficacy.

Critique of the Appraisal Consultation Document (ACD)

- **Disease severity**

The Trust is concerned that, despite the input of consultees, stakeholders and expert opinion the ACD presents a view of cystic fibrosis which is not consistent with the reality of the condition, its progressive nature, and its geno- and phenotypic expression.

Section	ACD extract
3.19	The ERG stated that because both trials included people with mild to moderate cystic fibrosis (that is, ppFEV1 of 40–90% at screening), the clinical evidence may not be generalisable to people with severe cystic fibrosis, or people with very mild cystic fibrosis.

Section 3.19 of the ACD refers to testimony from the Evidence Review group that describes mild, moderate and severe cystic fibrosis as definable by the measure of an individual's ppFEV1.

It should be made clear that, ultimately, cystic fibrosis disease severity depends on the type of mutations present and well as other modifying environmental and physiological factors. It is important that disease severity is not confused with acute health status.

- **Long term data uncertainty**

Section	ACD extract
3.23	The ERG noted that because the company's trials were short, the long-term effects of lumacaftor–ivacaftor were uncertain.
4.6	The committee recognised that longitudinal changes rather than acute changes in ppFEV1 were more clinically relevant for assessing long-term outcomes of cystic fibrosis. However, it concluded that the acute improvements in ppFEV1 seen with lumacaftor–ivacaftor were modest and unlikely to be clinically significant.
4.7	The committee heard from the clinical experts that pulmonary exacerbations are associated with long-term decline in ppFEV1, and a treatment that reduces the need for hospitalisation by 61% would be clinically significant.

Section 3.23 of the ACD acknowledges the ERG's conclusion that all long-term effects of the therapy are uncertain.

Section 4.6 demonstrates the committee's acknowledgement of the primacy of the importance of longitudinal change over acute change in ppFEV1. However, it must be more clearly recognised that cystic fibrosis is a progressive condition, where long-term maintenance of ppFEV1 is an important clinical achievement, given the measure's well-established relationship with long-term survivorship. The conclusion associated with Section 4.6 – that acute improvements in ppFEV1 are modest and unlikely to be clinically significant – appears to dismiss the concept of ppFEV1 maintenance as a positive clinical outcome, and appears to disregard the evidence provided by clinical and patient experts, recorded in Section 4.13, that, in converse, an annual decline in ppFEV1 of ≥2% is treated as a reflection of rapidly declining lung function. The Trust seeks the committee's comment on these points.

In Section 4.7 the committee acknowledges the significance of the therapy's impact on hospitalisation. This fundamental aspect of the positive benefit described by trial data, with reduction in pulmonary exacerbations, indicates the potential for this treatment to slow the disease's progression versus Standard of Care in the long-term. This data is given disproportionately low standing in the ACD and the Trust seeks the committee's reassurance that its relationship to health maintenance is well represented in the documentation.

Section	ACD extract
4.11	The committee concluded that, overall, the company's methods for estimating survival seemed valid but there was uncertainty about how the differences in outcomes between the whole cystic fibrosis population and the population with the F508del mutation would affect the cost-effectiveness results.
4.12	The committee highlighted that there was also considerable uncertainty associated with how the company modelled the decline in ppFEV1 after 24 weeks.
4.12	The committee commented that because extrapolations for ppFEV1 decline were based on different, non-randomised studies for each treatment group, it would have been appropriate for the company to explore the impact on the ICER using the ppFEV1 decline for standard of care alone based on the 24-week trial data. The committee concluded that the company's methods for estimating changes in ppFEV1 were associated with considerable uncertainty and were likely to have overestimated the benefits of lumacaftor–ivacaftor treatment.
4.15	Therefore, it concluded that there was uncertainty associated with the treatment effect on BMI in the company's model
4.20	The committee concluded that people could discontinue lumacaftor– ivacaftor after 24 weeks, but the rate of discontinuation was uncertain.

Addressing the comment in Section 4.11, in order to confidently estimate survival in the relevant population, supportive data is available to both NICE and the company upon request from the UK CF Registry.

Sections 4.12, 4.15 and 4.20 highlight the difficulty of estimating performance beyond the 24-week trial period and the Trust, again, indicates the potential of the UK CF Registry to explore and overcome this uncertainty using real-world evidence.

4.24	The committee acknowledged that the company had used the data from its trials when available, which were recognised as the largest trials in cystic fibrosis to date.
4.24	The committee also agreed that there was considerable uncertainty around: • the estimates of relative effectiveness for ppFEV1 decline • the rapid rate of ppFEV1 decline in the standard of care group • how the treatment effect was modelled when people came off treatment and over the longer term (that is, no waning effect of treatment over time) • how independent the effects of lumacaftor–ivacaftor on ppFEV1 and on pulmonary exacerbations were • potential double counting of cost savings associated with hospitalisations and • The company's utility estimates.

Section 4.24 outlines areas of **considerable uncertainty** whilst simultaneously acknowledging the scale of the trials used to source the novel data used to describe this treatment effect.

It must be acknowledged that the Single Technology Appraisal of Orkambi® has failed to produce an unequivocal recommendation, in the respect that, with or without the committee's preferred assumptions, the inherent uncertainty regarding the therapy's long-term performance leave the committee's conclusions begging more questions than are answered.

- **Concluding remarks**

In Section 6.1 of the ACD, NICE proposes to review the guidance issued 3 years from the publication of this guidance.

This timescale in unconscionable, whilst an alternative option exists. The Trust firmly believes that NICE, the NHS and Government must work cooperatively, alongside the company to address the challenge of

The Trust welcomes the committee's comment on the Trust's document describing the principles of using the data collected by the UK CF Registry to collect real world evidence supporting clinical- and cost-effectiveness assessments.

Utilising the UK CF Registry to support reimbursement decision-making

Principles of managed access to new cystic fibrosis therapies

Introduction

Around 10,500 people live with cystic fibrosis in the UK. It is a life-limiting, inherited disease.

Disease-modifying cystic fibrosis therapies are being developed for greater numbers of people with the condition. Vertex Pharmaceuticals Inc. have licensed two such medicines for use in Europe: ivacaftor monotherapy (Kalydeco®) and lumacaftor/ivacaftor combination therapy (Orkambi®).

Kalydeco® is prescribed through the NHS in the UK for around 410 eligible patients with indicated cystic fibrosis-causing genetic mutations. Orkambi's® license indicates that over 3000 people with cystic fibrosis in the UK could receive the drug.

The UK Cystic Fibrosis Registry currently monitors the safety and efficacy of ivacaftor, compiling reports for the European Medicines Agency (EMA), as part of a scalable post-marketing surveillance programme that enables comparison of people on drug with their own legacy data in additional to a comparator cohort matched from the entire CF population.

The Cystic Fibrosis Trust proposes that data collected routinely by UK CF Registry is utilised to create an early access programme that supports the NHS to invest securely in controlled, early access to novel cystic fibrosis medicines.

Challenge

Well-powered and designed clinical trials have demonstrated a clinical benefit and good safety profile for both therapies. The key data used to describe efficacy were derived from two clinical endpoints:

1. Absolute increase in percentage predicted Forced Expiratory Volume in 1 second ($ppFEV_1$)
2. Rate of pulmonary exacerbations (PEx)

Whilst the Trust recognises the importance of these endpoints, there are four important limitations to the nature of the data captured in the clinical trials:

1. By virtue of targeting disease-modification, these treatments may have a protective impact on future health deterioration. Where the experience of Kalydeco® indicates a growing body of evidence that the therapy slows disease progression and facilitates compound health improvement – the evidence from the clinical trials and rollover studies to see if this effect is replicated or not in newly licensed therapies will be immature.

2. People affected by the condition experience the benefit and value of therapies in more dynamic and personally meaningful ways than the trial is designed to capture. Many current trials have captured QoL data limited to the CFQ-R respiratory domain.

3. Typical trial data, set to meet clinical and safety regulatory standards, make it difficult to holistically model the value of these medicines to the NHS and create an evidence gap in prescribing practice and clinical use. Tools such as the EQ5-D, benchmarking against ONS national well-being scores, and CF QoL measures, utilised in a setting with greater opportunity for longitudinal comparison, can develop our understanding of the less tangible value of new CF therapies.

4. As new treatments become available, the population of people with cystic fibrosis eligible to participate in a clinical trials may be less – increasing the likelihood of traditional clinical trial design having insufficient power to assess outcomes of upcoming therapies.

Is the UK CF Registry a key tool in a solution?

With near-complete coverage of the UK's cystic fibrosis population, the UK CF Registry is uniquely positioned to demonstrate the effect of new CF treatments in the real world, with enough patients and over a long enough time period for the impact of breakthrough therapies to be understood.

The UK Cystic Fibrosis Registry

The UK Cystic Fibrosis (CF) Registry is a national, centralised web-based database that collects demographic, health and treatment data from consenting people with cystic fibrosis from every CF care centre in England, Wales, Scotland and Northern Ireland. The UK CF Registry is sponsored and managed the Cystic Fibrosis Trust.

Over 99% of people with cystic fibrosis consent to their anonymised data being collected in the Registry, which utilises data for research, annual reporting, quality improvement, and as the evidence base for the cost of cystic fibrosis care, informing proportionate tariff payments by NHS England. It is also relied upon by the European Medicines Agency to evaluate the safety and efficacy of therapies for post-marketing surveillance.

The Cystic Fibrosis Trust has committed to extensively enhancing the UK CF Registry, migrating it to a new agile software system that can collect data for Registry-based clinical trials. It has been designed with capability to enable direct access to people with cystic fibrosis via a patient portal in future. This portal would enable people with cystic fibrosis to view their clinical data, self-report data, and opt in to additional uses of Registry data that will enhance the value of the Registry to the CF community.

The Cystic Fibrosis Trust

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.

In October 2015, the Trust devised and rolled out a survey that asked about the life experience and treatment preferences of people affected by cystic fibrosis. We received over 1400 responses from our community. Analysis showed that a treatment's potential to protect future health and wellbeing is more important than a treatment's potential to reduce symptoms in the short term. These data will be published once further data mining has taken place.

We are committed to representing this view in the way new therapies for cystic fibrosis are assessed.

Question

What data collection methodology, including choice of quality indicators and analysis period, is necessary for the NHS to confidently predict the long-term value, including health-related quality and length of life, of new cystic fibrosis therapies to the NHS?

Proposed mechanism for discussion

The Trust proposes that new cystic fibrosis medicines should be made available for specialist clinical prescription immediately following marketing authorisation in the European Union, on the condition that an agreed set of data are routinely monitored through UK CF Registry data against the therapies' performance at a population level.

We suggest the therapy should be concurrently evaluated by a UK-wide technology appraisal body, with three options available to the Appraisal Committee at the conclusion of the process:

1. Recommended for routine use and funded from the baseline commissioning budget (a drug which thus demonstrates both clinical and cost effectiveness).

2. Not recommended for routine use and thus there is no baseline funding (a drug which thus does not demonstrate clinical effectiveness).

3. Recommended for use for evaluation within a predetermined period of time (e.g. 12 months evaluation period plus 6 months for data collection and analysis) in order to build both an extended and novel evidence base via the UK CF Registry's patient records.

After this time, an abbreviated appraisal process would be undertaken to formally review the collated data, and issue final guidance regarding the therapy's continued use.

Next steps

We invite you to help us to better understand the suitability of (1) change in the rate of pulmonary exacerbations (represented by home/hospital IV episodes), (2) absolute change in $ppFEV_1$, (3) change in rate of decline in $ppFEV_1$, and (4) change in BMI, as the key outcomes that meaningfully represent therapeutic added value, in cystic fibrosis and can help to build a real-world picture of the impact of a therapy, through extended longitudinal data beyond clinical trials and rollover studies.

Alongside these metrics, we would like to discuss the added benefit to an NHS assessment of value of a new CF therapy of reporting UK CF Registry data to describe (5) use of services (represented by medications, airway clearance, supplementary feeding, IV days, non IV admissions, transplant), (6) health utility scores (represented by EQ5-D or other), and (7) personal independence scores (represented by CFQ-R).

The establishment of any proposed mechanism of novel cystic fibrosis therapy appraisal must be underpinned by an acceptable interim commercial access arrangement, which confirms the cost of the drug to the NHS (agreed between the company and the NHS) and data collection arrangements. However, we are concerned with the practical arrangements needed to collect high-quality, real world data, in order to facilitate such an arrangement.

We believe participation in the data collection exercise should be open to all eligible individuals covered by the EMA's marketing-authorisation guidance to enable assessment of impact at population level, and understand that participants must be informed and provide written consent in advance, agreeing to the time-limited nature of the data collection exercise.

We believe Orkambi® is a therapy where this pilot could be initiated with low administrative and infrastructural burden, as the necessary data collection already happens.

Data from the UK CF Registry could support such a pilot, running for a period of 12 to 24 months to provide sufficient time for the publication of the data from the data collection period.

We believe that the appropriate model could act as a more powerful rollover study that can call upon both cumulative data from the initial trials and historical data stored in the UK CF Registry, while boosting our holistic understanding of the therapy through collection of broader data points.

British Thoracic Society

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To be submitted via NICE docs

April 2016

Dear Sir,

ACD - Consultees & Commentators: Cystic fibrosis - lumacaftor and ivacaftor [ID786]

Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD).

Lumacaftor-ivacaftor is a highly innovative treatment which shows significant promise in the treatment of cystic fibrosis. After the success of ivacaftor in the G551D mutation, patients with F508del/F508del mutations have been eagerly awaiting this treatment and will be disappointed that NICE is not recommending this treatment.

The statistically significant improvement in FEV1 demonstrated in the clinical trials may well also be clinically significant in the context of a disease which is characterized by a progressive decline in lung function. Regarding 5% improvement in FEV1 as clinically significant is a rather arbitrary cut-off point. Although the improvement in FEV1 is modest, when combined with the improvement in rates of exacerbations, the clinical trials provides preliminary evidence that this treatment may significantly improve the long term outcome for these patients.

CF is a progressive disease that ends in transplantation or death and the stability of FEV1 may be an indicator of important long term benefit.

This could form the basis for a different approach to this treatment. CF Clinicians and patients would favour conditional approval of ivacaftor-lumacaftor under a reduced cost patient access scheme whilst further long term outcome data is collected via the CF Registry and CF Centres.

Yours faithfully,

[redacted]
Dr [redacted]
[redacted]
British Thoracic Society

NHS England Response to NICE ACD – Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]

Please find NHS England's response to the ACD – Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation which has been reviewed by the Cystic Fibrosis CRG

Has all of the relevant evidence been taken into account?
Yes we believe all the relevant evidence has been taken into account
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes with respect to the clinical evidence. With respect to the cost effectiveness analysis, although we do not have the specific expertise to interpret this data, we believe the NICE conclusion that this intervention is not cost effective is also correct.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes. NHS England agree that the recommendations are a suitable guidance to the NHS and commissioners.
Any other comments
We understand that were the drug offered at a much lower price to the NHS that was deemed cost effective by NICE, clinicians would wish to have access to this drug.

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	[redacted]
Name	[redacted]
Job title or role	[redacted]
Email address	[redacted]

Title (e.g. Dr, Mr, Ms, Prof)	[redacted]
Name	[redacted]
Job title or role	[redacted], [redacted]
Email address	[redacted]

Single Technology Appraisal (STA): Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation [ID786]. Appraisal consultation document

We would agree with the majority of the conclusions of the appraisal consultation document (ACD), and they are much as might have been predicted from both the submission documentation and the discussion on the day.

We believe that all the relevant evidence been taken into account.

We believe the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Specifically we would support the ACD view that only the 24 week change in FEV_1% should be considered, which results in a revised figure of only 2.49% absolute improvement in FEV_1%. We are unclear on the clinical significance of this change in FEV_1%. Furthermore the company's economic modelling was always going to be challenging with the submitted ICERs, and the ACD has unpicked some contentious assumptions in the model. We believe that the revised ICERs are likely to be a more accurate representation.

We are of the opinion that the review is comprehensive and its conclusions appropriate, and thus the provisional recommendations are sound and a suitable basis for guidance to the NHS.

Iolo Doull on behalf of NICE Cystic Fibrosis Guideline Committee

- **Has all of the relevant evidence been taken into account?**

The only evidence available is the immediate/short term benefits from the trial itself which is frustrating as the longer term effects of the treatment are not reflected within this appraisal, which is a great shame.

Whilst all the clinical outcomes such as FEV1 and BMI are relevant, I need to re-emphasize that they are not a real life reflection of the patient experience such as daily symptoms, mental wellbeing and the longer term impact on health decline and treatment burden.

I would have like to have heard further patient representation (or at the very least a written statement) from a person with CF who had perhaps experience of taking Orkambi so that the panel could understand the impact of drug and the difference it had made.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

I am frustrated that the potential long term benefits of the drug are not captured or taken into account. I feel this is a significant failing of the appraisal process.

I feel there is too much emphasis on the immediate clinical benefits such as lung function or BMI, rather than the impact on the longer term health benefits such as improving quality of life, reduction of symptoms, stabilisation of health and life expectancy.

CF is a progressive disease that does not improve, it is in a condition that is in decline. The document does not perhaps reflect that lung function tends to generally go downwards and not upwards. The only exception would be during an exacerbation when lung function may dip lower but then recovers following treatment. Therefore any increase in lung function, no matter how small, is a perceived benefit to patients. On this basis I do feel that the FEV1 increase is downplayed.

The reduction in exacerbations and IV treatment is perhaps understated in the document and yet it is a significant outcome of this treatment for patients living with the condition. Both are of significant benefit because a reduction in exacerbations is a reduction in lung damage and less time spent on IV's is a huge reduction of treatment burden. It also limits disruption to education, work, family and social life.

A reminder that CF is still very much a young person's illness, as this is perhaps not very clear in the document. Around half the patients are actually children or young people and the median age of death is just 28 years old. Most of these patients are people who are just starting, developing or in the prime of their life with goals, dreams and aspirations. Please remember this.

Orkambi is a pill which is taken twice a day and relatively low burden in comparison to multiple IV therapies which are not just disruptive, but have a physical and mental impact too.

The document in section 4.1 onwards plays down the impact on everyday life for patients – there is no mention of the day to day symptoms, for example. Where treatment burden is stated – please note that this is not just tablets; but nebulisers, inhalers and physiotherapy as well as a high fat, high calorie diet.

There is no mention of the length of time taken each and every day to take treatments, impact on family planning or the psychological impact of a life expectancy which is nearly half that of a non-CF person.

Continuous reference and comparisons made to Kalydeco (Ivacaftor) seems excessive, given that the treatment is for a completely separate class of mutation with a different level of CFTR function. On this basis not sure how comparable to two are.

Orkambi may not be deemed as clinically effective as Kalydeco, but please do at least acknowledge within the document that the list price is actually significantly lower than the list price for Kalydeco.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

No. I am extremely disappointed and heartbroken at this decision. As stated at the meeting, many of us living with the condition have waited a lifetime for drugs like this to become available that can for the first time treat the underlying cause, whereas current medication only treats the symptoms.

I do believe Orkambi should be recommended for use in England on the basis that NICE have stated that this drug is clinically effective and this drug is the only treatment for this mutation group available now.

If the drug is clinically effective then cost should not be a barrier. There should be no cost placed on a patient's life.

Please consider that in the meantime if Orkambi is not recommend, that patient's like me will continue to decline and develop irreversible lung damage increasing our dependence on the NHS and need for transplantation.

This treatment has the potential to reduce the cost and burden on the NHS and I am disappointed more evidence was not presented and explored on this aspect.

I also wish to emphasise that Orkambi could help to address pressures around the increasing patient capacity on CF centres – particularly in adult care where access to inpatient and even home IV antibiotic care is becoming increasingly difficult with long waiting lists just to access basic and necessary care.

The decision may create a level of worry and uncertainty for patients like me that as more treatments like Orkambi are developed and become available, that this may set a prescient for access to future treatments. So despite all the fantastic research and exciting scientific breakthroughs in precision medicine for CF, the treatment is not able to reach the front line and patients like me may never actually get to try or ever benefit from these treatments. This seems cruel and unfair.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

This is a treatment specifically for homozygous delF508 and is the only precision medication if its kind available to those with this mutation. Another drug Kalydeco (referenced) is already available for 5% of the population with a class three mutation. Concern that refusing access will divide with the CF community – those mutations who can access precision medicines and those who cannot.

The overall impact of not recommending Orkambi on patients and their families' needs to be carefully considered. Patients who are not able to access a precision medicine whilst other groups with CF can, both in the UK and elsewhere globally may cause significant distress to patients and their families.

General comment that cost is cited as the most significant factor in not recommending this treatment. I wonder if those with the homozygous delF508 are perhaps at an unfair disadvantage from the offset, purely because of the sheer number of patients within the mutation group and how common the mutation is?

Name	[redacted]
Organisation	
Role	Grandparent
Job title	Security Consultant
Location	England
Conflict	No
Disclosure	
Comments	1326 You are discriminating against humans with a terminal illness ,how can any of you human beings on that committee possible deprive these people of a life transforming drug regardless of how transforming and costly it is, just the cost saving of hospitalisations and for someone to breathe easy is more than enough evidence, be human all of you.
Submission date	30 March 2016

Name	[redacted]
Organisation	
Role	Public
Job title	Fundraiser
Location	England
Conflict	No
Disclosure	
Comments	1327 I think there is enough evidence that Orkambi has a healing effect on people suffering from Cystic Fribosis and that should be enough when people pay a lot in taxes and work hard in this country for a health system that is being taken away from them. I think we need to put health before wealth and if you personally were a sufferer and there was a possibility you could be on less pain and get better you would expect that this was offered by a service which puts people before profit. I think as a tax payer it is our right to have this drug and I appreciate it's not a quick decision but I feel the evidence is enough proof this drug should be avalible on the NHS
Submission date	31 March 2016

Name	[redacted]
Organisation	
Role	Public
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1328 Orkambi and its use in the treatment of cystic fibrosis.

	Cystic fibrosis is a life limiting condition that has a huge impact on sufferers and their families. Many families affected by cystic fibrosis have placed a great deal of hope in this drug and believe particular care should be taken to assess its effectiveness. Although I understand that the preliminary recommendation is that this treatment is not cost effective, I do think that it is worth exploring if there is a way it can be made available to NHS patients.
Submission date	31 March 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	Owner of [redacted]
Location	England
Conflict	No
Disclosure	
Comments	1330 My 21 year old daughter has Cystic Fibrosis and as such attends hospital every 4 weeks throughout the year. In addition, on average she requires three hospital admissions each year for the duration of two weeks. Without Orkami, it is predicted that her disease will progress and she will require even more hospital admissions for longer periods of time. This is just one patient. We all agree that Orkabmi will reduce the necessity for hospital admissions, therefore it will be cost effective for the NHS to prescribe this drug. There is no argument. Cystic Fibrosis is still the most common genetic condition for the caucasian population, with 1 in 25 carriers. The disease has undeniably devastating consequences for the patient and their families but also financially on the state by way of benefits, medication, a plethera of professionals and additional complications as a result of Cystic Fibrosis. When all of these factors are taken into consideration, the actual cost of one patient to the NHS with Cystic Fibrosis is immense. To provide a treatment such as Orkambi which will benefit the patient by alleviating some of their ailments will in turn, benefit the financial strain on the NHS.
Submission date	1 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	Retired Community Matron for Long Term Condition
Location	England

Conflict	No
Disclosure	
Comments	1332 3.3 There is a cost to patients ,parents , informal carers and employers Loss of income due to reduced working which can be planned because of awareness of reduced health and stamina or unplanned time off due to exacerbations and admissions Care has to be found to support children when their siblings or parents are in hospital .Family members reduce working days or give up work to support patients or their children. Over all the worry of management and long term outcomes take their toll for patients and their family. 4.10 Tiredness, lack of energy ,shortness of breath on exertion and increased repiratory rate and heart rate to compensate are taken as normal for someone who has grown up with CF. They also have to put effort into physio if they feel like it or not . Depression and anger affect their motivation as it affects the motivation of those who support and encourage them on a day today basis .This will have an affect on their function and can lead to an exacerbation . Deprivation of known treatment also will have a negative effect .i am aware of this from your recent publication re Orkambi . 5.22 See comment 2 please Appendix A Decrease in pulmonary exacerbations when treating with Orkambi This is such a positive outcome in every way . Surely over time medication will be refined .there is no encouragement to firms to spend on this if treatment is not started and evaluated on a larger scale tha the trials. I refer to comments made in Comment 1 again .there is an ongoing acost to CF pts and their employers as well as to their families in the short term and in the long term reduction in working hours and retirement benefits .
Submission date	3 April 2016

Name	[redacted]
Organisation	Cystic Fibrosis
Role	Distant family member of sufferer from Cystic Fibrosis
Job title	Retired Health Worker
Location	England
Conflict	No
Disclosure	
Comments	1333 Use of Orkambi to assist with the treatment of Cystic Fibrosis. I have no formal knowledge of this debilitating disease but would urge serious consideration in the use of Orkambi in its use to relieve the condition. I do understand, however that these children and young adults are intelligent human beings who struggle through regardless. They are serious contenders to become successful adults who will contribute to the future of our society. If the drug Orkambi is a valuable tool, please consider strongly the benefits to help those afflicted by Cystic Fibroses.
Submission date	5 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1334 The appraisal committee did not give sufficient consideration or weight to the reduction in exacerbations requiring hospital treatment apparent in the treatment arms of TRAFFIC and TRANSPORT: such a reduction is not merely "clinically significant" (as per para 4.7 of the ACD): 1. A reduced need for admissions is vital for people with cystic fibrosis in order to allow them to live normal lives and to reduce interference with both education and employment. 2. There is a major issue in England with respect to the capacity of adult CF centres to admit patients for inpatient treatment; most - if not all - centres are routinely unable to meet target admission times laid down by the NHS England Service Specification. Anything which reduces the need for patients homozygous for F508del to be admitted will benefit not just those patients, but also patients with other mutations who will gain speedier access to an inpatient bed than would otherwise have been the case. Timely treatment of exacerbations is key to

	delaying disease progression, but these benefits (some of which would be to a part of the CF population who would not receive Orkambi) have not been taken into account at all by the appraisal committee. Further, the adoption of an ICER based on "all pulmonary exacerbations" (per para. 4.24) is likely to understate the benefits of Orkambi even when those benefits are assessed in the target population alone. The comment by the ERG that "because the companyâ€™s trials were short, the long-term effects of lumacaftorâ€“ivacaftor were uncertain" is concerning. Thr trials undertaken by the company were of standard length and it would be unreasonable to expect longer Phase 3 trials to be undertaken. If endorsed (as it appears to be at p.47 of the ACD in the comment that "There was uncertainty ... over the longer term (that is, no waning effect of treatment over time)", the ERG's approach would make it very difficult for any innovative treatments to gain reimbursement. The appraisal committee has taken no account of the potential adverse impact which its decision may have upon clinical research activity into innovative, gene-specific treatments: 1. In the field of cystic fibrosis generally. 2. In England in particular. As to the second of these points, if the NHS in England is not willing to reimburse the cost of such treatments, questions may be asked as to the ethics of English patients participating in trials for treatments from which they will not benefit; drug manufacturers may also see no point in enlisting participation from centres in England. Accordingly, the Appraisal Committee's provisional recommendation has (again) failed to take a key issue into account and, if maintained in the final recommendation, would be likely over time to diminish the research base in England, to the detriment of patients.
Submission date	5 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1335 As a parent of a child with Cystic Fibrosis, drugs such as Orakambi offer hope and a substantial difference to people lives. Cystic Fibrosis can be an all consuming disability and anything that helps sufferers with their daily lives should be

	made a priority!
Submission date	6 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	S/E P/T Cleaner
Location	England
Conflict	No
Disclosure	
Comments	1336 I have just finished another course of 3 monthly iv antibiotics, this was for three weeks due to the first medication my child was given she had a reaction to. I can not imagine, how much this one course of treatment must have cost, just for the medication alone. As I do them for her at home we did not take up the space of an NHS hospital bed, but this expense must come into it for other children, not to mention the the other 15 different types of medication she takes everyday. This is just one CF. When I think of the millions that is being spent on the EU leaflet, as a mum of a cf little girl I know where I would rather spend my money, and I am sure a lot of people would feel the same.
Submission date	7 April 2016

Name	[redacted]
Organisation	
Role	Patient
Job title	
Location	
Conflict	No
Disclosure	
Comments	1338 Lumacaftor-ivacaftor is a highly innovative treatment for people with Cystic Fibrosis who are homozygous for the F508del mutation in the CFTR gene. It is the first treatment that targets the underlying gene deficiency, rather than merely managing the symptoms of the condition and as such should be considered as a significant breakthrough in the treatment of those with the F508del mutation. It is stated in the appraisal consultation document that the increase seen in ppFEV1 â€œmay not be clinically significantâ€• , however it is important to realise that for a patient with Cystic Fibrosis even a stabilisation in ppFEV1 would be highly beneficial. Meaning that the condition would not

	progressively worsen over time. Current, highly invasive and time-consuming, treatments for the symptoms of Cystic Fibrosis (including intravenous antibiotics) may temporarily increase ppFEV1 by more than lumacafotr-ivacaftor, however these increases are short lived and the ppFEV1 of patients soon start to decrease again once intravenous antibiotics are stopped, requiring more hospitalisations and more time away from everyday life. Intravenous antibiotics, by their nature, are designed to be drugs that are used for finite periods of time, with their efficacy also waning over time in a patient population that needs to use them frequently. This means they are only ever provide a temporary increase in ppFEV1, by reducing infection levels in the Cystic Fibrosis lung, with this benefit being quickly lost as infection levels start to rise again. This means that the benefit of the ppFEV1 increase seen with these drugs should not really be compared with that seen from lumacaftor-ivacaftor, which due to the mechanism of the effect â€“ with the drug treating the underlying cause of the condition and designed to be taken continuously â€“ mean that this increase will provide a long-term increase/stabilisation of lung function rather than a temporary increase which is quickly lost. As a patient with Cystic Fibrosis I would also ask that the reduction in hospitalisations is recognised as clinically significant â€“ as is noted in the appraisal consulation document â€“ and that more weight is given to this when NICE make their final decision. I am 34 years old and have a full time job working as an education researcher, something that I am very passionate about. In addition I have a full and active life outside of work. However, over this past year I have been in hospital for 12 out of 52 weeks, with my condition worsening, as I age. This has taken a significant toll on my mental health and quality of life. I never know when I may need to go into hospital and this makes planning life events, including holidays and even my own wedding, very stressful as I am always filled with trepidation about whether I will be well enough to go ahead with plans. A reduction in the number of hospitalisations, along the lines of the effects seen in the lumacaftor-ivacaftor trial would therefore drastically improve my quality of life. As the consultation notes, due to the long-term nature of Cystic Fibrosis it is often hard for patients to assess their own quality of life compared to people without the condition and I therefore think the benefits of reduced hospitalisations may have been under-estimated. The fact that lumacaftor-ivacaftor is an oral tablet is also important. As a patient with Cystic Fibrosis I complete 3 hours of physiotherapy each day, 30 minutes of nebulized therapies and take 48 tablets. All of these treatments only slow my ppFEV1 decline and none of them result in an increase. The low treatment burden of lumacaftor-ivacaftor when compared with traditional treatments is therefore very important when considering whether it should be funded.

	In summary, having access to an effective treatment, which targets the underlying cause of Cystic Fibrosis, stabilises ppFEV1 and has a low treatment burden would be life-changing for me, my family and all other patients in the UK with the F508del mutation. I therefore ask that NICE reconsiders their draft guidance and that the drug is approved so that people with Cystic Fibrosis have the same opportunity as those without the disease to reach their full potential.
Submission date	9 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1339 The evidence about quality of life seems flawed. It seems to be saying that people with CF are used to feeling ill most of the time and see this as normal and so any improvement is negligible. I would also robustly question the lifestyle questionnaire itself: - who designed it? - was it co-designed with people with CF? - does it include questions about things which are important to people with CF rather than the general population? If it has been designed for a general population, this could potentially be discriminatory for people with CF, as the appraisal has admitted that the baseline for people with CF is skewed. The patient expert highlighted the huge negative impact that CF has on people's lives. This kind of evidence is hard to quantify and seems to have been given far less consideration than all the other numerical scientific evidence in the appraisal. If you asked people with CF which aspects of their lives are most important to them, you may need that these psycho-social aspects are more important to them than figures about BMI, FEV, etc. This appraisal seems to see people with CF as machines which can be measured, rather than human beings whose fears and feelings cannot be quantified and are therefore ignored. I actually cannot finish reading this appraisal as it's language and presentation is inaccessible and exhausting. I am currently exhausted from being a carer for my son, and the impact of that role means I don't have the energy to plough through this non-user friendly gobbledygook. I do think the appraisal should have included statements from people coping with CF - written statements about their everyday lives. This document is biased towards statistics and clinical language - I know you will argue

	that is a scientific necessity but I wish to argue that you are ignoring the psycho-social aspects at your peril. If people with CF cannot work full-time because of the unpredictability of their condition, what financial impact does that have on their lives and the country's economy? The appraisal does not include enough evidence about the complex psycho-social aspects of people's everyday lives and therefore discriminates against people with CF, as you are using scientific methods of assessment which ignore the complexity of CF. I wonder how many people with CF have actually contributed to your evidence? This consultation is inaccessible and will exclude a lot of people who will find this document linguistically biased towards clinicians and scientists. How can you say you have truly consulted with people with CF, when these documents are so hard to understand and don't reflect people's everyday lives and difficulties?
Submission date	9 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1340 Lumacaftor-ivacaftor is a highly innovative treatment for people with Cystic Fibrosis who are homozygous for the F508del mutation in the CFTR gene. It is the first treatment that targets the underlying gene deficiency, rather than merely managing the symptoms of the condition and as such should be considered as a significant breakthrough in the treatment of those with the F508del mutation. It is stated in the appraisal consultation document that the increase seen in ppFEV1 â€œmay not be clinically significantâ€• , however it is important to realise that for a patient with Cystic Fibrosis even a stabilisation in ppFEV1 would be highly beneficial. Meaning that the condition would not progressively worsen over time. Current, highly invasive and time-consuming, treatments for the symptoms of Cystic Fibrosis (including intravenous antibiotics) may temporarily increase ppFEV1 by more than lumacafotr-ivacaftor, however these increases are short lived and the ppFEV1 of patients soon start to decrease again once intravenous antibiotics are stopped, requiring more hospitalisations and more time away from everyday life. Intravenous antibiotics, by their nature, are designed to be

	drugs that are used for finite periods of time, with their efficacy also waning over time in a patient population that needs to use them frequently. This means they are only ever provide a temporary increase in ppFEV1, by reducing infection levels in the Cystic Fibrosis lung, with this benefit being quickly lost as infection levels start to rise again. This means that the benefit of the ppFEV1 increase seen with these drugs should not really be compared with that seen from lumacaftor-ivacaftor, which due to the mechanism of the effect â€“ with the drug treating the underlying cause of the condition and designed to be taken continuously â€“ mean that this increase will provide a long-term increase/stabilisation of lung function rather than a temporary increase which is quickly lost. As the partner of a patient with Cystic Fibrosis I would also ask that the reduction in hospitalisations is recognised as clinically significant â€“ as is noted in the appraisal consulation document â€“ and that more weight is given to this when NICE make their final decision. My fiancÃ© is 34 years old and has a full time job working as an education researcher, with an active life outside of work. However, over this past year she has been in hospital for 12 out of 52 weeks, with her condition worsening, as she ages. This has taken a significant toll on her and my mental health and quality of life, with the uncertainty making it very difficult to plan events. A reduction in the number of hospitalisations, along the lines of the effects seen in the lumacaftor-ivacaftor trial would therefore drastically improve our quality of life. As the consultation notes, due to the long-term nature of Cystic Fibrosis it is often hard for patients to assess their own quality of life compared to people without the condition and I therefore think the benefits of reduced hospitalisations may have been under-estimated. The fact that lumacaftor-ivacaftor is an oral tablet is also important. As a patient with Cystic Fibrosis, my fiancÃ© complete 3 hours of physiotherapy each day, 30 minutes of nebulized therapies and take 48 tablets. All of these treatments only slow her ppFEV1 decline and none of them result in an increase. The low treatment burden of lumacaftor-ivacaftor when compared with traditional treatments is therefore very important when considering whether it should be funded. While the preliminary recommendation is that this treatment is not cost effective, I do think that it is worth exploring if there is a way it can be made available to NHS patients. The Cystic Fibrosis Trust has suggested an interim arrangement between Vertex pharmaceuticals and the NHS, allowing for evidence about its long-term clinical impact to be collected by using the UK Cystic Fibrosis Data Registry. The long-term impact of the drug is likely to make it cost-effective, reducing the need for hospitalisations, other treatments and preventing lung transplantations in the long-term. It is therefore vitally important that this longitudinal data can be collected and that the long-term benefit can be assessed, as it is only through collecting this data that a fair assessment of its cost-effectiveness can be

	undertaken. In summary, having access to an effective treatment, which targets the underlying cause of Cystic Fibrosis, stabilises ppFEV1 and has a low treatment burden would be life-changing for my finance, our family and all other patients in the UK with the F508del mutation. I therefore ask that NICE reconsiders their draft guidance and that the drug is approved so that people with Cystic Fibrosis have the same opportunity as those without the disease to reach their full potential.
Submission date	10 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1341 As a scientist and father of a 19yr old boy who is homozygous Delta F508 I feel the committee has underestimated the importance of the benefits shown by Orkambi. Firstly the benefits of the major reduction in pulmonary exacerbations seen cannot be overestimated. These events can be major health threatening incidents that can be described as a â€˜lung attackâ€™ in much the same way as people suffer heart attacks. The cause of these attacks is usually microbial infection which even if cured, often leads to permanent lung damage and a reduction in FEV. In the appraisal document it is stated that hospital admission from such attacks are on average 21.7days and treatment is 12-14 days. While the 12-14 treatment days may refer to the length of time the person is on intravenous antibiotics in hospital the actual treatment for these infections usually goes on for months not days, typically three to six months of nebulised antibiotics and DNase and/or heavy doses of oral antibiotics etc. It is successive pulmonary exacerbations that lead to the major loss of lung function and any treatment that can significantly reduce them will have a much greater impact over the long term than is currently been accounted for in the drug appraisal. Secondly I would like to suggest that the committee has underestimated the value of Orkambi on the rest of the body. One of the other systems significantly affected in CF is the digestive tract and while dietary enzymes may deal with pancreatic insufficiency they do not tackle the thick mucus which lines the intestines. This mucus not only reduces uptake of nutrients leading to low BMIâ€™s and susceptibility to

	infection but can also clog the intestine. Many people with CF suffer with chronic constipation for which there is no treatment other than powerful laxatives, while others have to have feeding tubes inserted to try and increase their weight. CF related constipation can result in debilitating abdominal pain for days, unrelieved by pain killers while waiting for the strong laxatives to work. Anything that helps the digestive system work better would be a miracle. The increase in BMI observed by those taking Orkambi during the relatively short trial shows that the drug is functional in the digestive tract and should be a real asset in this department. Finally most people fail to understand the amount of work that is required by those inflicted with CF just to try and stay healthy, adherence to treatment is a significant problem in CF. The large treatment burden of multiple bouts of nebuliser treatment with all the associated washing and cleaning , bouts of physio, multiple tablets , dietary considerations etc. All this is expected of young people who just want to get on with life and be normal, young people trying to study at school or university, heading out to work, exploring the world. Many of the treatments currently associated with CF just get in the way of â€˜normalâ€™ life. That is why Orkambi, which is just a couple of pills twice a day, has 96.5% adherence rate, so even though itâ€™s currently observed benefit over conventional treatment in the trials has not met all the hopes of those involved, I would suggest that in the â€˜real worldâ€™ where not everyone is as motivated to do their treatment as those volunteering for trials, it would still be a real asset in the treatment of CF. Even the most recalcitrant teenager can manage some pills! It seems clear that Orkambi could be life changing if not life saving for some with CF if given the chance. It may offer them the chance to stay strong and healthy enough to benefit from the other new treatments that may come along in time, but they are in the future while Orkambi is now. If a better/cheaper drug comes along great, but it is of no benefit to you if you are dead. We are talking about the life and future of a group of young people who just want to be like the rest of us and we should help achieve that goal.
Submission date	10 April 2016

Name	[redacted]
Organisation	
Role	Parent of person with cystic fibrosis
Job title	
Location	England
Conflict	No
Disclosure	

Comments	1343 As the parent of a 19 year old and being his carer for 17 years I have much experience to draw on. The implications of lung exacerbations seem to have been poorly understood by NICE. They have two separate effects. The first is the amount of time and cost of treatment dealing with the exacerbation itself and the second is the consequent lung damage caused by the exacerbation. Firstly, an exacerbation does not just last for 2 weeks. The exacerbation manifests as an increase in physical symptoms and suffering of the patient and worsening of lung function. Because of the sticky mucus in the lungs there can be a prolonged period of time in which the cause of the exacerbation cannot be determined. In the case of my sonâ€™s last exacerbation, this period was 4 months. During this time there were many visits to hospital, with breathing difficulties, sometimes on a weekly basis, not only to try and alleviate the symptoms but also to try and determine the cause. Treatments do not always work, which can lead to chronic infection and more rapid deterioration on lung function. Treatments themselves have side effects and can damage the liver and kidneys. CF related liver disease can preclude intravenous Tobramycin for that reason. Even when IVâ€™s are done at home, there can be problems with the lines meaning stays in hospital and cost of nurses have to checking blood levels during the course. An exacerbation also makes it more likely for other pathogens to colonise the lungs e.g. my son was growing Aspergillus and Mycobacterium avium initially, causing damage and lung disease, then was colonised by Pseudomonas aeruginosa and Stenotrophomonas maltophilia. The exacerbation lasted for years causing lung disease and a permanent cough which were not there before the event. In terms of financial cost it has meant increased hospitalisations, cost of drugs to try and treat them, increased clinic visits in hospitals, lost days at work for myself and my husband, inability of myself to work in a full time well paid job (I had to give up a job in senior management to take a low paid part time job), lost days at school and then university, associated stress and anxiety, loss of sleep by the patient and other family members due to coughing, increased expense due to many trips to hospital, some a long way off when at university and increased food costs as he tries to replace calories that are being consumed by his body trying to fight the infection. The second consequence of an exacerbation is lung damage. Lung damage cannot be reversed. If the person recovers from the exacerbation, they are starting from a lower baseline because their lungs do not work as effectively and this happens

	time and again with each new episode, until the lungs are destroyed and the person drowns in their own mucus. Reducing exacerbations is therefore of critical importance when treating Cystic Fibrosis and Orkambi has been shown to do this. I have seen the refusal of NICE to recommend Orkambi being referred to as a disappointment. A disappointment is when you cannot go on holiday, or when you do not get the job that you want, or when your exam results are worse then you hoped. Disappointments are things that people with Cystic Fibrosis have to deal with every single day of their short lives and we are talking about thousands of people. Research and treatments for this group of people have consistently fallen short of that needed for decades and when a drug is finally developed which NICE have agreed is beneficial and which is available for people in other countries is refused, it is an utter travesty and a disgrace. Orkambi is not designed to be a cure for Cystic Fibrosis, but it is the only medicine which works towards correcting the flaw that causes the disease. There are no other medicines available that do this, all the others do is to try and stave off the inevitable early death. Orkambi buys time for people while research continues. By refusing to fund Orkambi you are writing off a whole section of our society of young people, with so much to offer and deeming that they are not worth saving. Your decision is ethically, morally and clinically unjustifiable.
Submission date	12 April 2016

Name	[redacted]
Organisation	
Role	Public
Job title	Community Development Worker
Location	England
Conflict	No
Disclosure	I have contact with families who are affected by cystic fibrosis and am aware of the effects of the condition.
Comments	1344 Please take into account the Cystic Fibrosis Trust's proposal on making Orkambi available to certain people through an interim arrangement between the drug's manufacturer and the NHS. It is accepted that Orkambi helps with the management of the condition and reducing the number of hospitalisations, therefore this saving needs to be balanced out against the cost of the

	drug.
Submission date	12 April 2016

Name	[redacted]
Organisation	
Role	Public
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1345 That the reduction in sudden hospitalisations alone should be considered as a great improvement to those with this condition
Submission date	12 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	Parent of 5 year old with Cystic Fibrosis
Location	England
Conflict	No
Disclosure	
Comments	1349 I urge you to consider the cost benefits of 'holding back the tide' of Cystic Fibrosis. My son was born nearly 6 years ago when substantial benefits had been made in antibiotic treatment and pancreatic treatment (with enzymes) so that patients no longer died in childhood with CF. However, this prolonged life is one of huge expense to the NHS as the patients become progressively ill, with frequent hospitalisations, development of CF related diabetes and in some cases transplant. My son, [redacted], had a lung function of 110+% until his first hospitalisation following a severe chest infection. It now is never more than 93%. He had to have a Bronchoscopy, IV antibiotics and 14 days stay up at Kings College Hospital with amazing around the clock, multi-disciplinary care. That was his first major set-back. He now has to have daily DNase (Â£500+ a month) twice daily Promixin (another expensive drug) Domperidone and Omeprazole, that he did not require before. I know that the next hospitalisation will be just as costly to his health and to the NHS. Since birth [redacted] has seen Specialists, physiotherapists and dieticians every month. He has had too many courses of antibiotics to count and this is all before he's 6 years old. I know worse is to come, if we cannot access new drugs that 'hold back the tide' of CF while a better and more

	decisive treatment - or even cure - comes along. [redacted] and all other patients are loosing lung function after every hospitalisation, so the next one comes sooner and the effects are worse and the spiral continues. As a drain on the NHS they become more and more so as they age. I am aware that my son is using up probably 1000+ patients allocation of funds within the NHS and is still getting progressively more ill, so progressively using more funds. If a drug that can slow this progression is expensive it needs to be balanced against what it is saving in future cost and that is not only in hospitalisations. If more people with CF can be fit enough to work at age 18/21 they can contribute to society and pay back some of the funds they've had in NI payments. They will not be a future drain on public funds. Most people with CF are so grateful for their life, that given any opportunity for increased wellness they will use it positively. This is all aside from how much mentally more healthy a person can be when their general health is better and they have a full potential for a lot longer. I urge you to consider the medical, emotional and societal benefits that slowing the onset of CF has. While short term gains in lung function might appear moderate on the face of it, the effect that small percentage has on the frequency of hospitalisations is huge., saving every patient, the NHS and society from a large amount of money and detriment to health and wellbeing.
Submission date	13 April 2016

Name	[redacted]
Organisation	
Role	Public
Job title	Retired Statistician
Location	England
Conflict	No
Disclosure	
Comments	1350 I hope the committee will consider carefully the compromise suggestion put forward by the Cystic Fibrosis Trust. And also take into account the extra costs of withholding this treatment, in terms of the foregone costs of reducing sudden hospitalisations and the stress illnesses caused to CF sufferers and their carers if they are left feeling that NICE is not sympathetic to their situation.
Submission date	13 April 2016

Name	[redacted]
Organisation	
Role	Grandad of a sufferer
Job title	Electrician
Location	England
Conflict	No

Disclosure	
Comments	1351 I feel that this drug is very important and even as a non medical person it will help to keep overall costs of hospital stays/transplants down. Surely if this drug can extend lives and also give better quality of life to C F sufferers it is essential. It would also be important in helping parents and sufferers themselves to be in full time employment and live a normal life. My granddaughter of 1 years old and is a CF sufferer would benefit greatly as she has the F508 mutation.
Submission date	13 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	CF Parent
Location	England
Conflict	No
Disclosure	
Comments	1352 By not approving ORKAMBI, you are helping people to die. I believe that American CFers are not different from British CFers. If they are getting benefitted how can you say that the impact of the drug is not significant. Let every CFer decide how ORKAMBI affects him or her. The one who is suffering should be the judge and not the one who is treating....It is simply unacceptable that some people decide on how long others should live, just to save the money ...
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	Dr Retired technical director [redacted]
Location	England
Conflict	No
Disclosure	
Comments	1353 I write this from the point of view of a grandfather of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a

	certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1354 I write this from the point of view of a auntie of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,)

	Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.
Submission date	14 April 2016

Name	[redacted] [redacted]
Organisation	
Role	Carer
Job title	Grandmother of patient with CF
Location	England
Conflict	No
Disclosure	
Comments	1355 I love my little grandson so much and desperately want some new treatments to come out that can help him. I understand from my daughter, who keeps me updated with information on CF drugs, that Orkambi could help slow down the progression of CF and reduce the amount of time people with CF have to spend in Hospital. [redacted] is a wonderful, intelligent little boy, doing well at school. He loves Sports and does so well with his Mum taking all his medications and treatments. Please re-consider your advice on Orkambi because anything that helps [redacted] and others like him would be a blessing. Thank you
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1356 I write this from the point of view of a grandmother of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated.
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer

Job title	
Location	England
Conflict	No
Disclosure	
Comments	1357 I'm very disappointed with the initial recommendation... My son has a lung function of just over 30% and even a very small percentage improvement makes him feel considerably better. As you say yourselves, Orkambi reduces hospital admissions which must almost mean that it would pay for itself. I fully accept that the cost of new drugs to the NHS must be considered carefully but genuinely feel this recommendation is wrong. Probably none of you have a child with Cystic Fibrosis.
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1358 As parents of a little boy with F508del Cystic Fibrosis, the results showing Orkambi to increase lung function and reduce infection and hospital stays are very significant, extremely important and give us (our son and us as parents and carers) hope for the first time since he was born. That's why we are asking NICE to recommend Orkambi maybe with the solution put forward by the CF Trust to provide Orkambi to patients while further evidence is collected on its long-term clinical impact using the UK Cystic Fibrosis Data Registry. Please give us the chance to see if this medicine will give us the benefits we desperately need. Thank you, from tired, sad, unhappy and depressed but hopeful parents.
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	Mother/Teacher
Location	England
Conflict	No

Disclosure	
Comments	1359 I write this from the point of view of a mother, my son is 3 years old and has Cystic Fibrosis. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF, if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, as they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,00 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased to receive the medication and report on its effectiveness or otherwise, I know we as a family certainly would be. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated. Thank you for your time. [redacted]
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Patient
Job title	Construction Manager

Location	England
Conflict	No
Disclosure	
Comments	1360 My name is [redacted]. My son [redacted] was born on the 12th June 2010. 3 weeks later we had the horrifying news that he had the condition (Cystic fibrosis) Our life's have been turned upside down, but we manage to cope as you have to. Let's talk about [redacted]. He's already been in hospital for 2 weeks on course of I v's & many other children with CF have been hospitalized many times. All Luis's family from my side & his mums are & have always been get up & goers , hard workers & always paid our way in this life. [redacted] is the same, he is a determined Young boy & I will want take the bull by the horns everyday of his working life, please don't hold him back from this by not funding drugs that could help him stay well & get out of bed in the morning & go to work to earn a honest living & contribute to the N I, Or are you saying you can't afford to fund these drugs? Let CF suffers be unwell & be in hospital & cost NHS more money. There are many people out there wwho have good health & able bodied & drain the system. Please fund the new drugs that people are spending brain taxing time researching these new life changing drugs to change the life's of people, then you won't fund them. With tears [redacted]
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Patient
Job title	
Location	England
Conflict	No
Disclosure	

Comments	1361 I am 32 and suffer from CF. My lung function is 32% (FEV1) and I notice every single percent, I'm able to predict what my lung function will be before I take the test. Anything that can give me even a few extra percent would be literally life changing as it'd mean I could jog and do more exercise, which is currently difficult. Also, the main thing I struggle with is numerous exacerbations following one after the other. This often requires IV or oral antibiotics which can be a big practical distraction to every day life. Anything that can help keep me stable and reduce the ups and downs would be worth its weight in gold to me and make my life more predictable and help me plan better for the future.
Submission date	14 April 2016

Name	[redacted]
Organisation	
Role	Public
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1362 I write this from the point of view of an uncle of a young boy suffering from CF. Whilst progress has been made over the last few years with the introduction of the Guthrie heel prick test and consequent analysis the introduction of a screening test of potential parents is still considered to be not cost effective to be universally and routinely introduced. (This screening of prospective parents could effectively and efficiently eliminate CF if it was adopted). As this has not been implemented a certain proportion of new borns will be born with CF (approx. 5 a week,) Whilst Orkambi does not improve lung function, it has beneficial clinical effects on CF sufferers with the CF F508del mutation. Results have been shown to stabilize the symptoms of deterioration associated with CF. This must be considered as a positive in that the need for heart/lung transplants of those affected will reduce. A saving in both NHS resources and patient and relatives trauma. The median age of death is 28 and most sufferers spend 3 hours a day attempting to manage their conditions with most spending weeks each year receiving acute intensive hospital treatment for the treatment of lung infections and other complications. NHS beds and other resources that could be available for others. IF NICE, has they have reported, is uncertain about the long term clinical impact even though they agree that there are clinical benefits of sufferers taking the drug, it must be in their

	interest to support and be involved in a longer term evaluation. As there are a limited number of sufferers of CF with F508 Del mutation (the Cystic Fibrosis Trust suggests over 3,000 but less than 10,000) then I am sure that these sufferers and/or their relatives would be only too pleased for sufferers to receive the medication and report on its effectiveness or otherwise. I sincerely hope that when NICE reviews its findings a route can be found to enable those CF sufferers with the CF508 del strain to be allowed some management of their immediate condition whilst the longer term clinical effectiveness is evaluated
Submission date	15 April 2016

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	1363 Vertex have made significant steps towards the revolutionary treatment of people with Cystic Fibrosis. Unfortunately it would seem that the analysis made by NICE of Orkambi appears short termed in its views. Cystic Fibrosis is a gradual disease - with relatively small reductions in lung function each year culminating to a point when the patient is typically 30-40 and their lungs eventually can cope no more. Therefore a drug like Orkambi does not need to see dramatic effects but merely reduce or even stop this gradual decline. The sooner Orkambi can ben taken, the sooner this decline can be reduced, with the hope that patients could have a near normal life expectancy. My daughter is 4 years old, she is healthy and her lungs have very good function - I have done everything I possibly can to keep her this way - encouraging her to be active, ensuring she is nt in higher risk environments, giving her percussion 2-3 times per day. All of this has been in the hope I can keep her as well as possible until a revolutionary new drug can come along. Well it would appear that revolutionary drug has come along, but the analysis taken by Nice has nt addressed the bigger picture of the fact that CF is a gradual disease. Yes it would be great if it could take a person with CF with a 40% lung function and improve it drastically. But for my daughter, 1000's of others and every future generation Orkambi could be enough - please don't rob my daughter of her future when it appears modern science does nt need it to be this way. I would also point out that Vertex has a pipeline of future drugs for cystic fibrosis, and in particular the most common DD508 mutation that Orkambi treats. Clinical trials on these "second

	generation correctors" are showing to be 3 times as effective as Orkambi which would obviously be fantastic and could be in clinic within two years. Could Nice, NHS, and Vertex not come to agreement where Orkambi can be agreed upon for now, knowing that it would help stop lung function declines until these second generation correctors are available, and which given their results, Nice would have to recommend.
Submission date	15 April 2016

From: [redacted]
Sent: 25 April 2016 11:27
To: Martyn Burke
Cc: Kate Moore; Fay McCracken; [redacted]; [redacted].; [redacted]
Subject: RE: Potential additional data: Cystic fibrosis - lumacaftor and ivacaftor [ID786]

Dear Martyn,

Many thanks for your email. G.J. is currently out of office, so I'm responding on behalf of Warwick Evidence.

Please see below our responses to issues 8-10.

Issue 8 – Rate ratios for all pulmonary exacerbations
The ERG thinks the company has a reasonable case here, as the model they use to relate ppFEV1 to number of exacerbations (Goss - reference 69 in the original submission) only uses exacerbations requiring hospitalisation or IV, so it isn't easy for the company to go beyond that. However, we note that the company then used this number in their Liou equation for adjusting mortality (Table 44) which the ERG believes uses all exacerbations (not just those requiring hospitalisation or IV) . Therefore we do still have this concern that the company may be over-estimating mortality reductions.

Issue 9 - Double-counting of pulmonary exacerbation costs
The ERG thinks the company is correct here. In our ERG report we have not stated that the company may be double counting cost reductions. However, the ERG believes that the company may be double counting quality of life gains and mortality reductions, and that they may be overestimating cost reductions by using the 61% reduction, but we do not consider that they are double counting cost reductions.

Issue 10 - Treatment effects after discontinuation
The ERG thinks that the company has a reasonable case here. It is perfectly reasonable to be concerned that a) the model assumes some benefits e.g. that BMI persists indefinitely and b) the base-case assumes that no-one discontinues post 24-weeks. However, worrying about the treatment effect up to 24 weeks is not reasonable as that is a weighted average of the effects of those who did and did not discontinue in the trial. Unless we believe the levels of adherence would be substantially lower in the real world than in a trial, we do not think this statement is relevant.

Many thanks,
[redacted]

[redacted] | Warwick Evidence | Division of Health Sciences | Warwick Medical School | University of Warwick