National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Thoracic Society	The 2 populations are appropriate. Tezacaftor/ivacaftor would be used in Homozygous DF508 patient only, as this is the group studied in the Phase 3 study.	Comment noted. No changes to the scope are needed.
	Cystic Fibrosis Trust	This topic is important. There is an unmet need in cystic fibrosis with no disease modifying treatment available for this indication.	Comment noted. No changes to the scope are needed.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Yes	Comment noted. No changes to the scope are needed.

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	Cochrane Cystic Fibrosis and Genetic Disorders Group	This is an appropriate topic to be referred to NICE as it should be considered a priority issue in the treatment of patients with CF.	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	A NICE STA process is *not the appropriate* mechanism to assess Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation for the following reasons: 1. Vertex believes tezacaftor/ivacaftor should be subject to an appropriate Health Technology Appraisal for its use within the NHS 2. Vertex is of the opinion that an STA process evaluation would result in a negative decision on a cost effectiveness 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 Tezacaftor/ivacaftor represents 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	Comments noted. The topic selection group agreed that the STA process is appropriate to appraise this technology.

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		• For CF, demonstrating gains in QALYs is challenging because CF is a genetic disorder with manifestations from birth, individual's life expectations are therefore impacted and so they score very high in terms of their quality of life on standard of care (SOC). This makes showing a significant improvement in these scores much more challenging with the addition of new therapies • Treatments which extend life have increased costs compared to SOC, and also the survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms 4. The NICE STA process is far better suited to CCG funded non-specialised medicines. Currently specialised treatments for CF are specialist commissioned by NHS England and not via CCG funding routes 5. A negative NICE STA decision would lead to no access for a patient population with significant unmet need and a reduced life expectancy. This would result in a detrimental impact on CF patients' health and lives, CF caregivers lives and would create a higher burden of care on the NHS 6. Although the medicine does not qualify for NICE HST appraisal, elements of the NICE HST process are appropriate for this medicine, including: a. Stakeholder-led process b. Lower emphasis on QALY c. Holistic and ethical approach to account for the positive impact this precision medicine could have on people with CF and their carers	

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Wording	Cystic Fibrosis Trust	Please amend the remit to accurately reflect the expected indication: "for treating cystic fibrosis in people with the F508del mutation" should be replaced with "people with cystic fibrosis (CF) ages 12 and older who have two copies of the F508del mutation or one F508del mutation and one residual function mutation"	Comment noted. The remit states that tezacaftor and ivacaftor combination therapy will be appraised within its marketing authorisation. No changes are needed.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Yes	Comment noted. No changes to the scope are needed.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	Yes	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	Yes	Comment noted. No changes to the scope are needed.
Timing Issues	Cystic Fibrosis Trust	Urgent. Tezacaftor and ivacaftor combination therapy appears an effective therapy on a selected group of patients with cystic fibrosis with unmet need.	Comment noted.
	NHS England Specialised Commissioning	This will be a welcome addition to the current therapies for CF if NICE deem it to be cost effective.	Comment noted.

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	Specialised Respiratory Clinical Reference Group		
	Cochrane Cystic Fibrosis and Genetic Disorders Group	It is considered that there would be some urgency to this appraisal as the impact on quality and disease burden has the potential to be significant.	Comment noted.
	Vertex Pharmaceuticals	It is of great concern that timely patient access would not be facilitated by NICE STA process and that most orphan medicines previously assessed via a NICE STA have not been positively recommended	Comment noted. Technology appraisals are scheduled to provide guidance to the NHS as soon as possible after the marketing authorisation is granted. No changes to the scope are needed.
Any additional comments on the draft remit	Vertex Pharmaceuticals	Even though disease specific quality of life instruments are available for CF (e.g. CFQR) these do not capture fully the significant health related quality of life benefits of treatments which address the underlying cause of the disease rather than the symptoms. These benefits include the impact on academic and professional achievements, changes in patients' life ambitions and goals and reducing family/caregiver concerns about their children's futures. There is also a significant impact on carer's lives including ability to work which is not captured in the STA process.	Comment noted. The company is encouraged to identify and provide necessary evidence for any potential uncaptured benefits of the technology in its evidence submission.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Cystic Fibrosis Trust	Please amend the remit to accurately reflect the expected indication: "people with cystic fibrosis (CF) ages 12 and older who have two copies of the F508del mutation or one F508del mutation and one residual function mutation" The UK CF Registry 2016 report is now available and data from the report should be updated and referenced. Please reference The Cystic Fibrosis Trust (2017), UK CF Registry: 2016 annual data report. Accurate data detailing the total indication of this technology is available in the UK CF Registry 2016 report. The relative incidence of homozygous F508del is irrelevant to this technology appraisal. The background information misrepresents authorised medicines that target F508del mutations. Please amend this information: Proposed wording - "There are currently no treatments that target F508del mutations in the CFTR gene available on the NHS. Lumacaftor/ivacaftor is authorised for the treatment of cystic fibrosis F508del homozygotes throughout the European Union but currently is not recommended for use by the NHS (NICE technology appraisal 398).	Comment noted. The remit states that tezacaftor and ivacaftor combination therapy will be appraised within its marketing authorisation. The reference to the latest UK CF Registry report has been updated in the scope. The scope is intended to provide a general overview of any available treatment options to the NHS for the treatment of cystic fibrosis homozygous or heterozygous for the F508del mutation. The scope has been amended to make this clearer.

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			For information, the technology appraisal on lumacaftor/ivacaftor is acknowledged in the relevant NICE recommendations section of the scope.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Yes	Comment noted. No changes to the scope are needed.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	Considered to be accurate.	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	It should be noted that Ivacaftor (Kalydeco) is a commissioned treatment for patients with certain gating mutations that treats both the symptoms and the underlying cause of the disease And lumacaftor/ivacaftor has been available for over two years and received a negative recommendation from NICE in 2015 and is not currently routinely available for patients with the F508del mutation	Comment noted. No changes to the scope are needed. The background information is intended to provide a general overview of any available treatment options to the NHS for the treatment of cystic fibrosis

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			homozygous or heterozygous for the F508del mutation only. For information, the technology appraisal on lumacaftor/ivacaftor is acknowledged in the relevant NICE recommendations section of the scope.
The technology/ intervention	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Yes	Comment noted. No changes to the scope are needed.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	Yes	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	Yes	Comment noted. No changes to the scope are needed.

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Population	British Thoracic Society	Although in the description there is a reference to the age, there is no mention of age in the scope section although obviously the research currently has only been done in 12+years. There should therefore at least be an acknowledgment that the population in the scope goes down to 12+years	Comment noted. The population is kept broad at this stage because the technology is yet to receive a marketing authorisation in the UK. However, the remit states that tezacaftor and ivacaftor combination therapy will be appraised within its marketing authorisation. Therefore the appraisal will focus on the specific population covered by the marketing authorisation. For information, the technology section of the scope acknowledges the age group included in the clinical trial. No changes to the scope are needed.
	Cystic Fibrosis Trust	Please amend the remit to accurately reflect the expected indication: "people with cystic fibrosis (CF) ages 12 and older who have two copies of the F508del mutation or one F508del mutation and one residual function mutation"	Comment noted. The population is kept broad at this stage because the technology is yet to receive a marketing authorisation in the UK. However, the remit states that tezacaftor and ivacaftor combination

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			therapy will be appraised within its marketing authorisation. Therefore the appraisal will focus on the specific population covered by the marketing authorisation. For information, the technology section of the scope acknowledges the age group included in the clinical trial. No changes to the scope are needed.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	The populations are: 1. Phe508del homozygous, and 2. Phe508del/residual function (not all heterozygotes as in the draft TA)	Comment noted. The populations have been updated in the scope.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	The population identified is considered to be appropriate for this intervention.	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Comment noted. No changes to the scope are needed.

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		No	
Comparators	British Thoracic Society	In DF508 patients Ivacaftor /lumicaftor is being used through a compassionate use programme for those with fev1 less than 40% in most large CF centres in the UK. Although this is not funded on the NHS, as the technology appraisal XTA 398 did not recommend its use.	Comment noted. Ivacaftor/ Lumacaftor was not included as a comparator because it is not considered established practice in the NHS for treating cystic fibrosis homozygous or heterozygous for the F508del CFTR mutation.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	There is not a true comparator for Phe508del/residual function patients	Comment noted.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	The comparators are representative of best supportive care currently used in the NHS.	Comment noted. No changes to the scope are needed.
	Vertex Pharmaceuticals	None.	Comment noted. No changes to the scope are needed.

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Outcomes	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	It is unlikely mortality difference will be apparent in a short time frame Respiratory symptoms will not be captured alone, but will be part of QOL scores – suggest remove respiratory symptoms and keep QOL scores Suggest use rescue antibiotic use as a surrogate for "frequency and severity of acute infections" CF is a multisystem condition. The data will not capture the other potential benefits on the systems non-respiratory eg arthropathy, bowel symptoms, fatigue, etc	Comments noted. The outcomes in the scope are consistent with the outcomes identified by stakeholders during the scoping and appraisal of lumacaftor/ivacaftor (TA398). The appraisal committee will consider any additional outcomes presented to it as part of the evidence base if this topic is referred for appraisal. No changes to the scope are needed. Rescue antibiotic use will fall within the general outcome of "frequency and severity of acute infections".

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	Cochrane Cystic Fibrosis and Genetic Disorders Group	These outcomes are inclusive and capture objective and subjective clinical parameters used in Cystic Fibrosis care	Comments noted. No changes to the scope are needed.

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	Vertex Pharmaceuticals	No - Other outcome measures must be included 1. Pulmonary exacerbations should be included because: a. These are significant clinical events in the lives of CF patients and caregivers b. They have an effect on longer term outcomes, being associated with an accelerated decline in lung function, a greater risk of death and lung transplant and an impact on CF patients quality of life The financial and psychological patient impact of avoidance of unplanned hospitalisations should be taken into account to reflect the potentially significant economic and clinical patient impact. For pulmonary exacerbations associated with hospitalisation, the mean length of stay in the UK was 9.2 days (Bradley et al, 2013) and costs from £5000 to £8000 per episode (Ragopalan et al, 2014)	Comment noted. The current scope already includes pulmonary exacerbations and the need for hospitalisation and other treatments as outcomes of interest. No changes to the scope are needed.
Economic analysis	Cystic Fibrosis Trust	The time horizon of tezacaftor and ivacaftor combination therapy is bound by the development of 'triple combination' therapies.	Comment noted.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	What would be considered "sufficiently long" when considering estimates of clinical and cost effectiveness?	Comment noted. The Guide to the methods of technology appraisal 2013 notes that the time horizon used in the NICE appraisal should reflect

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			the period over which the main differences in health effects and use of healthcare resources between interventions are expected to be experienced.
	Vertex Pharmaceuticals	1. Whilst the reference time horizon is accepted the issues with extrapolation in limited clinical data is unlikely to reflect accurately the benefit for the patient. 2. Technological innovation and precision medicines cannot be adequately recognised within the current NICE STA process cost analysis techniques as the established cost effectiveness thresholds are not appropriate for orphan disease high value / low volume patient populations 3. There is a need to consider the issues that cost/clinical effectiveness evaluation should address, including wider holistic and societal benefits to the patient, caregiver, family and society. Vertex are concerned that this will not be accurately reflected in the current NICE STA process 4. NICE STA process cost effectiveness thresholds are not appropriate to accurately incorporate the wider societal benefits of the medicines that treat CF patient populations 5. The NICE STA process considers absolute health gains rather than relative health gains, which is challenging for rare diseases with short life expectancy 6. For CF, demonstrating gains in QALYs is challenging because CF is a genetic disorder with manifestations from birth, so patients score very	Comment noted. The Guide to the methods of technology appraisal 2013 notes that the cost effectiveness of a technology is a necessary, but is not the sole, basis for decision-making. No changes to the scope are needed.

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		high in terms of their quality of life on SOC, meaning it is not possible to significantly improve these scores with the addition of new therapies **7.** Treatments which extend life have increased costs compared to SOC, and also the survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms	
Equality and Diversity	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Not aware of any issues	Comment noted.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	As this intervention will be appropriate for those heterozygotes or homozygotes with F508del mutation there would appear to be equality of opportunity.	Comment noted.
	Vertex Pharmaceuticals	1. There is an ethical duty to provide a fair appraisal of this precision medicine 2. The current NICE STA process is not designed for the context of high value / low volume orphan diseases. 3. If tezacaftor/ivacaftor were to receive a negative decision there would still be a significant burden of disease for these CF patients. In other areas of similar burden, such as cancer, there are alternative forms of funding that is currently available (e.g. the Cancer Drug fund)	Comments noted. No changes to the scope are needed.

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		There is potential for inequality of access for CF patients based on their genotype. For example if a CF patient had a G551D mutation then they would be eligible to receive a precision medicines that treats the underlying cause of the disease on the NHS ie: ivacaftor (Kalydeco): ref http://www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf	
Other considerations	Cochrane Cystic Fibrosis and Genetic Disorders Group	Potential additional outcome measure would be exercise tolerance which can be a useful predictor of life expectancy.	Comment noted.
Innovation	Cystic Fibrosis Trust	Yes. Current treatments manage the symptoms and complications rather than the cause of the disease. There is an unmet need in cystic fibrosis with no disease modifying treatment available for this indication. Tezacaftor and ivacaftor combination therapy is a disease modifying therapies that targets the root cause of cystic fibrosis disease. Tezacaftor and ivacaftor combination therapy has the potential to preserve or restore lung function, slowing the rate of decline and positively impacting life expectancy. This effect is unparalleled by any other current treatment option for this indication (excluding lung transplant). This technology is a step change therapy, constituting a fundamental shift in the treatment of cystic fibrosis.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	Yes This is the first ever medication to act on the basic defect in CF for patients who are homozygous for Phe508del carry a copy of the Phe508del mutation and a residual function mutation and therefore represents a significant step change in the management of this condition. Other available treatments for these patients only tackle the downstream consequences of CFTR dysfunction therapies	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.

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		The therapy will also act on the other multisystem abnormalities that occur as a result of CFTR dysfunction, such as arthropathy, fatigue, bowel disturbance, etc.	
	Cochrane Cystic Fibrosis and Genetic Disorders Group	Tezacaftor/Ivacaftor offers people an oral treatment option that has potential to ease the treatment burden In addition this treatment would likely be offered as an adjunct to current best supportive care until health related benefits are evidenced.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
	Vertex Pharmaceuticals	Yes – for the following reasons 1. Tezacaftor/ivacaftor is a highly innovative medicine in an area of severe unmet need, providing a treatment that changes the course of disease for a specific proportion of CF patients with specific genetic mutations. 2. Tezacaftor/ivacaftor continues to demonstrate Vertex's ongoing commitment to developing new precision medicines to improve quality of life for CF patients, their caregivers and families. This level of innovation is not benchmarked or weighted appropriately by a NICE STA process Life Sciences Minister and NICE leaders acknowledge current processes require reform to adapt to the requirements of emerging precision medicines	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
Questions for consultation	British Thoracic Society	*How should best supportive care be defined? Are the outcomes listed appropriate?*	Comments noted. No changes to the scope is needed.

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		It might be better to say “standard care” rather than best supportive care. The outcomes are appropriate. *Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom tezacaftor in combination with ivacaftor is expected to be more clinically effective and cost effective or other groups that should be examined separately?* No, not at this stage. *Do you consider that the use of tezacaftor in combination with ivacaftor can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Results of Phase 3 study N Engl J Med 2017; 377:2013-2023 – show well tolerated with less side effects compared to Orkambi. Fev1 increases of 6.8 % relative change compared with placebo. *Please identify the nature of the data, which you understand to be available to enable the Appraisal Committee to take account of these benefits.* N Engl J Med 2017; 377:2013-2023 *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* There are no barriers to adoption	

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	Cystic Fibrosis Trust	The NICE Clinical Guideline (NG78) was published in October 2017.	Comment noted. This has been updated in the scope.
	Cochrane Cystic Fibrosis and Genetic Disorders Group	As cost has not been specified or estimated there may be concern that this is a potential barrier to adoption of Tezacaftor Ivacaftor combination therapy.	Comment noted.
Additional comments on the draft scope	NHS England Specialised Commissioning Specialised Respiratory Clinical Reference Group	The 2 references should be included in the document: Taylor-Cousar et al, Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508delN Engl J Med 2017; 377:2013-2023 November 23, 2017DOI: 10.1056/NEJMoa1709846 Rowe et al, Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis N Engl J Med 2017; 377:2024-2035 November 23, 2017DOI: 10.1056/NEJMoa1709847	Comment noted. The references has been added to the scope.
	Vertex Pharmaceuticals	1. The NICE STA process is not an adequate mechanism to assess precision medicines for small patient populations / orphan diseases because: • NICE STA process cost effectiveness thresholds are not appropriate to accurately incorporate the wider societal benefits of the medicines that treat CF patient populations	Comment noted. The topic selection group agreed that the STA process is appropriate to appraise this technology.

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		• 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 SOC, meaning it is not possible to significantly improve these scores with the addition of new therapies. • Treatments which extend life have increased costs compared to SOC, and also the survival benefits which accrue much later in life are discounted, significantly reducing their value in today's terms.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health