Single Technology Appraisal

Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [ID6132]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [ID6132]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Eli Lilly

2. **Comments on the Draft Guidance Document from experts:**
   a. Kirstie Purnell – patient expert, nominated by AMEND

There were no comments on the Draft Guidance received through the NICE website

3. **External Assessment Group critique of company response to the DG**

4. **NICE Managed Access Feasibility Assessment**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2024. Please submit via NICE Docs.

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

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

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive summary Lilly appreciate the opportunity to comment on the NICE draft guidance document (DGD) for the appraisal of selpercatinib in advanced thyroid cancer with rearranged during transfection (*RET)* alterations that have not been treated with systemic therapy. While Lilly are disappointed to learn that the appraisal committee's initial decision is to not recommend selpercatinib within this patient population, Lilly is committed to continue working with NICE to address the appraisal committee's key concerns, and are hopeful that these issues may be resolved to allow selpercatinib to be recommended for use within the National Health Service (NHS). Lilly would firstly like to reiterate the severe unmet need experienced by patients with untreated, advanced *RET*-mutant medullary thyroid cancer (MTC) and *RET*-fusion positive thyroid cancer (TC); patients with advanced stage thyroid cancer face a poor prognosis, with distant stage papillary thyroid cancer (PTC) and MTC having five-year survival rates of 74% and 43%,

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respectively.[1] There is currently no consensus as to whether *RET* fusions in thyroid cancer are associated with a poorer prognosis versus *RET* wild-type disease, however, evidence indicates that somatic mutations of *RET* correlate with a poor prognosis versus *RET* wild-type tumours in MTC.[2, 3] In addition to a high symptom burden including neck pain, coughing and hoarseness, and diarrhoea and bone pain in the case of MTC, patients with advanced *RET*-altered thyroid cancer are faced with a lack of effective and tolerable treatments.[4, 5]

Currently, the majority of patients in UK clinical practice are treated with the multi-kinase inhibitors (MKIs) cabozantinib (MTC) or lenvatinib (TC), which are associated with sub-optimal survival outcomes and substantial toxicity profiles.[6] For example, in the pivotal clinical trial for cabozantinib, EXAM, patients with progressive medullary thyroid carcinoma treated with cabozantinib had a comparatively poor median overall survival (OS) of 26.6 months, with 82% of patients experiencing dose reductions.[7]

A subset of patients who may not be able to tolerate the toxicity profile of MKIs, or patients with comorbidities, may instead receive palliative best supportive care (BSC) in UK clinical practice. Furthermore, adolescent patients (aged 12–17 years old) are ineligible for the MKIs lenvatinib, sorafenib and cabozantinib, which are licenced in adults only. Therefore, these individuals are currently unable to routinely access an active treatment for their advanced disease and may only be able to access BSC. There is therefore a high unmet need in the untreated *RET*-altered thyroid cancer patient population for a systemic treatment with improved efficacy and tolerability than that offered by the currently available treatments in UK clinical practice, particularly in adolescent patients and adult patients considered ineligible for MKI treatment.

Results of indirect treatment comparisons (ITCs) conducted by Lilly indicate that selpercatinib addresses this unmet need; in the *RET*-mutant MTC population, treatment with selpercatinib reduces the risk of death by around 80% compared to treatment with cabozantinib (OS HR: 0.20 [95% CI: 0.13, 0.32; p<0.001]).[8] While associated with uncertainty, naïve comparisons indicate that selpercatinib also reduces the risk of death by around [redacted] compared to lenvatinib (OS HR: [redacted] [redacted, redacted; p<redacted]) in the *RET* fusion-positive TC population. It is therefore imperative that selpercatinib is made available to the small group of patients with advanced, *RET*-altered thyroid cancer in the UK, who experience a severe disease burden and otherwise face a lack of effective and tolerable treatment options, resulting in a poor prognosis.[9]

In order to facilitate access to selpercatinib in UK clinical practice, Lilly have provided a response which focuses on key areas of uncertainty and concerns identified by the appraisal committee. Overall, this response covers the following key topics:

1. An updated cost-effectiveness model and corresponding results, aligned with the appraisal committee's preferences and incorporating a revised patient access scheme (PAS) discount
2. The relevance of sorafenib as a comparator in UK clinical practice
3. The acceptance of utility values derived from the LIBRETTO-001 trial
4. Considerations regarding the severity multiplier met by each comparator in the *RET* fusion-positive TC and *RET*-mutant MTC populations
5. Lilly's position regarding a managed access agreement for selpercatinib in this indication

As indicated above, a revised PAS for selpercatinib has been provided alongside this response, representing a [redacted]% discount to the list price of selpercatinib.

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	It should be noted that the incremental cost-effectiveness ratios (ICERs) presented herein are substantially lower than those reviewed at the first appraisal committee meeting. Furthermore, Lilly maintain that the high unmet need, severity and rarity of disease in this patient population should be taken into account when determining a cost-effective ICER for this innovative technology.
1	**Updated cost-effectiveness results** In the DGD, the appraisal committee found that all cost-effectiveness estimates that compared selpercatinib with relevant treatments are above what NICE considers an acceptable use of NHS resources (page 4). The appraisal committee also provided several preferred modelling assumptions (page 15, Section 3.12). To ensure that cost-effectiveness estimates for selpercatinib reflect an acceptable use of NHS resources, and to align the modelling approach with committee preferred assumptions, updated cost-effectiveness results are presented in Appendix A. The following amendments have been made to the economic model to achieve these results: • A revised PAS for selpercatinib (a discount of [redacted]% to the list price) has been added to the model • Health state utility values mapped from the LIBRETTO-001 trial have been used in place of the Fordham, et al. 2015 health state utility values, in line with the appraisal committee's preferences (please see comment number 3) • The extrapolation for cabozantinib OS has been based on a stratified spline knot 1 distribution for BSC (*RET*-mutant MTC population only) in line with the appraisal committee's preferences • The relative dose intensity (RDI) inputs for cabozantinib, lenvatinib and sorafenib have been removed, and maintained for selpercatinib, in line with the appraisal committee's preferences • A severity modifier of 1.2 has only been applied to the comparisons with BSC in the *RET*-mutant MTC and *RET*-fusion positive TC populations, in line with the appraisal committee's preferences (please see comment number 4) • A scenario analysis exploring the cost-effectiveness of selpercatinib versus sorafenib has been presented, in line with the appraisal committee's preferences (please see comment number 2) In the updated fully incremental cost-effectiveness results for the *RET*-mutant MTC population presented in Table 6, cabozantinib is extendedly dominated by selpercatinib and BSC. With the 1.2 severity modifier applied, selpercatinib is associated with an ICER of £26,623 per quality-adjusted life year (QALY) gained versus BSC. As such, selpercatinib represents a cost-effective use of NHS resources versus both relevant comparators in UK clinical practice at a willingness to pay threshold of £30,000/QALY. In the updated cost-effectiveness results for the *RET* fusion-positive TC population presented in Table 7, lenvatinib is extendedly dominated by selpercatinib and BSC. With the 1.2 severity modifier applied, selpercatinib is associated with an ICER of £24,506 per QALY gained versus BSC. As such, these results demonstrate that selpercatinib represents a cost-effective use of NHS resources versus both relevant comparators in both populations in UK clinical practice, at a willingness to pay threshold of £30,000/QALY.

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2	**Sorafenib as a relevant comparator** Page 6, Section 3.2 of the DGD states: "*For RET fusion-positive thyroid cancer, the company stated that lenvatinib was the main comparator, because it had received clinical advice that about 5 to 10% of people would have sorafenib in NHS clinical practice. The clinical experts agreed that most people would have lenvatinib, because clinicians perceive it to be more effective than sorafenib and offer treatment with lenvatinib first. But the committee considered that sorafenib should be included as a comparator because some people do have it, it is recommended by NICE technology appraisal guidance, and it was unclear why lenvatinib was preferred over sorafenib."* ***Clinical validation for the treatment of RET fusion-positive TC*** Lilly would like to reiterate the justification behind excluding sorafenib as a relevant comparator in the present appraisal for selpercatinib. To support the development of this submission, two clinical validation interviews were conducted in September 2023, consulting UK-based oncologists experienced in the treatment of thyroid cancer. In these interviews, the clinical experts indicated that the vast majority of patients in the UK would receive lenvatinib over sorafenib, with feedback indicating that this is due to the improved efficacy of lenvatinib versus sorafenib. Subsequently, the clinical experts estimated that [redacted]% of patients are expected to receive sorafenib in UK clinical practice in a world without selpercatinib, and [redacted]% of patients were expected to receive lenvatinib.[10] Based on the above clinical validation and available published literature, which supports the improved efficacy of lenvatinib versus sorafenib in patients with differentiated thyroid cancer (DTC; see below), sorafenib was excluded as a comparator in the Company submission. Subsequently, the external assessment group (EAG) appraising this submission agreed that lenvatinib represents the main comparator for patients with differentiated *RET* fusion-positive TC, with page 29, Section 2.5 of the EAG report further stating that "clinical advice to the EAG is that <5% of NHS patients with radioactive iodine therapy-refractory differentiated TC are treated with sorafenib".[11] Lilly remain aligned with the clinical expert opinion received to support the development this submission and the clinical expert opinion provided to the EAG, maintaining that sorafenib is not a relevant comparator to selpercatinib in this submission. However, in recognition of the appraisal committee's preference to assess the cost-effectiveness of selpercatinib versus sorafenib, for completeness, a scenario analysis has been provided which sorafenib is included as a relevant comparator to selpercatinib in the *RET* fusion-positive TC population (see below). Results of this analysis are presented in Appendix A. ***Inclusion of sorafenib as a comparator in the cost-effectiveness model*** In the company submission, the comparative efficacy of selpercatinib versus lenvatinib, sorafenib and BSC in the *RET* fusion-positive TC population was calculated using naïve ITCs, due to a lack of comparator data availability and small patient populations. Results of the ITCs are presented in Section B.2.9.2 of the company submission, and as noted on page 121, Section B.2.9.3, the ITC comparing selpercatinib and sorafenib should be interpreted with caution, as the results are associated with clinical plausibility concerns. A comparison of the PFS results of the SELECT and the DECISION trials indicates that lenvatinib results in substantially higher PFS (18.3 months) when compared with sorafenib (10.8 months). Results of the ITCs indicate that the hazard ratio for PFS for selpercatinib versus lenvatinib was [redacted] compared to [redacted] for selpercatinib versus sorafenib, respectively. In contrast, OS results for lenvatinib and sorafenib from the SELECT and DECISION trials, respectively, differ from the trends observed for PFS. By combining the OS KM data from SELECT

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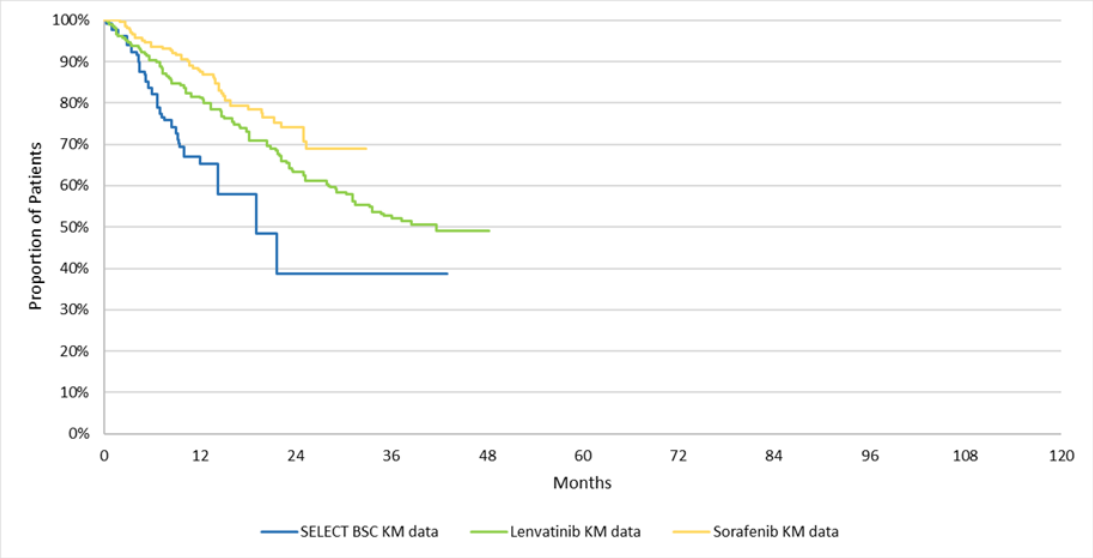
(BSC and lenvatinib) and DECISION (sorafenib only), presented in Figure 34 of the company submission and reproduced in Figure 1 below, OS appears to be improved for sorafenib compared to lenvatinib.[7, 12] Accordingly, the hazard ratio for OS for selpercatinib versus lenvatinib in the ITC was [redacted] compared to [redacted] for selpercatinib versus sorafenib, respectively. It is not clinically plausible for sorafenib to be associated with increased OS and substantially reduced PFS versus lenvatinib, as indicated by the ITC results. Furthermore, the OS results contradict clinical opinion to Lilly and the published literature which supports the improved efficacy of lenvatinib versus sorafenib (see below). Therefore, these data indicate that the OS results of the DECISION trial do not accurately replicate OS for patients receiving sorafenib. As such, in order to include sorafenib as a comparator in the economic model in a scenario analysis, adjustment to the observed OS KM data for sorafenib from the DECISION trial was required in order for the cost-effectiveness results of selpercatinib versus sorafenib to be clinically plausible.

Figure 1: OS KM data for lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)



Abbreviations: BSC: best supportive care; KM: Kaplan-Meier; OS: overall survival.

Published evidence for the improved efficacy of lenvatinib versus sorafenib

The pivotal clinical trials for lenvatinib and sorafenib were the SELECT and the DECISION trials. These studies were both Phase III, double-blind, parallel group RCTs which permitted treatment crossover from the placebo arm to the active treatment arm upon disease progression.[12, 13] The trials were identified in a systematic literature review (SLR) and economic evaluation conducted by Fleeman et al., investigating lenvatinib and sorafenib for treating progressive, locally advanced or metastatic DTC after treatment with radioactive iodine.[14]

In this SLR, it was noted that OS results in the SELECT trial, adjusted for crossover using the rank-preserving structural failure time model (RPSFTM), indicated that patients in the lenvatinib arm had a statistically significant improvement in OS when compared to patients treated with placebo.[14] However, improvement in OS was not statistically significant for patients in the sorafenib arm versus the placebo arm in the DECISION trial when adjusting for crossover using RPSFTM nor the iterative parameter estimation (IPE).[14, 15] Additionally, there was a median improvement in PFS of 14.7 months observed with lenvatinib when compared with placebo in the SELECT trial, with only a 5-month median improvement in PFS observed for sorafenib when

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compared to placebo in the DECISION trial.[14] While these results suggest improved efficacy of lenvatinib versus sorafenib, the SLR cautioned comparisons of these data due to substantial differences between the trial designs and patient populations, concluding, after a feasibility assessment, that it was not appropriate for an ITC to be conducted for the trials due to these differences.[14]

In addition to the pivotal clinical trials, the more recent Kim, et al. 2023 study provides direct evidence for the comparative efficacy of lenvatinib versus sorafenib in a multicentre cohort study that recruited 136 Asian patients with advanced, progressive, radioactive iodine-refractory DTC.[16] The study found a statistically significant ($p<0.001$) increase in PFS in the lenvatinib group (median PFS: 35.3 months [95% CI: 18.2, NR]); N=56) versus the sorafenib group (median PFS: 13.3 months [95% CI: 9.9, 18.1]; N=80], resulting in a hazard ratio for PFS of 0.34 (95% CI: 0.19, 0.60; $p<0.001$). This statistically significant result was observed after adjusting for age, sex, pathology, disease-related symptoms, lung-only metastasis, cumulative radioactive iodine dose, time from diagnosis, treatment duration, and longest diameter of the target lesion. Relatedly, response rates in the lenvatinib group were higher, with a partial response achieved in 59% of patients receiving lenvatinib versus 24% of patients receiving sorafenib ($p<0.001$). These improvements in PFS and response rates are expected to translate to an improved survival of patients with advanced DTC receiving lenvatinib when compared to sorafenib and therefore this trial provides head-to-head evidence of the improved efficacy of lenvatinib versus sorafenib.[16] As such, the results of the ITC presented in the company submission are not considered clinically plausible, due to the evidence provided by this study and clinical opinion to Lilly.

Adjustments to sorafenib OS

In order to generate clinically plausible survival estimates (OS and PFS) for patients with *RET* fusion-positive TC, clinicians in the aforementioned clinical validation exercises were asked to provide survival estimates for patients receiving sorafenib at 5, 10, 15 and 20 years.[10] These estimates were provided alongside the original company submission and are replicated in Appendix B. Clinician estimates for OS are also reproduced in Table 1 below, for convenience. In line with the approach used for selpercatinib OS in the revised company base case submitted during clarification – the results of which were accepted for decision-making by the appraisal committee (as noted on page 10 of the DGD) – Lilly have applied an adjustment factor to sorafenib OS to align the survival estimates to those provided by clinical experts for patients with advanced *RET* fusion-positive TC.

Specifically, an adjustment factor of 2.7 was applied from 26 months and onwards in the model submitted alongside this response document. This adjustment factor was selected to ensure that the sorafenib OS extrapolation aligned with 5-, 10-, 15-, and 20-year survival estimates provided by clinical experts, see Table 1.

Table 1: Sorafenib OS estimates

Year	Sorafenib OS estimates		
	Clinician landmark estimate	Before adjustment factor application	After adjustment factor application
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]

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	Footnotes; OS: overall survival. As shown in Figure 2, the application of an adjustment factor to sorafenib OS ensured that the OS KM curves for selpercatinib, lenvatinib, BSC and sorafenib reflected clinically plausible comparative efficacies for the treatments (i.e., survival of patients receiving sorafenib was lower than lenvatinib). However, the company note that OS estimates are higher for sorafenib than lenvatinib until the adjustment factor is applied, and 5-year survival remains materially higher than estimates from clinical experts. As such, this adjustment may still represents a more favourable assumption of survival for patients receiving sorafenib, resulting in a conservative estimate of the cost-effectiveness of selpercatinib versus sorafenib. **Figure 2: Adjusted survival curves for selpercatinib, lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)**  **Footnote:** All survival extrapolations are fit with the piecewise exponential function. Adjustment factors are applied for selpercatinib (1.2; 5 years and onwards) and sorafenib (2.7; 26 months and onwards). Abbreviations: BSC: best supportive care; EAG: External Assessment Group; KM: Kaplan-Meier. Fully incremental results of the scenario analysis in which sorafenib is included as a comparator versus selpercatinib in patients with *RET*-fusion positive TC are provided in Appendix A, Table 8. The results of the fully incremental analysis demonstrate that selpercatinib remains the most cost-effective use of NHS resources at a willingness-to-pay threshold of £30,000/QALY, with both sorafenib and lenvatinib being extendedly dominated versus selpercatinib.
3	**Health state utility values** Page 11, Section 3.8 and page 15, Section 3.12 of the DGD notes the committee's preferred approach of using health state utility values mapped from EORTC-QLQ-C30 data collected in the LIBRETTO-001 trial for patients with *RET* fusion-positive TC (any-line population) in the economic model, for both the *RET*-mutant MTC and *RET*-altered TC patient populations. Lilly recognise the appraisal committee's preference for health state utility values (HSUVs) taken from the LIBRETTO-001 trial. Therefore, in the updated company base case presented alongside this response, HSUVs have been aligned to those derived from EORTC-QLQ-C30 data collected from the any-line *RET* fusion-positive TC population in LIBRETTO-001, mapped to EQ-5D data using the Young et al. 2005 mapping algorithm.[17] The HSUVs for the progression-free and

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	progressed-disease health state in both the *RET* fusion-positive TC and *RET*-mutant MTC populations have therefore been updated to [redacted] and [redacted], respectively, to reflect to Committee's preferences.
4	**Severity modifier calculations** In line with the appraisal committee's preferences for health state utility values, and to correct the mean age used for the *RET*-mutant MTC population, an updated QALY shortfall analysis is provided in Appendix C. In these updated results, selpercatinib is eligible for a 1.2 severity modifier versus BSC in both the *RET*-mutant MTC and *RET* fusion-positive TC populations. While selpercatinib is not eligible for the 1.2 severity modifier versus lenvatinib and sorafenib (*RET* fusion-positive TC population) and cabozantinib (*RET*-mutant MTC population), there are substantial benefits associated with selpercatinib that cannot be captured in the QALY calculations, as noted in the previous appraisal for selpercatinib for treating advanced thyroid cancer with *RET*-alterations in the second-line indication (TA742).[6] In the final appraisal document for this submission, the appraisal committee considered the rarity of the condition and the lack of effective treatment options available for these patients in their decision making, also noting the devastating effect of the disease on children and young people with *RET*-mutant MTC and that the benefits of selpercatinib to carers could not be captured in the economic model. Similarly to TA742, there is also a devasting unmet need faced by the patient population of relevance to this appraisal. The advanced *RET*-altered thyroid cancer population represents an exceedingly small population in UK clinical practice, and as highlighted in the first appraisal committee meeting and patient group organisation submissions, these patients experience severe disease and a high symptom burden translating to substantial decrements in health-related quality of life.[9] There also exists a lack of effective treatment options in this indication, with the patient group organisation submissions highlighting the toxicity profile of currently available active treatments, such as lenvatinib, that may result in suboptimal survival outcomes in addition to unfavourable side effects due to the non-targeted design of these treatments.[9] It is also important to highlight that, for adolescent patients who would experience a much larger QALY detriment when compared to the age-matched general population, the severity modifier would certainly be met. This is of particular relevance given that, as noted above, there are currently no active treatment options available for these patients in UK clinical practice and therefore they have a substantially high unmet need. In summary, Lilly would strongly recommend that the value of selpercatinib to these patients be considered during the decision-making process, in addition to the severity modifiers applicable to BSC in each population, particularly considering that selpercatinib represents the first targeted treatment for advanced *RET*-altered thyroid cancer.
5	**Position on managed access** As outlined in the DGD (page 16, Section 3.13), a full managed access proposal for selpercatinib in the indication of relevance was not presented in the company submission. Lilly maintain that selpercatinib should be considered for routine commissioning in the first instance based on the available data from the LIBRETTO-001 trial, which features greater follow-up and patient numbers than the DCO used to inform the second-line submission for selpercatinib in *RET*-altered thyroid cancer, TA742.[6] For example, median duration of follow-up for PFS was 11.1 months for the cabozantinib/vandetanib naïve *RET*-mutant MTC population at the 16th

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	December 2019 DCO used to inform the second-line submission, compared with 42.4 months at the 13th January 2023 DCO used to inform this submission.[6, 18] Furthermore, a revised PAS has been submitted alongside this response, in addition to an updated cost-effectiveness model incorporating the appraisal committee's preferred assumptions outlined in the DGD. For these reasons, uncertainty surrounding cost-effectiveness estimates are reduced with respect to the original company base case. When considering the available evidence for selpercatinib in this indication, Lilly would encourage the appraisal committee to consider the revised cost-effectiveness estimates within the context of the high unmet need in this patient population, and the rarity of the condition.
6	**Typographical error** ***Description of problem*** Page 8, Section 3.4 of the draft DGD states: "The company used the placebo arm data from SELECT as a proxy for BSC, and because 87.8% of people in the placebo arm crossed over to receive lenvatinib, it adjusted the Kaplan–Meier overall survival curves for crossover." ***Description of proposed amendment*** Please can the text be amended to: "The company used the placebo arm data from SELECT as a proxy for BSC, and because **95.6%** of people in the placebo arm crossed over to receive lenvatinib, it adjusted the Kaplan–Meier overall survival curves for crossover." ***Justification for amendment*** Typographical error. The value currently presented in this statement (87.8%) is the proportion of patients in the placebo arm of the DECISION trial that crossed over to receive sorafenib.[19] In the SELECT trial, 109/114 (95.6%) patients receiving placebo crossed over to lenvatinib treatment.[13] The correct data are reported on page 112, Section B.2.9.2 of the CS.
7	**Minor Clarifications** ***Description of problem*** Page 11, Section 3.8 of the draft DGD states: "It also noted that the utility values from Fordham 2015 had been accepted in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer." ***Description of proposed amendment*** Please can the text be amended to: "It also noted that the utility values from Fordham 2015 had been accepted in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer**, lenvatinib and**

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	sorafenib for treating differentiated thyroid cancer after radioactive iodine, and selpercatinib for treating advanced thyroid cancer with RET alterations." ***Justification for amendment*** To improve clarity, the DGD should acknowledge that the health-state utility estimates reported by Fordham 2015 have been accepted by multiple NICE appraisal committees (TA516, TA535 and TA742), as presented on page 177 Section B.3.4.2 of the CS.

Insert extra rows as needed

Checklist for submitting comments

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

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Appendix A: Updated cost-effectiveness results

Amendments to the company base case

To illustrate the stepwise impact on the ICER for each of the appraisal committee's preferred assumptions, deterministic results for selpercatinib versus cabozantinib and BSC in the *RET* mutant MTC population and selpercatinib versus lenvatinib and BSC in the *RET* fusion-positive TC population are presented in Table 2–Table 5. During the model update, a small number of minor errors were identified in the *RET*-fusion TC economic model and have been corrected for this analysis. A description of these corrections is provided in Appendix D.

Table 2: Deterministic results for the *RET*-mutant MTC population (selpercatinib versus cabozantinib, no severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,900**	**2.08**	[redacted]	[redacted]	**£35,656**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£89,900**	**2.08**	[redacted]	[redacted]	**£35,656**	**£0**
Amendment 1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£90,573	2.21	[redacted]	[redacted]	£36,666	£1,011
Amendment 2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£89,900	2.42	[redacted]	[redacted]	£35,306	-£350
Amendment 3) Removal of cabozantinib RDI	[redacted]	[redacted]	£116,815	2.08	[redacted]	[redacted]	£28,756	-£6,899
Amendment 4) application of revised PAS for selpercatinib	[redacted]	[redacted]	£89,900	2.08	[redacted]	[redacted]	£17,773	-£17,883
Updated company base case: B. + Amendments 1–4	[redacted]	[redacted]	**£117,572**	**2.59**	[redacted]	[redacted]	**£11,073**	**-£24,583**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 3: Deterministic results for the *RET*-mutant MTC population (selpercatinib versus BSC, x1.2 severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (1.2x multiplier)	£/QALY (1.2x multiplier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£17,089**	**1.51**	[redacted]	[redacted]	**£39,481**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£17,089**	**1.51**	[redacted]	[redacted]	**£39,481**	**£0**
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£17,089	1.91	[redacted]	[redacted]	£39,689	£209
Amendment 4) application of revised PAS for selpercatinib	[redacted]	[redacted]	£17,089	1.51	[redacted]	[redacted]	£26,483	-£12,998
Updated company base case: B. + Amendments 1–4	[redacted]	[redacted]	**£17,089**	**1.91**	[redacted]	[redacted]	**£26,623**	**-£12,858**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 4: Deterministic results for the *RET* fusion-positive TC population (selpercatinib versus lenvatinib, no severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,507**	**2.62**	[redacted]	[redacted]	**£36,329**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£107,658**	**2.62**	[redacted]	[redacted]	**£31,901**	**-£4,428**
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£107,658	2.99	[redacted]	[redacted]	£30,851	-£5,478
Amendment 2) Removal of lenvatinib RDI	[redacted]	[redacted]	£131,345	2.62	[redacted]	[redacted]	£22,476	-£13,853
Amendment 3) application of revised PAS for selpercatinib	[redacted]	[redacted]	£107,658	2.62	[redacted]	[redacted]	£9,667	-£26,662
Updated company base case: B. + Amendments 1–3	[redacted]	[redacted]	**£131,345**	**2.99**	[redacted]	[redacted]	**£235**	**-£36,094**

Abbreviations: EAG: External Assessment Group; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 5: Deterministic results for the *RET* fusion-positive TC population (selpercatinib versus BSC, x1.2 severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (1.2x multiplier)	£/QALY (1.2x multiplier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£16,030**	**1.27**	[redacted]	[redacted]	**£37,092**	**-**
B. Company correction of errors	[redacted]	[redacted]	£16,030	1.27	[redacted]	[redacted]	£37,055	-£37
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£16,030	1.65	[redacted]	[redacted]	£36,319	-£773
Amendment 2) application of revised PAS for selpercatinib	[redacted]	[redacted]	£16,030	1.27	[redacted]	[redacted]	£25,003	-£12,089
Updated company base case: B. + Amendments 1–2	[redacted]	[redacted]	**£16,030**	**1.65**	[redacted]	[redacted]	**£24,506**	**-£12,586**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Updated cost-effectiveness results

Updated deterministic cost-effectiveness results for selpercatinib versus relevant comparators in UK clinical practice are provided in Table 6 for the *RET*-mutant MTC population and Table 7 for the *RET* fusion-positive TC population. When conducting the QALY shortfall analysis (Appendix C) incorporating the committee's preferences, selpercatinib is eligible for a 1.2 severity modifier versus BSC in both the *RET*-mutant MTC and the *RET* fusion-positive TC populations.

Table 6: Updated cost-effectiveness results (fully incremental analysis) for *RET*-mutant MTC population, committee preferences for utility values and RDI, severity modifiers applied as appropriate, and revised PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER (£/QALY) compared to	
			Lowest cost alternative	Non-dominated alternative
BSC	£17,089	1.91	-	-
Cabozantinib	£117,572	2.59	£146,285	ED
Selpercatinib	[redacted]	[redacted]	£26,623*	£26,623*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier
Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ED: extendedly dominated, ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection.

Table 7: Updated cost-effectiveness results (fully incremental analysis) for *RET* fusion-positive TC population including committee preferences for utility values and RDI, severity modifiers applied as appropriate, and revised PAS price for selpercatinib

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY) compared to	
			Lowest cost alternative	Non-dominated alternative
BSC	£16,030	1.65	-	-
Lenvatinib	£131,345	2.99	£85,858	ED
Selpercatinib	[redacted]	[redacted]	£24,506*	£24,506*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier
Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ICER: incremental cost effectiveness ratio; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection; TC: thyroid cancer originating in the follicular cells; ED: extendedly dominated

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Scenario analysis results including sorafenib for RET fusion-positive TC population

A scenario analysis providing cost-effectiveness results for selpercatinib versus sorafenib, in addition to the relevant comparators in UK clinical practice, is presented in Table 8 in recognition of the committee's preference to assess the cost-effectiveness of selpercatinib versus this treatment. However, Lilly maintain that sorafenib is not a relevant comparator to selpercatinib in population, for the reasons outlined in Comment 2.

Table 8: Scenario analysis (fully incremental analysis) for *RET* fusion-positive TC population including committee preferences for utility values and RDI, severity modifiers applied as appropriate, revised PAS price for selpercatinib, and including sorafenib

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY) compared to		
			Lowest cost alternative	Next lowest cost alternative	Non-dominated alternative
BSC	£16,030	1.65	-	-	-
Sorafenib	£60,524	2.34	£63,879	£63,879	ED
Lenvatinib	£131,345	2.99	£85,858	ED	ED
Selpercatinib	[redacted]	[redacted]	£24,506*	£22,009	£24,506*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier

Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ED: extendedly dominated; ICER: incremental cost effectiveness ratio; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection; TC: thyroid cancer originating in the follicular cells.

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Appendix B: Clinical parameters and healthcare cost and resource use inputs informing scenario analysis for sorafenib in the economic model

This appendix summarises the relevant model inputs used to compare selpercatinib versus sorafenib in the economic model.

Time-to-event analyses: sorafenib in RET fusion-positive TC

Progression-free survival

In line with the survival extrapolations selected for selpercatinib and all relevant comparators for PFS in the *RET* fusion-positive TC population, the stratified Weibull was selected for sorafenib PFS. As outlined in Section B.3.3.4 of the CS, this extrapolation aligns with committee preferences in TA742.[6] Landmark estimates predicted by the stratified Weibull curve are presented alongside clinical expert estimates for sorafenib PFS in Table 9, indicating that this survival extrapolation generally aligns with clinical expert estimates.

Table 9: Median and landmark rate estimates of PFS for sorafenib in *RET* fusion-positive TC

Parametric curve	5-year PFS (%)	10-year PFS (%)	20-year PFS (%)
Clinical expert estimates			
NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for selected extrapolation			
Stratified Weibull; no adjustment factor applied	[redacted]	[redacted]	[redacted]

Abbreviations: NA: not applicable; PFS: progression-free survival; RET; rearranged during transfection; TC: thyroid cancer.

Overall survival

In line with the survival extrapolations selected for selpercatinib and all relevant comparators for OS in the *RET* fusion-positive TC population, the piecewise exponential curve was selected for sorafenib OS. As outlined in Section B.3.3.4 of the CS, this extrapolation aligns with committee preferences in TA742.[6] Alignment of the piecewise exponential extrapolation with clinical expert estimates is presented in Table 1 of this response document and is also reproduced in Table 10 below; as shown in this table, an adjustment factor of 2.7 was applied from 26 months and onwards in order to align sorafenib OS with clinical expert estimates.

Table 10: Landmark rate estimates of OS for sorafenib in *RET* fusion-positive TC

Year	Sorafenib OS estimates		
	Clinician landmark estimate	Before adjustment factor application	After adjustment factor application
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.

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Healthcare resource use

Adverse events

Probabilities of individual AEs, specifically, AEs above Grade 3 with at least a 2% difference in frequency between selpercatinib and relevant comparators, for sorafenib were sourced from the DECISION trial and are provided in Table 11.[12] Costs for each individual AE in the *RET* fusion-positive TC population are presented in Section B.3.5.3 of the company submission; any new costs for AEs that are specific to sorafenib are presented in Table 12 below.

Table 11: Incidence of Grade 3 or 4 adverse events included in the model for the *RET* fusion-positive TC population receiving sorafenib

Adverse event	Sorafenib (n=207)
Diarrhoea	5.80%
Hand foot syndrome	19.32%
Hypertension	9.18%
Decreased weight	5.80%
Abdominal pain	0.97%
Fatigue	4.83%
Decreased appetite	1.93%
Rash	4.83%
Vomiting	0.48%
Back pain	0.97%
Dyspnoea	4.35%
Alanine aminotransferase increased	2.90%
Aspartate aminotransferase increased	0.97%
Hypocalcaemia	8.70%
Stomatitis	0.48%

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.
Source: Brose et al. (2014)[19]

Table 12: Costs associated with adverse events included in the model for the *RET* fusion-positive TC population receiving sorafenib

Adverse event	Cost (£)	Source
Abdominal pain	1,789.01	NHS Reference costs 2021/22; TA516 (FD05B Abdominal Pain without Interventions; Non-Elective Inpatient)
Vomiting	3,042.95	NHS Reference costs 2021/22; TA516 (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Back pain	2,096.09	NHS Reference costs 2021/22; TA516 (HC32K Low Back Pain without Interventions, with CC

		Score 0-2; Non-Elective Inpatient)

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.
Source: NHS Reference Costs 2021/2022.[20]

Drug acquisition costs for sorafenib

Drug acquisition costs for sorafenib are presented in

Table 13. The approach to administration costs for sorafenib is in line with administration costs of oral treatments provided in Section B.3.5.1 of the CS.

Table 13: Drug acquisition costs for sorafenib

Regimen	Regimen description	Capsule strength	Capsules per pack	Pack cost	PAS discount	PAS pack cost
Sorafenib	400mg, orally, once daily	200 mg	112	£2,567.00	NA	NA

Abbreviations: BNF: British National Formulary; PAS: Patient Access Scheme.
Source: List prices for each treatment are sourced from the BNF.[21-25]

Additional inputs associated with sorafenib

- Health state utility values used for patients receiving sorafenib are aligned with the appraisal committee's preferences (see comment 3).
- A RDI multiplier was not included for sorafenib in the model, aligned with the appraisal committee's preferences for sorafenib (page 12, Section 3.9 of the DGD).
- Health state unit costs and resource use frequencies for patients receiving sorafenib in the model were aligned with the costs presented in the company submission, Section B.3.5.2.
- For sorafenib, TTD is assumed equal to PFS due to a lack of data on TTD in the DECISION trial; this likely represents a conservative assumption that underestimates sorafenib treatment costs.[12]
- No subsequent treatments were modelled for patients progressing on sorafenib in the model, aligned with the approach taken for all other comparators in the company submission. As noted in the company submission, this is based on feedback from UK clinical experts that no subsequent treatments are routinely available in UK clinical practice for patients with advanced, *RET*-altered TC or MTC who experience disease progression on currently available treatments or selpercatinib.[10]

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Appendix C: Updated QALY Shortfall Analysis

The QALY shortfall analysis for all comparators in the *RET*-mutant MTC and *RET* fusion-positive TC populations, in addition to those for sorafenib, have been re-run using the corrected age in the *RET*-mutant MTC population and the committee's preferred health state utility values, as shown in Table 14. Results of the QALY shortfall analysis are presented in Table 15, demonstrating that selpercatinib is eligible for the 1.2 severity modifier versus BSC in both populations.

Table 14: Summary features of QALY shortfall analysis

Factor	Value	Updated from Company base case?
***RET*-mutant MTC**		
Sex distribution	39.0%	No
Starting age (mean)	[redacted]	Yes
Health state utility: PF	[redacted]	Yes
Health state utility: PD	[redacted]	Yes
***RET*-fusion positive TC**		
Sex distribution	50.8%	No
Starting age	[redacted]	No
Health state utility: PF	[redacted]	Yes
Health state utility: PD	[redacted]	Yes

Abbreviations: MTC: medullary thyroid cancer; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year; TC: thyroid cancer.

Table 15: Summary of QALY shortfall analysis

Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
***RET*-mutant MTC**			
Cabozantinib	11.44	81.59%	1
BSC	12.11	86.37%	1.2
***RET*-fusion positive TC**			
Lenvatinib	10.41	77.74%	1
Sorafenib	11.05	82.52%	1
BSC	11.74	87.67%	1.2

Abbreviations: MTC: medullary thyroid cancer; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

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Appendix D: Model corrections

During updates made to the cost-effectiveness model for this response (as outlined in comment number 1), a small number of minor errors were identified in the most recent version of the cost-effectiveness model for TC (submitted alongside the clarification question responses). These errors have subsequently been updated in the model for this response. These errors are outlined below:

1. In the "Country-Specific Data TC" tab; cells U79:W83, costs for 20mg lenvatinib alone were calculated from the second cycle and onwards, which resulted in no change in the costs when updating the dose intensity to 100%. This has now been corrected to 24mg lenvatinib with a 100% relative dose intensity multiplier, as illustrated below:

Figure 3: Illustration of original model (left) and updated model (right) for lenvatinib dose intensity

Active dose, cycle 2+		% Patients by tablet combination	
		53%	47%
Actual	17.20		
Check	17.20		1
		2	1
		63%	37%
Actual	325.60	2	1
Check	325.60		

Active dose, cycle 2+		% Patients by tablet combination	
		100%	0%
Actual	24.00		
Check	24.00	1	1
		2	1
		100%	0%
Actual	400.00	2	1
Check	400.00		

2. In the "Utilities – TC" tab, cell C19 previously featured a #REF! error – this has now been updated in the corrected model to "Sorafenib".
3. The formula in column N of the "TC S(t) (2)" was originally as follows, in the model submitted following clarification questions:

   "=IF(AND(hSO3=1,B10>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"

   This has now been updated to:

   "=IF(AND($O$3=1,B11>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"

   This update ensures that the adjustment factor (relevant to selpercatinib and sorafenib OS) is applied from the correct timepoint in the model.

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

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Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [ID6132]

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

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I do not think the positive lived-experiences have been documented effectively. The ease of administration, monitoring and lack of side effects are barely mentioned in this summary yet were clearly mentioned by me, and the health professionals in attendance.

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2	Evidence is often difficult to obtain due to small numbers of patients suffering from this condition, therefore it can be hard to provide 'hard' evidence to support such a recommendation. This discriminates against people who suffer from such rare conditions as it is always harder to get the evidence required to satisfy such a committee.
3	Best supportive care is referred to as if it were an acceptable treatment option – as a medical professional myself, I would not agree with this belief. Best supportive care essentially means 'end of the road'. I appreciate it is a relative comparator from a study perspective, though.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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

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

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly and Company

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive summary Lilly appreciate the opportunity to comment on the NICE draft guidance document (DGD) for the appraisal of selpercatinib in advanced thyroid cancer with rearranged during transfection (*RET)* alterations that have not been treated with systemic therapy. While Lilly are disappointed to learn that the appraisal committee's initial decision is to not recommend selpercatinib within this patient population, Lilly is committed to continue working with NICE to address the appraisal committee's key concerns, and are hopeful that these issues may be resolved to allow selpercatinib to be recommended for use within the National Health Service (NHS). Lilly would firstly like to reiterate the severe unmet need experienced by patients with untreated, advanced *RET*-mutant medullary thyroid cancer (MTC) and *RET*-fusion positive thyroid cancer (TC); patients with advanced stage thyroid cancer face a poor prognosis, with distant stage papillary thyroid cancer (PTC) and MTC having five-year survival rates of 74% and 43%, respectively.[1] There is currently no consensus as to whether *RET* fusions in thyroid cancer are associated with a poorer prognosis versus *RET* wild-type disease, however, evidence indicates

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that somatic mutations of *RET* correlate with a poor prognosis versus *RET* wild-type tumours in MTC.[2, 3] In addition to a high symptom burden including neck pain, coughing and hoarseness, and diarrhoea and bone pain in the case of MTC, patients with advanced *RET*-altered thyroid cancer are faced with a lack of effective and tolerable treatments.[4, 5]

Currently, the majority of patients in UK clinical practice are treated with the multi-kinase inhibitors (MKIs) cabozantinib (MTC) or lenvatinib (TC), which are associated with sub-optimal survival outcomes and substantial toxicity profiles.[6] For example, in the pivotal clinical trial for cabozantinib, EXAM, patients with progressive medullary thyroid carcinoma treated with cabozantinib had a comparatively poor median overall survival (OS) of 26.6 months, with 82% of patients experiencing dose reductions.[7]

A subset of patients who may not be able to tolerate the toxicity profile of MKIs, or patients with comorbidities, may instead receive palliative best supportive care (BSC) in UK clinical practice. Furthermore, adolescent patients (aged 12–17 years old) are ineligible for the MKIs lenvatinib, sorafenib and cabozantinib, which are licenced in adults only. Therefore, these individuals are currently unable to routinely access an active treatment for their advanced disease and may only be able to access BSC. There is therefore a high unmet need in the untreated *RET*-altered thyroid cancer patient population for a systemic treatment with improved efficacy and tolerability than that offered by the currently available treatments in UK clinical practice, particularly in adolescent patients and adult patients considered ineligible for MKI treatment.

Results of indirect treatment comparisons (ITCs) conducted by Lilly indicate that selpercatinib addresses this unmet need; in the *RET*-mutant MTC population, treatment with selpercatinib reduces the risk of death by around 80% compared to treatment with cabozantinib (OS HR: 0.20 [95% CI: 0.13, 0.32; p<0.001]).[8] While associated with uncertainty, naïve comparisons indicate that selpercatinib also reduces the risk of death by around [redacted] compared to lenvatinib (OS HR: [redacted] [redacted], [redacted]; p<[redacted]) in the *RET* fusion-positive TC population. It is therefore imperative that selpercatinib is made available to the small group of patients with advanced, *RET*-altered thyroid cancer in the UK, who experience a severe disease burden and otherwise face a lack of effective and tolerable treatment options, resulting in a poor prognosis.[9]

In order to facilitate access to selpercatinib in UK clinical practice, Lilly have provided a response which focuses on key areas of uncertainty and concerns identified by the appraisal committee. Overall, this response covers the following key topics:

1. An updated cost-effectiveness model and corresponding results, aligned with the appraisal committee's preferences and incorporating a revised patient access scheme (PAS) discount
2. The relevance of sorafenib as a comparator in UK clinical practice
3. The acceptance of utility values derived from the LIBRETTO-001 trial
4. Considerations regarding the severity multiplier met by each comparator in the *RET* fusion-positive TC and *RET*-mutant MTC populations
5. Lilly's position regarding a managed access agreement for selpercatinib in this indication

As indicated above, a revised PAS for selpercatinib has been provided alongside this response, representing a [redacted] % discount to the list price of selpercatinib.

It should be noted that the incremental cost-effectiveness ratios (ICERs) presented herein are substantially lower than those reviewed at the first appraisal committee meeting. Furthermore, Lilly

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	maintain that the high unmet need, severity and rarity of disease in this patient population should be taken into account when determining a cost-effective ICER for this innovative technology.
1	**Updated cost-effectiveness results** In the DGD, the appraisal committee found that all cost-effectiveness estimates that compared selpercatinib with relevant treatments are above what NICE considers an acceptable use of NHS resources (page 4). The appraisal committee also provided several preferred modelling assumptions (page 15, Section 3.12). To ensure that cost-effectiveness estimates for selpercatinib reflect an acceptable use of NHS resources, and to align the modelling approach with committee preferred assumptions, updated cost-effectiveness results are presented in Appendix A. The following amendments have been made to the economic model to achieve these results: • A revised PAS for selpercatinib (a discount of [redacted] % to the list price) has been added to the model • Health state utility values mapped from the LIBRETTO-001 trial have been used in place of the Fordham, et al. 2015 health state utility values, in line with the appraisal committee's preferences (please see comment number 3) • The extrapolation for cabozantinib OS has been based on a stratified spline knot 1 distribution for BSC (*RET*-mutant MTC population only) in line with the appraisal committee's preferences • The relative dose intensity (RDI) inputs for cabozantinib, lenvatinib and sorafenib have been removed, and maintained for selpercatinib, in line with the appraisal committee's preferences • A severity modifier of 1.2 has only been applied to the comparisons with BSC in the *RET*-mutant MTC and *RET*-fusion positive TC populations, in line with the appraisal committee's preferences (please see comment number 4) • A scenario analysis exploring the cost-effectiveness of selpercatinib versus sorafenib has been presented, in line with the appraisal committee's preferences (please see comment number 2) In the updated fully incremental cost-effectiveness results for the *RET*-mutant MTC population presented in Table 6, cabozantinib is extendedly dominated by selpercatinib and BSC. With the 1.2 severity modifier applied, selpercatinib is associated with an ICER of £26,623 per quality-adjusted life year (QALY) gained versus BSC. As such, selpercatinib represents a cost-effective use of NHS resources versus both relevant comparators in UK clinical practice at a willingness to pay threshold of £30,000/QALY. In the updated cost-effectiveness results for the *RET* fusion-positive TC population presented in Table 7, lenvatinib is extendedly dominated by selpercatinib and BSC. With the 1.2 severity modifier applied, selpercatinib is associated with an ICER of £24,506 per QALY gained versus BSC. As such, these results demonstrate that selpercatinib represents a cost-effective use of NHS resources versus both relevant comparators in both populations in UK clinical practice, at a willingness to pay threshold of £30,000/QALY.

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EAG response	The EAG can verify that the company corrections have been correctly implemented and that the company model generates all the cost effectiveness results listed in the tables presented in this document.
2	**Sorafenib as a relevant comparator** Page 6, Section 3.2 of the DGD states: "*For RET fusion-positive thyroid cancer, the company stated that lenvatinib was the main comparator, because it had received clinical advice that about 5 to 10% of people would have sorafenib in NHS clinical practice. The clinical experts agreed that most people would have lenvatinib, because clinicians perceive it to be more effective than sorafenib and offer treatment with lenvatinib first. But the committee considered that sorafenib should be included as a comparator because some people do have it, it is recommended by NICE technology appraisal guidance, and it was unclear why lenvatinib was preferred over sorafenib.*" ***Clinical validation for the treatment of RET fusion-positive TC*** Lilly would like to reiterate the justification behind excluding sorafenib as a relevant comparator in the present appraisal for selpercatinib. To support the development of this submission, two clinical validation interviews were conducted in September 2023, consulting UK-based oncologists experienced in the treatment of thyroid cancer. In these interviews, the clinical experts indicated that the vast majority of patients in the UK would receive lenvatinib over sorafenib, with feedback indicating that this is due to the improved efficacy of lenvatinib versus sorafenib. Subsequently, the clinical experts estimated that [redacted] % of patients are expected to receive sorafenib in UK clinical practice in a world without selpercatinib, and [redacted] % of patients were expected to receive lenvatinib.[10] Based on the above clinical validation and available published literature, which supports the improved efficacy of lenvatinib versus sorafenib in patients with differentiated thyroid cancer (DTC; see below), sorafenib was excluded as a comparator in the Company submission. Subsequently, the external assessment group (EAG) appraising this submission agreed that lenvatinib represents the main comparator for patients with differentiated *RET* fusion-positive TC, with page 29, Section 2.5 of the EAG report further stating that "clinical advice to the EAG is that <5% of NHS patients with radioactive iodine therapy-refractory differentiated TC are treated with sorafenib".[11] Lilly remain aligned with the clinical expert opinion received to support the development this submission and the clinical expert opinion provided to the EAG, maintaining that sorafenib is not a relevant comparator to selpercatinib in this submission. However, in recognition of the appraisal committee's preference to assess the cost-effectiveness of selpercatinib versus sorafenib, for completeness, a scenario analysis has been provided which sorafenib is included as a relevant comparator to selpercatinib in the *RET* fusion-positive TC population (see below). Results of this analysis are presented in Appendix A. ***Inclusion of sorafenib as a comparator in the cost-effectiveness model*** In the company submission, the comparative efficacy of selpercatinib versus lenvatinib, sorafenib and BSC in the *RET* fusion-positive TC population was calculated using naïve ITCs, due to a lack of comparator data availability and small patient populations. Results of the ITCs are presented in Section B.2.9.2 of the company submission, and as noted on page 121, Section B.2.9.3, the ITC comparing selpercatinib and sorafenib should be interpreted with caution, as the results are associated with clinical plausibility concerns. A comparison of the PFS results of the SELECT and the DECISION trials indicates that lenvatinib results in substantially higher PFS (18.3 months) when compared with sorafenib (10.8 months). Results of the ITCs indicate that the hazard ratio for PFS for selpercatinib versus lenvatinib was [redacted] compared to [redacted] for selpercatinib versus sorafenib, respectively.

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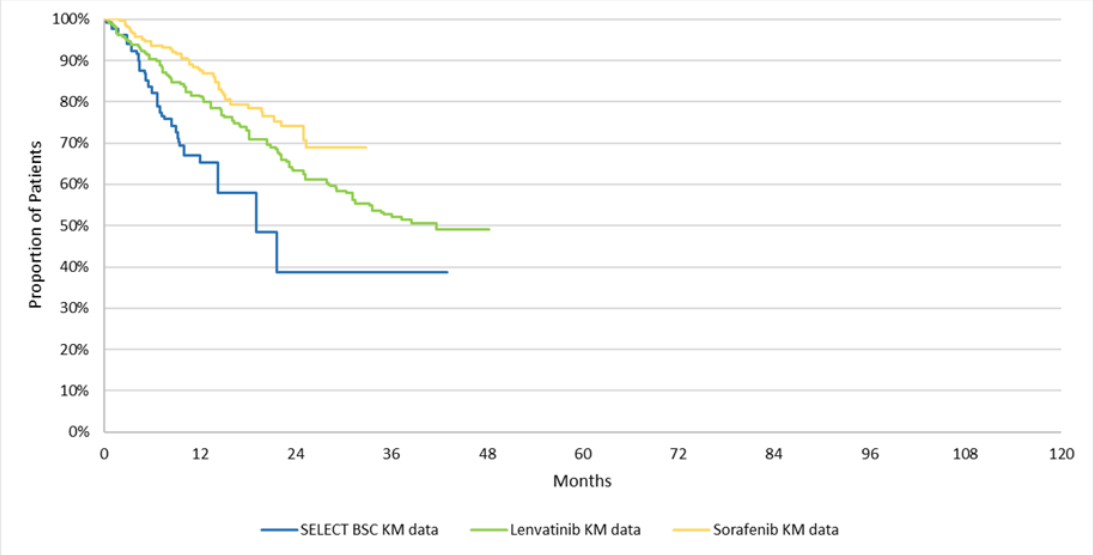
In contrast, OS results for lenvatinib and sorafenib from the SELECT and DECISION trials, respectively, differ from the trends observed for PFS. By combining the OS KM data from SELECT (BSC and lenvatinib) and DECISION (sorafenib only), presented in Figure 34 of the company submission and reproduced in Figure 1 below, OS appears to be improved for sorafenib compared to lenvatinib.[7, 12] Accordingly, the hazard ratio for OS for selpercatinib versus lenvatinib in the ITC was [redacted] compared to [redacted] for selpercatinib versus sorafenib, respectively. It is not clinically plausible for sorafenib to be associated with increased OS and substantially reduced PFS versus lenvatinib, as indicated by the ITC results. Furthermore, the OS results contradict clinical opinion to Lilly and the published literature which supports the improved efficacy of lenvatinib versus sorafenib (see below). Therefore, these data indicate that the OS results of the DECISION trial do not accurately replicate OS for patients receiving sorafenib. As such, in order to include sorafenib as a comparator in the economic model in a scenario analysis, adjustment to the observed OS KM data for sorafenib from the DECISION trial was required in order for the cost-effectiveness results of selpercatinib versus sorafenib to be clinically plausible.

Figure 1: OS KM data for lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)



Abbreviations: BSC: best supportive care; KM: Kaplan-Meier; OS: overall survival.

Published evidence for the improved efficacy of lenvatinib versus sorafenib

The pivotal clinical trials for lenvatinib and sorafenib were the SELECT and the DECISION trials. These studies were both Phase III, double-blind, parallel group RCTs which permitted treatment crossover from the placebo arm to the active treatment arm upon disease progression.[12, 13] The trials were identified in a systematic literature review (SLR) and economic evaluation conducted by Fleeman et al., investigating lenvatinib and sorafenib for treating progressive, locally advanced or metastatic DTC after treatment with radioactive iodine.[14]

In this SLR, it was noted that OS results in the SELECT trial, adjusted for crossover using the rank-preserving structural failure time model (RPSFTM), indicated that patients in the lenvatinib arm had a statistically significant improvement in OS when compared to patients treated with placebo.[14] However, improvement in OS was not statistically significant for patients in the sorafenib arm versus the placebo arm in the DECISION trial when adjusting for crossover using RPSFTM nor the iterative parameter estimation (IPE).[14, 15] Additionally, there was a median

improvement in PFS of 14.7 months observed with lenvatinib when compared with placebo in the SELECT trial, with only a 5-month median improvement in PFS observed for sorafenib when compared to placebo in the DECISION trial.[14] While these results suggest improved efficacy of lenvatinib versus sorafenib, the SLR cautioned comparisons of these data due to substantial differences between the trial designs and patient populations, concluding, after a feasibility assessment, that it was not appropriate for an ITC to be conducted for the trials due to these differences.[14]

In addition to the pivotal clinical trials, the more recent Kim, et al. 2023 study provides direct evidence for the comparative efficacy of lenvatinib versus sorafenib in a multicentre cohort study that recruited 136 Asian patients with advanced, progressive, radioactive iodine-refractory DTC.[16] The study found a statistically significant ($p<0.001$) increase in PFS in the lenvatinib group (median PFS: 35.3 months [95% CI: 18.2, NR]); N=56) versus the sorafenib group (median PFS: 13.3 months [95% CI: 9.9, 18.1]; N=80], resulting in a hazard ratio for PFS of 0.34 (95% CI: 0.19, 0.60; $p<0.001$). This statistically significant result was observed after adjusting for age, sex, pathology, disease-related symptoms, lung-only metastasis, cumulative radioactive iodine dose, time from diagnosis, treatment duration, and longest diameter of the target lesion. Relatedly, response rates in the lenvatinib group were higher, with a partial response achieved in 59% of patients receiving lenvatinib versus 24% of patients receiving sorafenib ($p<0.001$). These improvements in PFS and response rates are expected to translate to an improved survival of patients with advanced DTC receiving lenvatinib when compared to sorafenib and therefore this trial provides head-to-head evidence of the improved efficacy of lenvatinib versus sorafenib.[16] As such, the results of the ITC presented in the company submission are not considered clinically plausible, due to the evidence provided by this study and clinical opinion to Lilly.

Adjustments to sorafenib OS

In order to generate clinically plausible survival estimates (OS and PFS) for patients with *RET* fusion-positive TC, clinicians in the aforementioned clinical validation exercises were asked to provide survival estimates for patients receiving sorafenib at 5, 10, 15 and 20 years.[10] These estimates were provided alongside the original company submission and are replicated in Appendix B. Clinician estimates for OS are also reproduced in Table 1 below, for convenience. In line with the approach used for selpercatinib OS in the revised company base case submitted during clarification – the results of which were accepted for decision-making by the appraisal committee (as noted on page 10 of the DGD) – Lilly have applied an adjustment factor to sorafenib OS to align the survival estimates to those provided by clinical experts for patients with advanced *RET* fusion-positive TC.

Specifically, an adjustment factor of 2.7 was applied from 26 months and onwards in the model submitted alongside this response document. This adjustment factor was selected to ensure that the sorafenib OS extrapolation aligned with 5-, 10-, 15-, and 20-year survival estimates provided by clinical experts, see Table 1.

Table 1: Sorafenib OS estimates

Year	Sorafenib OS estimates		
	Clinician landmark estimate	**Before adjustment factor application**	**After adjustment factor application**
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

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	20 | [redacted] | [redacted] | [redacted] Footnotes; OS: overall survival. As shown in Figure 2, the application of an adjustment factor to sorafenib OS ensured that the OS KM curves for selpercatinib, lenvatinib, BSC and sorafenib reflected clinically plausible comparative efficacies for the treatments (i.e., survival of patients receiving sorafenib was lower than lenvatinib). However, the company note that OS estimates are higher for sorafenib than lenvatinib until the adjustment factor is applied, and 5-year survival remains materially higher than estimates from clinical experts. As such, this adjustment may still represents a more favourable assumption of survival for patients receiving sorafenib, resulting in a conservative estimate of the cost-effectiveness of selpercatinib versus sorafenib. **Figure 2: Adjusted survival curves for selpercatinib, lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)** [redacted] **Footnote:** All survival extrapolations are fit with the piecewise exponential function. Adjustment factors are applied for selpercatinib (1.2; 5 years and onwards) and sorafenib (2.7; 26 months and onwards). Abbreviations: BSC: best supportive care; EAG: External Assessment Group; KM: Kaplan-Meier. Fully incremental results of the scenario analysis in which sorafenib is included as a comparator versus selpercatinib in patients with *RET*-fusion positive TC are provided in Appendix A, Table 8. The results of the fully incremental analysis demonstrate that selpercatinib remains the most cost-effective use of NHS resources at a willingness-to-pay threshold of £30,000/QALY, with both sorafenib and lenvatinib being extendedly dominated versus selpercatinib.
EAG response	The EAG agrees with the company that the OS ITC results (selpercatinib versus sorafenib and versus lenvatinib) do not align with clinical opinion and/or published evidence. The EAG considers that the company OS ITC results should only be considered as exploratory. As company OS ITC results are unreliable, any cost effectiveness results generated using these results will also be unreliable.
3	**Health state utility values** Page 11, Section 3.8 and page 15, Section 3.12 of the DGD notes the committee's preferred approach of using health state utility values mapped from EORTC-QLQ-C30 data collected in the LIBRETTO-001 trial for patients with *RET* fusion-positive TC (any-line population) in the economic model, for both the *RET*-mutant MTC and *RET*-altered TC patient populations.

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	Lilly recognise the appraisal committee's preference for health state utility values (HSUVs) taken from the LIBRETTO-001 trial. Therefore, in the updated company base case presented alongside this response, HSUVs have been aligned to those derived from EORTC-QLQ-C30 data collected from the any-line *RET* fusion-positive TC population in LIBRETTO-001, mapped to EQ-5D data using the Young et al. 2005 mapping algorithm.[17] The HSUVs for the progression-free and progressed-disease health state in both the *RET* fusion-positive TC and *RET*-mutant MTC populations have therefore been updated to [redacted] and [redacted], respectively, to reflect to Committee's preferences.
EAG response	No comment
4	**Severity modifier calculations** In line with the appraisal committee's preferences for health state utility values, and to correct the mean age used for the *RET*-mutant MTC population, an updated QALY shortfall analysis is provided in Appendix C. In these updated results, selpercatinib is eligible for a 1.2 severity modifier versus BSC in both the *RET*-mutant MTC and *RET* fusion-positive TC populations. While selpercatinib is not eligible for the 1.2 severity modifier versus lenvatinib and sorafenib (*RET* fusion-positive TC population) and cabozantinib (*RET*-mutant MTC population), there are substantial benefits associated with selpercatinib that cannot be captured in the QALY calculations, as noted in the previous appraisal for selpercatinib for treating advanced thyroid cancer with *RET*-alterations in the second-line indication (TA742).[6] In the final appraisal document for this submission, the appraisal committee considered the rarity of the condition and the lack of effective treatment options available for these patients in their decision making, also noting the devastating effect of the disease on children and young people with *RET*-mutant MTC and that the benefits of selpercatinib to carers could not be captured in the economic model. Similarly to TA742, there is also a devasting unmet need faced by the patient population of relevance to this appraisal. The advanced *RET*-altered thyroid cancer population represents an exceedingly small population in UK clinical practice, and as highlighted in the first appraisal committee meeting and patient group organisation submissions, these patients experience severe disease and a high symptom burden translating to substantial decrements in health-related quality of life.[9] There also exists a lack of effective treatment options in this indication, with the patient group organisation submissions highlighting the toxicity profile of currently available active treatments, such as lenvatinib, that may result in suboptimal survival outcomes in addition to unfavourable side effects due to the non-targeted design of these treatments.[9] It is also important to highlight that, for adolescent patients who would experience a much larger QALY detriment when compared to the age-matched general population, the severity modifier would certainly be met. This is of particular relevance given that, as noted above, there are currently no active treatment options available for these patients in UK clinical practice and therefore they have a substantially high unmet need. In summary, Lilly would strongly recommend that the value of selpercatinib to these patients be considered during the decision-making process, in addition to the severity modifiers applicable to BSC in each population, particularly considering that selpercatinib represents the first targeted treatment for advanced *RET*-altered thyroid cancer.
EAG response	No comment

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5	**Position on managed access** As outlined in the DGD (page 16, Section 3.13), a full managed access proposal for selpercatinib in the indication of relevance was not presented in the company submission. Lilly maintain that selpercatinib should be considered for routine commissioning in the first instance based on the available data from the LIBRETTO-001 trial, which features greater follow-up and patient numbers than the DCO used to inform the second-line submission for selpercatinib in *RET*-altered thyroid cancer, TA742.[6] For example, median duration of follow-up for PFS was 11.1 months for the cabozantinib/vandetanib naïve *RET*-mutant MTC population at the 16th December 2019 DCO used to inform the second-line submission, compared with 42.4 months at the 13th January 2023 DCO used to inform this submission.[6, 18] Furthermore, a revised PAS has been submitted alongside this response, in addition to an updated cost-effectiveness model incorporating the appraisal committee's preferred assumptions outlined in the DGD. For these reasons, uncertainty surrounding cost-effectiveness estimates are reduced with respect to the original company base case. When considering the available evidence for selpercatinib in this indication, Lilly would encourage the appraisal committee to consider the revised cost-effectiveness estimates within the context of the high unmet need in this patient population, and the rarity of the condition.
EAG response	No comment
6	**Typographical error** ***Description of problem*** Page 8, Section 3.4 of the draft DGD states: "The company used the placebo arm data from SELECT as a proxy for BSC, and because 87.8% of people in the placebo arm crossed over to receive lenvatinib, it adjusted the Kaplan–Meier overall survival curves for crossover." ***Description of proposed amendment*** Please can the text be amended to: "The company used the placebo arm data from SELECT as a proxy for BSC, and because **95.6%** of people in the placebo arm crossed over to receive lenvatinib, it adjusted the Kaplan–Meier overall survival curves for crossover." ***Justification for amendment*** Typographical error. The value currently presented in this statement (87.8%) is the proportion of patients in the placebo arm of the DECISION trial that crossed over to receive sorafenib.[19] In the SELECT trial, 109/114 (95.6%) patients receiving placebo crossed over to lenvatinib treatment.[13] The correct data are reported on page 112, Section B.2.9.2 of the CS.
EAG response	The EAG considers that this is not a typographical error. Data from the second and third SELECT trial data cuts (presented in the Eisai TA535 CS, Table 15) show that 115/131 (87.8%) patients in the placebo arm crossed over to receive lenvatinib. Data from the first SELECT trial data cut show that 109/131 patients crossed over to receive lenvatinib.

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7	**Minor Clarifications** ***Description of problem*** Page 11, Section 3.8 of the draft DGD states: "It also noted that the utility values from Fordham 2015 had been accepted in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer." ***Description of proposed amendment*** Please can the text be amended to: "It also noted that the utility values from Fordham 2015 had been accepted in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer, **lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine, and selpercatinib for treating advanced thyroid cancer with RET alterations**." ***Justification for amendment*** To improve clarity, the DGD should acknowledge that the health-state utility estimates reported by Fordham 2015 have been accepted by multiple NICE appraisal committees (TA516, TA535 and TA742), as presented on page 177 Section B.3.4.2 of the CS.
EAG response	No comment

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Appendix A: Updated cost-effectiveness results

Amendments to the company base case

To illustrate the stepwise impact on the ICER for each of the appraisal committee's preferred assumptions, deterministic results for selpercatinib versus cabozantinib and BSC in the *RET* mutant MTC population and selpercatinib versus lenvatinib and BSC in the *RET* fusion-positive TC population are presented in Table 2–Table 5. During the model update, a small number of minor errors were identified in the *RET*-fusion TC economic model and have been corrected for this analysis. A description of these corrections is provided in Appendix D.

Table 2: Deterministic results for the *RET*-mutant MTC population (selpercatinib versus cabozantinib, no severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,900**	**2.08**	[redacted]	[redacted]	**£35,656**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£89,900**	**2.08**	[redacted]	[redacted]	**£35,656**	**£0**
Amendment 1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£90,573	2.21	[redacted]	[redacted]	£36,666	£1,011
Amendment 2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£89,900	2.42	[redacted]	[redacted]	£35,306	-£350
Amendment 3) Removal of cabozantinib RDI	[redacted]	[redacted]	£116,815	2.08	[redacted]	[redacted]	£28,756	-£6,899
Amendment 4) application of revised PAS for selpercatinib	[redacted]	[redacted]	£89,900	2.08	[redacted]	[redacted]	£17,773	-£17,883
Updated company base case: B. + Amendments 1–4	[redacted]	[redacted]	**£117,572**	**2.59**	[redacted]	[redacted]	**£11,073**	**-£24,583**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 3: Deterministic results for the *RET*-mutant MTC population (selpercatinib versus BSC, x1.2 severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (1.2x multiplier)	£/QALY (1.2x multiplier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£17,089**	**1.51**	[redacted]	[redacted]	**£39,481**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£17,089**	**1.51**	[redacted]	[redacted]	**£39,481**	**£0**
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£17,089	1.91	[redacted]	[redacted]	£39,689	£209
Amendment 4) application of revised PAS for selpercatinib	[redacted]	[redacted]	£17,089	1.51	[redacted]	[redacted]	£26,483	-£12,998
Updated company base case: B. + Amendments 1–4	[redacted]	[redacted]	**£17,089**	**1.91**	[redacted]	[redacted]	**£26,623**	**-£12,858**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 4: Deterministic results for the *RET* fusion-positive TC population (selpercatinib versus lenvatinib, no severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,507**	**2.62**	[redacted]	[redacted]	**£36,329**	**-**
B. Company correction of errors	[redacted]	[redacted]	**£107,658**	**2.62**	[redacted]	[redacted]	**£31,901**	**-£4,428**
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£107,658	2.99	[redacted]	[redacted]	£30,851	-£5,478
Amendment 2) Removal of lenvatinib RDI	[redacted]	[redacted]	£131,345	2.62	[redacted]	[redacted]	£22,476	-£13,853
Amendment 3) application of revised PAS for selpercatinib	[redacted]	[redacted]	£107,658	2.62	[redacted]	[redacted]	£9,667	-£26,662
Updated company base case: B. + Amendments 1–3	[redacted]	[redacted]	**£131,345**	**2.99**	[redacted]	[redacted]	**£235**	**-£36,094**

Abbreviations: EAG: External Assessment Group; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Table 5: Deterministic results for the *RET* fusion-positive TC population (selpercatinib versus BSC, x1.2 severity modifier), PAS price for selpercatinib

Company scenarios	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (1.2x multiplier)	£/QALY (1.2x multiplier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£16,030**	**1.27**	[redacted]	[redacted]	**£37,092**	**-**
B. Company correction of errors	[redacted]	[redacted]	£16,030	1.27	[redacted]	[redacted]	£37,055	-£37
Amendment 1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£16,030	1.65	[redacted]	[redacted]	£36,319	-£773
Amendment 2) application of revised PAS for selpercatinib	[redacted]	[redacted]	£16,030	1.27	[redacted]	[redacted]	£25,003	-£12,089
Updated company base case: B. + Amendments 1–2	[redacted]	[redacted]	**£16,030**	**1.65**	[redacted]	[redacted]	**£24,506**	**-£12,586**

Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality adjusted life year; *RET*: rearranged during transfection.

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Updated cost-effectiveness results

Updated deterministic cost-effectiveness results for selpercatinib versus relevant comparators in UK clinical practice are provided in Table 6 for the *RET*-mutant MTC population and Table 7 for the *RET* fusion-positive TC population. When conducting the QALY shortfall analysis (Appendix C) incorporating the committee's preferences, selpercatinib is eligible for a 1.2 severity modifier versus BSC in both the *RET*-mutant MTC and the *RET* fusion-positive TC populations.

Table 6: Updated cost-effectiveness results (fully incremental analysis) for *RET*-mutant MTC population, committee preferences for utility values and RDI, severity modifiers applied as appropriate, and revised PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER (£/QALY) compared to	
			Lowest cost alternative	Non-dominated alternative
BSC	£17,089	1.91	-	-
Cabozantinib	£117,572	2.59	£146,285	ED
Selpercatinib	[redacted]	[redacted]	£26,623*	£26,623*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier
Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ED: extendedly dominated, ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection.

Table 7: Updated cost-effectiveness results (fully incremental analysis) for *RET* fusion-positive TC population including committee preferences for utility values and RDI, severity modifiers applied as appropriate, and revised PAS price for selpercatinib

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY) compared to	
			Lowest cost alternative	Non-dominated alternative
BSC	£16,030	1.65	-	-
Lenvatinib	£131,345	2.99	£85,858	ED
Selpercatinib	[redacted]	[redacted]	£24,506*	£24,506*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier
Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ICER: incremental cost effectiveness ratio; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection; TC: thyroid cancer originating in the follicular cells; ED: extendedly dominated

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Scenario analysis results including sorafenib for RET fusion-positive TC population

A scenario analysis providing cost-effectiveness results for selpercatinib versus sorafenib, in addition to the relevant comparators in UK clinical practice, is presented in Table 8 in recognition of the committee's preference to assess the cost-effectiveness of selpercatinib versus this treatment. However, Lilly maintain that sorafenib is not a relevant comparator to selpercatinib in population, for the reasons outlined in Comment 2.

Table 8: Scenario analysis (fully incremental analysis) for *RET* fusion-positive TC population including committee preferences for utility values and RDI, severity modifiers applied as appropriate, revised PAS price for selpercatinib, and including sorafenib

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY) compared to		
			Lowest cost alternative	Next lowest cost alternative	Non-dominated alternative
BSC	£16,030	1.65	-	-	-
Sorafenib	£60,524	2.34	£63,879	£63,879	ED
Lenvatinib	£131,345	2.99	£85,858	ED	ED
Selpercatinib	[redacted]	[redacted]	£24,506*	£22,009	£24,506*

* selpercatinib versus BSC is eligible for a 1.2x severity modifier

Abbreviations: BSC: best supportive care; EAG: External Assessment Group; ED: extendedly dominated; ICER: incremental cost effectiveness ratio; PAS: Patient Access Scheme; QALYs: quality adjusted life years; *RET*: rearranged during transfection; TC: thyroid cancer originating in the follicular cells.

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Appendix B: Clinical parameters and healthcare cost and resource use inputs informing scenario analysis for sorafenib in the economic model

This appendix summarises the relevant model inputs used to compare selpercatinib versus sorafenib in the economic model.

Time-to-event analyses: sorafenib in RET fusion-positive TC

Progression-free survival

In line with the survival extrapolations selected for selpercatinib and all relevant comparators for PFS in the *RET* fusion-positive TC population, the stratified Weibull was selected for sorafenib PFS. As outlined in Section B.3.3.4 of the CS, this extrapolation aligns with committee preferences in TA742.[6] Landmark estimates predicted by the stratified Weibull curve are presented alongside clinical expert estimates for sorafenib PFS in Table 9, indicating that this survival extrapolation generally aligns with clinical expert estimates.

Table 9: Median and landmark rate estimates of PFS for sorafenib in *RET* fusion-positive TC

Parametric curve	5-year PFS (%)	10-year PFS (%)	20-year PFS (%)
Clinical expert estimates			
NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for selected extrapolation			
Stratified Weibull; no adjustment factor applied	[redacted]	[redacted]	[redacted]

Abbreviations: NA: not applicable; PFS: progression-free survival; RET; rearranged during transfection; TC: thyroid cancer.

Overall survival

In line with the survival extrapolations selected for selpercatinib and all relevant comparators for OS in the *RET* fusion-positive TC population, the piecewise exponential curve was selected for sorafenib OS. As outlined in Section B.3.3.4 of the CS, this extrapolation aligns with committee preferences in TA742.[6] Alignment of the piecewise exponential extrapolation with clinical expert estimates is presented in Table 1 of this response document and is also reproduced in Table 10 below; as shown in this table, an adjustment factor of 2.7 was applied from 26 months and onwards in order to align sorafenib OS with clinical expert estimates.

Table 10: Landmark rate estimates of OS for sorafenib in *RET* fusion-positive TC

Year	Sorafenib OS estimates		
	Clinician landmark estimate	Before adjustment factor application	After adjustment factor application
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.

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Healthcare resource use

Adverse events

Probabilities of individual AEs, specifically, AEs above Grade 3 with at least a 2% difference in frequency between selpercatinib and relevant comparators, for sorafenib were sourced from the DECISION trial and are provided in Table 11.[12] Costs for each individual AE in the *RET* fusion-positive TC population are presented in Section B.3.5.3 of the company submission; any new costs for AEs that are specific to sorafenib are presented in Table 12 below.

Table 11: Incidence of Grade 3 or 4 adverse events included in the model for the *RET* fusion-positive TC population receiving sorafenib

Adverse event	Sorafenib (n=207)
Diarrhoea	5.80%
Hand foot syndrome	19.32%
Hypertension	9.18%
Decreased weight	5.80%
Abdominal pain	0.97%
Fatigue	4.83%
Decreased appetite	1.93%
Rash	4.83%
Vomiting	0.48%
Back pain	0.97%
Dyspnoea	4.35%
Alanine aminotransferase increased	2.90%
Aspartate aminotransferase increased	0.97%
Hypocalcaemia	8.70%
Stomatitis	0.48%

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.
Source: Brose et al. (2014)[19]

Table 12: Costs associated with adverse events included in the model for the *RET* fusion-positive TC population receiving sorafenib

Adverse event	Cost (£)	Source
Abdominal pain	1,789.01	NHS Reference costs 2021/22; TA516 (FD05B Abdominal Pain without Interventions; Non-Elective Inpatient)
Vomiting	3,042.95	NHS Reference costs 2021/22; TA516 (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Back pain	2,096.09	NHS Reference costs 2021/22; TA516 (HC32K Low Back Pain without Interventions, with CC

		Score 0-2; Non-Elective Inpatient)

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.
Source: NHS Reference Costs 2021/2022.[20]

Drug acquisition costs for sorafenib

Drug acquisition costs for sorafenib are presented in

Table 13. The approach to administration costs for sorafenib is in line with administration costs of oral treatments provided in Section B.3.5.1 of the CS.

Table 13: Drug acquisition costs for sorafenib

Regimen	Regimen description	Capsule strength	Capsules per pack	Pack cost	PAS discount	PAS pack cost
Sorafenib	400mg, orally, once daily	200 mg	112	£2,567.00	NA	NA

Abbreviations: BNF: British National Formulary; PAS: Patient Access Scheme.
Source: List prices for each treatment are sourced from the BNF.[21-25]

Additional inputs associated with sorafenib

- Health state utility values used for patients receiving sorafenib are aligned with the appraisal committee's preferences (see comment 3).
- A RDI multiplier was not included for sorafenib in the model, aligned with the appraisal committee's preferences for sorafenib (page 12, Section 3.9 of the DGD).
- Health state unit costs and resource use frequencies for patients receiving sorafenib in the model were aligned with the costs presented in the company submission, Section B.3.5.2.
- For sorafenib, TTD is assumed equal to PFS due to a lack of data on TTD in the DECISION trial; this likely represents a conservative assumption that underestimates sorafenib treatment costs.[12]
- No subsequent treatments were modelled for patients progressing on sorafenib in the model, aligned with the approach taken for all other comparators in the company submission. As noted in the company submission, this is based on feedback from UK clinical experts that no subsequent treatments are routinely available in UK clinical practice for patients with advanced, *RET*-altered TC or MTC who experience disease progression on currently available treatments or selpercatinib.[10]

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Appendix C: Updated QALY Shortfall Analysis

The QALY shortfall analysis for all comparators in the *RET*-mutant MTC and *RET* fusion-positive TC populations, in addition to those for sorafenib, have been re-run using the corrected age in the *RET*-mutant MTC population and the committee's preferred health state utility values, as shown in Table 14. Results of the QALY shortfall analysis are presented in Table 15, demonstrating that selpercatinib is eligible for the 1.2 severity modifier versus BSC in both populations.

Table 14: Summary features of QALY shortfall analysis

Factor	Value	Updated from Company base case?
***RET*-mutant MTC**		
Sex distribution	39.0%	No
Starting age (mean)	[redacted]	Yes
Health state utility: PF	[redacted]	Yes
Health state utility: PD	[redacted]	Yes
***RET*-fusion positive TC**		
Sex distribution	50.8%	No
Starting age	[redacted]	No
Health state utility: PF	[redacted]	Yes
Health state utility: PD	[redacted]	Yes

Abbreviations: MTC: medullary thyroid cancer; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year; TC: thyroid cancer.

Table 15: Summary of QALY shortfall analysis

Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
***RET*-mutant MTC**			
Cabozantinib	11.44	81.59%	1
BSC	12.11	86.37%	1.2
***RET*-fusion positive TC**			
Lenvatinib	10.41	77.74%	1
Sorafenib	11.05	82.52%	1
BSC	11.74	87.67%	1.2

Abbreviations: MTC: medullary thyroid cancer; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

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Appendix D: Model corrections

During updates made to the cost-effectiveness model for this response (as outlined in comment number 1), a small number of minor errors were identified in the most recent version of the cost-effectiveness model for TC (submitted alongside the clarification question responses). These errors have subsequently been updated in the model for this response. These errors are outlined below:

1. In the "Country-Specific Data TC" tab; cells U79:W83, costs for 20mg lenvatinib alone were calculated from the second cycle and onwards, which resulted in no change in the costs when updating the dose intensity to 100%. This has now been corrected to 24mg lenvatinib with a 100% relative dose intensity multiplier, as illustrated below:

Figure 3: Illustration of original model (left) and updated model (right) for lenvatinib dose intensity

Active dose, cycle 2+		% Patients by tablet combination	
		53%	47%
Actual	17.20		
Check	17.20		1
		2	1
		63%	37%
Actual	325.60	2	1
Check	325.60		

Active dose, cycle 2+		% Patients by tablet combination	
		100%	0%
Actual	24.00		
Check	24.00	1	1
		2	1
		100%	0%
Actual	400.00	2	1
Check	400.00		

2. In the "Utilities – TC" tab, cell C19 previously featured a #REF! error – this has now been updated in the corrected model to "Sorafenib".
3. The formula in column N of the "TC S(t) (2)" was originally as follows, in the model submitted following clarification questions:

   "=IF(AND(hSO3=1,B10>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"

   This has now been updated to:

   "=IF(AND($O$3=1,B11>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"

   This update ensures that the adjustment factor (relevant to selpercatinib and sorafenib OS) is applied from the correct timepoint in the model.

Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [ID6132]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2024. Please submit via NICE Docs.

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Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [ID6132]

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Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Selpercatinib for untreated advanced thyroid cancer with RET alterations**
Topic ID: **6132**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **24/01/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	Selpercatinib is an anti-cancer drug and therefore eligible for the CDF. Further data collection via the LIBRETTO-531 clinical trial and the SACT dataset could offer further certainty in overall survival estimates. However, it is unclear whether this would be sufficient to enable a clear decision at the end of managed access.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Suitable candidate for CDF.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Yes	OS data is still being collected through LIBRETTO-531 trial.
Can data collection be completed without undue burden on patients or the NHS system	Yes	Ongoing trial + SACT dataset
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered

1	In the draft guidance, the committee alluded to both wanting more data to be collected but also possibly being satisfied with survival extrapolations as currently presented. Which of these 2 scenarios is committee most happy with?
2	Given the above, are the committee satisfied that the burden of additional data collection, a managed access process and a reappraisal at managed access exit will produce benefits that outweigh that burden?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	30/01/2024

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	As an anti-cancer medicine, selpercatinib is eligible for funding through the CDF.

NICE internal considerations	Supporting Evidence
Potential to address a high unmet need	One-year survival rates of patients with Stage IV thyroid cancer is 77%.
Potential to provide significant clinical benefits to patients	QALY gains are significant for patients.
represents a step-change in medicine for patients and clinicians	Targeted treatment earlier in the pathway would allow patients with RET fusion to experience fewer toxic side effects.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	See uncertainties tab

System implementation	Supporting Evidence
The technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning	

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Low	With the help of LIBRETTO-531 and SACT data, it would be possible to collect (OS) data to establish the impact of RET mutation status and line of treatment on clinical effectiveness results. However, committee were content at ACM1 with the extrapolations shown, so it is unclear whether managed access would be appropriate.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
DG1	RET fusion-positive TC: limitations of company naïve, unadjusted indirect treatment comparisons	Due to a lack of direct evidence, the company performed naïve, unadjusted indirect treatment comparisons (selpercatinib versus lenvatinib, versus sorafenib and versus BSC). Naïve, unadjusted indirect treatment comparisons do not account for differences in baseline patient characteristics and results are highly uncertain and subject to bias. These comparisons were populated with any-line data from the LIBRETTO-001, the SELECT, and the DECISION trials. LIBRETTO-001 trial patients had RET fusion-positive TC. The RET mutation status of patients enrolled in the SELECT and DECISION trials is unknown. Therefore, the generalisability of company indirect comparison results to the population specified in the final scope issued by NICE (i.e., systemic therapy-naïve patients with RET fusion-positive TC) is unclear.	None. The EAG is not aware of any: • methods that could be used to generate robust evidence of comparative efficacy for systemic therapy-naïve patients with RET fusion-positive TC • comparator data for systemic therapy-naïve patients with RET fusion-positive TC. Therefore, the EAG is not able to suggest any alternative approaches.	Unquantified	Seek clinical advice to assess the impact of RET fusion-positive status and line of treatment on clinical effectiveness results.	Further evidence submission ahead of ACM	No further data collection possible / proposed	The committee concluded it was likely that selpercatinib improved progression-free and overall survival compared with cabozantinib, lenvatinib, sorafenib and BSC, but that it was uncertain by how much, because of the many uncertainties in the 2 indirect treatment comparisons. The committee would also like to see analyses including sorafenib.

DG2	RET-mutant MTC and RET fusion-positive TC populations: selpercatinib overall survival estimates	The company selpercatinib OS estimates did not match company clinician 10-year and 20-year estimates. This issue was raised in the clarification letter. In response to clarification, the company applied an adjustment factor at 5 years so that OS estimates were more closely aligned with clinical expert 10-year and 20-year estimates than with the estimates generated by the unadjusted distribution.	The EAG has generated exploratory cost effectiveness results using pessimistic and optimistic adjustment factors to provide an indication of the impact of the uncertainty around the 10-year and 20-year survival estimates suggested by company clinical experts.	Medium	Clinical advice to identify the most appropriate approach to generating OS estimates for patients treated with selpercatinib may be helpful.	Further evidence submission ahead of ACM / LIBRETTO-531	Medium	Whilst clinical advice may help to somewhat address this uncertainty, further evidence collection through managed access within the CDF is limited to 5 years and could not provide sufficient insight on the 10-year or 20-year survival. LIBRETTO-531 trial started in 2020 and is expected to complete in 2026 and SACT data would be collected for a maximum of 5 years. Further data cuts from LIBRETTO-531 are only expected for the MTC population. The committee concluded that the overall survival extrapolations were uncertain, but that the company's extrapolations were in line with the clinical experts' estimations and therefore could be used for decision-making. The committee also agreed that the EAG's optimistic and pessimistic scenarios showed the plausible range of uncertainty.
DG3	RET-mutant MTC population: cabozantinib overall survival estimates	The company generated cabozantinib OS estimates by applying the EXAM trial HR to the stratified Weibull distribution (applied to EXAM trial placebo arm data) that was used to generate BSC OS estimates.	The EAG considers that OS estimates that are closer to company clinical expert 10-year and 20-year OS estimates can be generated by applying the EXAM trial HR to spline 1 knot distribution fitted to EXAM trial placebo arm (BSC) data.	Medium	Clinical advice to identify the most appropriate approach to generating OS estimates for patients treated with cabozantinib may be helpful.	Further evidence submission ahead of ACM	No further data collection possible / proposed	The committee agreed that the EAG's extrapolation of cabozantinib was more in line with the clinical experts' estimates of overall survival. It therefore concluded that it was more appropriate to use the EAG's method of generating an overall survival curve for cabozantinib.
DG4	RET-mutant MTC and RET fusion-positive TC populations: health state utility values	The company progression-free health state utility value appears quite high (0.8) as they are close to the population norm. The company progressed-disease health state value (0.5) appears implausibly low, particularly as clinical advice to the EAG is that patient health-related quality of life usually only deteriorates during the last 6 months of life and all patients spend more than 2 years in the progressed disease health state regardless of treatment.	Alternative health state utility values based on LIBRETTO-001 trial EORTC-QLQC-C30 data collected from the any-line RET fusion-positive TC population, whilst not without limitations, appear more plausible.	Medium	Clinical opinion.	Further evidence submission ahead of ACM / Committee judgement required	No further data collection possible / proposed	The committee concluded that the utility values mapped from LIBRETTO-001 should be used in the model.
DG5	Cabozantinib and lenvatinib drug costs: use of RDI rather than adherence data	The company applied RDI multipliers to doses of cabozantinib and lenvatinib. As the lenvatinib and cabozantinib pack prices are the same regardless of dose size, dose adherence data should have been used to calculate treatment costs instead of RDI. When discussing cabozantinib, the NICE TA928 AC preferred adherence data to RDI data.	None.	Unquantified	Cabozantinib adherence data may be available from the LIBRETTO-531 trial.	Further evidence submission ahead of ACM	No further data collection possible / proposed	The committee concluded that in the absence of adherence data, relative dose intensity should be removed in the model for cabozantinib and lenvatinib, but not for selpercatinib. The committee also noted that an analysis comparing selpercatinib with sorafenib in the RET fusion-positive thyroid cancer population should not include relative dose intensity for sorafenib.

DG6	RET-mutant MTC population: severity modifier calculation	The company used the incorrect age in the severity modifier calculation tool. The mean age of the LIBRETTO-001 trial RET-mutant MTC population is not an integer and as the severity modifier tool only accepts integers, a rounded up version of the age should have been used.	The EAG used an integer value of the rounded average years in the severity modifier tool.	Unquantified	None.	Committee judgement required	No further data collection possible / proposed	RET-mutant MTC population: severity modifier of 1.2 is no longer appropriate for the comparison of selpercatinib versus cabozantinib when using the probabilistic cabozantinib QALY value. When using the deterministic cabozantinib QALY value, a severity modifier of 1.2 is appropriate. The committee concluded that in a pairwise analysis, a severity modifier of 1.2 could be applied to the comparisons with BSC for both populations, but not to the comparisons with cabozantinib or lenvatinib. It also concluded that it was unknown whether a severity modifier would apply to a comparison with sorafenib.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	The LIBRETTO-531 trial is still ongoing with outcome measures such as OS still being measured. However, data cuts are only expected for patients with medullary thyroid cancer with a RET mutation and not for all RET-fusion positive thyroid cancers.

LIBRETTO-531 Clinical trial data	
Anticipated completion date	Feb-26
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT04211337
Start date	Feb-20
Data cut presented to committee	Jan-23
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/35969032/
Description of trial	Primary completion data May 2023. Primary outcome measure:PFS. A Multicentre, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients With Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer, n=291

LIBRETTO-001 Clinical trial data	
Anticipated completion date	Feb-26
Link to clinicaltrial.gov	https://classic.clinicaltrials.gov/ct2/show/NCT03157128
Start date	May-17
Data cut presented to committee	Jan-23
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/32846061/
Description of trial	Phase 1/2 open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity of selpercatinib (also known as LOXO-292) administered orally to participants with advanced solid tumours, including rearranged during transfection (RET)-fusion-positive solid tumours, medullary thyroid cancer (MTC) and other tumours with RET activation. n=875. Cohort 4 is Advanced RET-mutant MTC participants who are treatment naïve (closed). 7 cohorts overall. Primary completion estimated to be February 2025.

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	This is an anti-cancer drug, with the primary data source being the ongoing clinical trials. The secondary data source could be the SACT dataset.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHSE's SACT dataset is an established mandatory dataset.
Prior experience with managed access	High	NHSE have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHSE have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHSE follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS Digital have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHSE's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, Blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSE to link Blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	-
Analyses		

How easily could collected data be incorporated into an economic model	High	Individual-level patient data is available for the economic model. Subgroups of interest should be identified at the point of managed access entry so all relevant analyses can be produced.
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	-
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Not applicable	-
Patient consent	Yes	No prior patient consent required
Funding		
Existing funding	Yes	
Additional funding required for MA	No	-
If yes, has additional funding been agreed in principle	Not applicable	-
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created

Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	-

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	RET status testing would need to be incorporated into routine practice in order to ensure the relevant patients are offered the treatment, but this would not stop access to a MAA.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Primary source of evidence generation is the clinical trial. Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access.
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Not applicable	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative drugs fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Unclear	This is unlikely at this stage as managed access is not yet confirmed. However, the company have experience with managed access and know what is expected of them.

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	RET status testing is available on the NHS but and currently part of routine practice/screening at the NHS Genomic Medicine Service. According to the company, "testing is included in the 2023/2024 National Genomic Test Directory for Cancer, with NGS panel testing now available on the National Health Service (NHS) for all solid and blood cancers."
	Will implementation subject the NHS to irrecoverable costs?	No	It is unlikely that there will be irrecoverable costs, as this is already available.

	Is there an existing service specification which will cover the new treatment?	Yes	Selpercatinib and RET fusion screening available, even if not currently routinely offered.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	
	If yes, are these different to what would be used if the technology had been recommended for routine use?	No	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There is not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access. The company already have this technology in the CDF.