NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Eli Lilly
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. NCRI-ACP-RCP-RCR
   b. Society for Endocrinology
      Thyroid Cancer Forum-UK
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews Ltd
5. **Evidence Review Group – factual accuracy check**
6. **Technical engagement response** from Eli Lilly
7. **Technical engagement response & expert statement from experts:**
   a. [redacted], patient expert nominated by Association for Multiple Endocrine Neoplasia Disorders
   b. Kirstie Purnell, patient expert nominated by Association for Multiple Endocrine Neoplasia Disorders
   c. Kate Garcez, clinical expert nominated by NCRI-ACP-RCP-RCR
8. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews Ltd

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for the treatment of advanced RET-fusion positive thyroid cancer and advanced RET-mutant medullary thyroid cancer [ID3744]

Document B

Company evidence submission

6th October 2020

File name	Version	Contains confidential information	Date
ID3744_Eli Lilly_Selpercatinib in TC_Document B_ACIC	Final	Yes – ACIC	6th October 2020

Contents

Tables and figures

List of Abbreviations

Abbreviation	Definition
ACIC	Academic/commercial in confidence
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	Adverse event of special interest
AG	Analysis group
AIC	Academic in confidence
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society for Clinical Oncology;
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid cancer
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criteria
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BOR	Best objective response
BSC	Best supportive care
CAP	College of American Pathologists
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
cfDNA	cell free DNA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computerised tomography
CUA	Cost utility analysis
CYP3A4	Cytochrome P450 3A4
DLT	Dose limiting toxicity
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DTC	Differentiated thyroid cancer
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
ED	Extendedly dominated
EMA	European Medicines Agency
EORTC QLQ-C30	European Platform of Cancer Research Quality of Life Questions C30
EQ-5D	EuroQol-5D
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy–General
FISH	Fluorescein in-situ hybridisation
FTC	Follicular thyroid cancer
HR	Hazard ratio
HRQoL	Health related quality of life
IAS	Integrated analysis set
ICER	Incremental cost-effectiveness ratio
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardisation/Independent Ethics Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan–Meier
LPS	Lansky Performance Score
LTFU	Long term follow-up
LYG	Life years gained
MAIC	Matching-adjusted indirect comparisons
MEN2	Multiple endocrine neoplasia type 2
MKI	Multikinase inhibitor
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NE	Not evaluable
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OSAS	Overall safety analysis set
PAS	Patient access scheme
PAS	Primary analysis set

PASLU	Patient Access Scheme Liaison Unit
PCR	Polymerase chain reaction
PD	Progressed disease
PD1	Programmed death receptor 1
PDTC	Poorly differentiated thyroid cancer
PF	Progression free
PFS	Progression free survival
PH	Proportional hazards
PK	Pharmacokinetics
PPI	Proton pump inhibitors
PPPY	Per patient per year
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Papillary thyroid cancer
QALY	Quality-adjusted life years
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAI	Radioactive iodine
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised control trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RET	Rearranged during transfection
RP2D	Recommended Phase II dose
RPSFT	Rank preserving structural failure time
RR-DTC	Radioactive iodine refractory differentiated thyroid cancer
SACT	Systemic anticancer therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SAS1/2/3	Supplemental analysis set 1/2/3
SD	Stable disease
SE	Standard error
SFU	Safety follow-up
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of Product Characteristics

SRC	Safety Review Committee
STiDAT	Systemic Treatment-Induced Diarrhoea Assessment Tool
TC	Thyroid cancer
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitors
TLR	Targeted literature review
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TTD	Time to discontinuation
UK	United Kingdom
US	United States
VEGFR	Vascular endothelial growth factor receptor
WTP	Willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The submission for the advanced *RET* fusion-positive thyroid cancer (TC) population is narrower than the technology's full anticipated marketing authorisation for selpercatinib 'as monotherapy for advanced *RET* fusion-positive TC adults with who require systemic therapy and whose disease has progressed following prior ***systemic*** treatment'. It is in line with the full anticipated marketing authorisation for MTC 'as monotherapy in adults and people aged 12 years and over with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy'.

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal as outlined in Table 1.

CDF statement

Data, in particular the OS data, from the LIBRETTO-001 trial are immature and thus there are considerable uncertainties in the evidence base which can be resolved with further data collection. For example, the LIBRETTO-001 trial is ongoing and further data cuts may be available following the publication of the appraisal, a Phase III trial to investigate the efficacy and safety of selpercatinib versus standard treatment (cabozantinib or vandetanib) in adult patients with untreated RET-Mutant MTC (LIBRETTO-531; NCT04211337) is currently recruiting and collection of data via the systemic anticancer therapy (SACT) cohort may further reduce uncertainty. Therefore, selpercatinib is positioned as a candidate for approval on the Cancer Drugs Fund (CDF) in this submission.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Populations	***RET*-fusion positive TC:** People with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment ***RET*-mutant positive MTC:** People with advanced *RET* mutation-positive medullary thyroid cancer (MTC) who require systemic therapy	***RET*-fusion positive TC:** Adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment ***RET*-mutant MTC:** Adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy	***RET*-fusion positive thyroid cancer:** The population considered in the decision problem specifies that patients must have received prior systemic therapy. This is in narrower than the full anticipated marketing authorisation for selpercatinib in TC, and is in line with the subgroup in the LIBRETTO-001 trial that received prior systemic therapy. ***RET*-mutant MTC:** This patient population is in line with the full anticipated marketing authorisation for selpercatinib in MTC and the eligibility criteria for the LIBRETTO-001 trial, where patients with MTC either received prior systemic therapy with 1 or more lines of prior cabozantinib or vandetanib, or were naïve to cabozantinib or vandetanib.
Intervention	Selpercatinib	Selpercatinib	N/A – in line with the NICE final scope
Comparator(s)	For advanced *RET* fusion-positive thyroid cancer which has progressed following prior treatment: • Lenvatinib or sorafenib for differentiated thyroid cancer which did not respond to radioactive iodine (adults only) • Best supportive care or palliative care	***RET*-fusion positive TC:** • Best supportive care (BSC) or palliative care ***RET*-mutant MTC:** • Cabozantinib • Best supportive care or palliative care	***RET*-fusion positive TC:** The population for the submission focusses on patients who have received prior systemic therapy, in line with the previously treated subgroup of the LIBRETTO-001 trial. In clinical practice, this leaves the only remaining treatment as BSC (MKI following radioactive iodine and MKI retreatment not being permitted by TA535), thus representing the relevant comparator

	For advanced *RET* mutation-positive MTC: • Cabozantinib (adults only) • Best supportive care or palliative care		for *RET*-fusion positive differentiated TC patients. For other subtypes of TC (i.e. anaplastic or undifferentiated TC) there are no suitable systemic alternatives. Therefore, BSC is also considered a suitable comparator for these patients. ***RET*-mutant MTC:** N/A – in line with the NICE final scope. Cabozantinib is associated with significant toxicity, and thus a proportion of patients may not be eligible for first-line systemic therapy, with BSC representing the only remaining treatment option. Thus, BSC is considered a relevant comparator for patients who have progressed beyond or who are ineligible for first-line systemic therapy.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	**Primary endpoints** • Best overall response and objective response rate **Major secondary endpoints** • Duration of response • Time to response and time to best response • Clinical benefit rate • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	N/A – in line with the NICE final scope

Subgroups to be considered	If the evidence allows, subgroups based on the following will be considered: • Type of thyroid cancer within advanced *RET* fusion-positive TC (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma) • Specific type of *RET* alteration (within *RET* fusion-positive TC or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib • Line of treatment (position in pathway)	• No subgroups have been considered for the economic analysis by type of thyroid cancer • No subgroups have been considered for the economic analysis by specific type of *RET* alteration • For *RET* fusion-positive TC, no subgroups have been considered for the economic analysis by line of treatment	• Insufficient data were available to conduct subgroup analyses for selpercatinib according to thyroid cancer type. Patients in the thyroid cancer arm were predominantly papillary, therefore analysis is not possible for the TC population. • Insufficient data for comparator therapies were available to conduct subgroup analyses according to *RET*-alteration. • In the *RET* fusion-positive TC population, the population for the submission focusses on patients who have received prior systemic therapy, in line with the previously treated subgroup of the LIBRETTO-001 trial, thus subgroup analysis by line of therapy is not relevant to the decision problem. • In the *RET*-mutant MTC population, data are presented in the submission separately for patients who had received prior cabozantinib or vandetanib or who were treatment-naïve to cabozantinib or vandetanib in the LIBRETTO-001 trial. However, no data were available for comparators that were stratified by line of therapy, and thus the base case economic analysis focuses on the pooled “any-

			line" population as more data was available for the analysis making it more robust.

Abbreviations: MKI: multikinase inhibitor; MTC: medullary thyroid cancer; NICE: National Institute for Health and Care Excellence; RET: rearranged during transfection; TC: thyroid cancer.
Source: Selpercatinib Draft SmPC[1], ID3744: NICE Final Scope[2]

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of selpercatinib in the treatment of RET-fusion positive TC and RET-mutant MTC is presented in Table 2.

Table 2: Technology being appraised

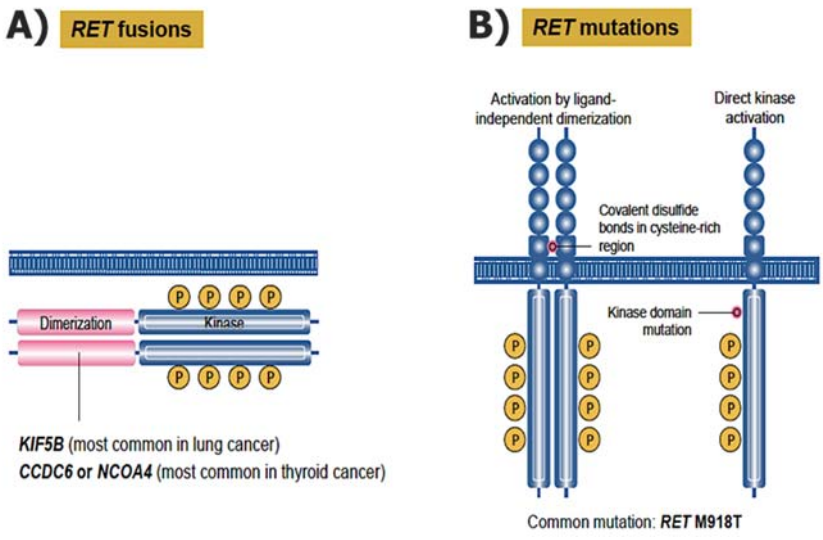
UK approved name and brand name	Selpercatinib (Retsevmo®)
Mechanism of action	Selpercatinib is an highly potent, orally available, selective small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. The RET receptor tyrosine kinase is essential for normal development and maturation of various tissues and vital for the development, proliferation, differentiation, and survival of central and peripheral nerve lineages of neuroendocrine cells, notably of the thyroid, adrenal, and pituitary glands.[3] Chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET-fusion proteins that can act as oncogenic drivers, promoting cell proliferation and survival in tumour cell lines (Figure 1A). Point mutations in RET can also result in constitutively activated RET proteins that can promote cell growth and survival in tumour cell lines (Figure 1B).[1] Selpercatinib targeting within the kinome (the complete set of protein kinases encoded within the genome) is displayed in Figure 2. In contrast to mutilkinase inhibitors, which are non-selective and thus can be associated with off-target effects, selpercatinib is highly selective for RET, RET-fusion and RET-mutant variants.[1] **Figure 1: Domains of the RET receptor and sites of fusion and point mutation relevant in thyroid cancer**  **Abbreviations:** RET: rearranged during transfection. **Source:** Drilon *et al.* (2018)[4]

	Figure 2: Kinome selectivity of selpercatinib  **Abbreviations:** RET; rearranged during transfection **Source:** Drilon *et al.* (2018)[4]
Marketing authorisation/CE mark status	A conditional marketing authorisation application for selpercatinib for the treatment of RET-fusion positive TC and RET-mutant MTC was submitted to the European Medicines Agency (EMA) on [redacted] and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated EU marketing authorisation wording for the selpercatinib indications of interest for this submission are: "as monotherapy for the treatment of adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment" "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy" **Contraindications** • Hypersensitivity to the active substance or to any of the excipients
Method of administration and dosage	**Method of administration** • Oral **Dosage** • The recommended dose of selpercatinib is 160 mg orally, twice daily • Treatment should be continued until disease progression or unacceptable toxicity
Additional tests or investigations	An accurate and validated assay for the presence of a RET gene fusion (NSCLC and thyroid cancer) or mutation (MTC) in tumour specimens is necessary for the selection of patients for treatment with selpercatinib. Either RET fusion-positive or RET-mutant status should be established prior to initiation of selpercatinib therapy. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. While *RET*-mutant or *RET* fusion-positive status must be established prior to initiation of selpercatinib therapy, *RET*, next generation sequencing (NGS) and fluorescent in situ hybridisation (FISH) testing is included in the 2019/2020 National Genomic Test Directory for Cancer. In England, the transition to NGS testing, completed at Genomic Hubs, means it will be possible to test for *RET*

	rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres.
List price and average cost of a course of treatment	The proposed list price of a 60 capsule bottle of 80 mg or 40 mg selpercatinib is £[redacted]. The cost of a 28-day cycle of selpercatinib is £[redacted].
Patient access scheme (if applicable)	[redacted]

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EU: European Union; FISH: fluorescent in situ hybridisation; MTC: medullary thyroid cancer; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Drilon *et al.* (2018)[4], Mulligan *et al.* (2018) [3], Selpercatinib Draft SmPC[1]

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of the health condition

- Thyroid cancer (TC) is an uncommon type of cancer. In the UK, it is the twentieth most common cancer, accounting for 1% of all new cancer cases[5]
- There are five major histological subtypes of TC. Papillary thyroid cancer (PTC) and follicular thyroid cancer are classified as differentiated thyroid cancers (DTC) and account for around 90% of all TCs.[6] Hürthle cell TC accounts for approximately 4%[7] and anaplastic, or undifferentiated, TCs account for 1–3%.[6] These TCs develop in the follicular cells of the thyroid
- Medullary thyroid cancer (MTC), an etiologically distinct type of thyroid cancer developing in non-follicular cells, accounts for approximately 3% (adult) to 10% (paediatric) of TCs[8]
- TC is associated with generally good prognosis, though this is dependent on the subtype. Metastatic TCs, accounting for 4–15%, are associated with a higher mortality, with the more aggressive forms (anaplastic, MTC and Hürthle cell) having higher rates of metastases[9]
- *RET* alterations vary in prevalence by histological subtype. *RET* fusions have been identified in ranges from 5–40% in PTC, with incidence varying by geography, and are uncommon in other types of follicular TCs.[3, 10] Around 25% of MTC cases are hereditary and are predominantly associated with the *RET* mutations. MTC arises sporadically in about 75% of cases and *RET* somatic mutations, occur in about 40–50% of sporadic MTC[11]
- Relative tumour aggressiveness has also been associated with different *RET* alterations. Expression of the NCOA4-RET (RET/PTC3) fusion has been associated with a relatively aggressive variant of PTC.[12, 13] The most aggressive variants of hereditary MTC are associated with the M918T gene, which is also found predominantly in *RET*-mutant somatic MTC.[3, 14]
- Patients with thyroid cancer have poorer health-related quality of life (HRQoL) than the general population.[15] Key concerns include fatigue, pain, fear of recurrence of disease or second surgery, quality of sleep and sudden attacks of tiredness, physical and mental exhaustion, employment, and lumps in the neck.[16]
- MTC is associated with additional debilitating symptoms, including severe diarrhoea, Cushing syndrome, facial flushing, bone pain, lethargy and weight loss, as well as distant metastases.[17, 18] These symptoms may lead to workplace absence and lost productivity.[19]

Summary of the treatment pathway

- Following initial diagnosis and staging, where the size and tumour extension is evaluated, TC patients will typically either undergo a partial or full thyroidectomy. Patients with DTC will then typically undergo ablation with radioactive iodine.[20]
- In the UK, lenvatinib and sorafenib are the only treatments recommended for patients with DTC which is classified as progressive, advanced or metastatic which was not responsive to radioactive iodine, if they are tyrosine kinase inhibitor (TKI) naïve.[21] There is an unmet need for safe and effective treatments following TKI treatment as patient's only option is best supportive care (BSC)
- Anaplastic TC is associated with a worse prognosis, and BSC has a principal role in management of these patients[20]
- Cabozantinib,[22] but not vandetanib,[23] is recommended in the UK for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. There is an unmet need for safe and effective treatments following cabozantinib as patient's only option is best supportive care (BSC)

- Cabozantinib is also associated with a poor adverse event profile, leading to dose reductions and discontinuations.[24, 25] There is therefore a subset of cabozantinib naïve patients who are unable to tolerate the toxicity profile and will therefore receive BSC, highlighting the unmet need for safer, more effective treatments as an alternative to cabozantinib in untreated patients[26]
- Patients with *RET* altered thyroid cancer currently do not have access to a targeted therapy in England
- The transition to next generation sequencing panel tests for common oncogenic drivers (including RET) performed at Genomic Hubs in England, is anticipated to expedite the diagnostic process. This should allow clinicians to prescribe targeted therapies like selpercatinib with greater ease and convenience[27]

Position of selpercatinib

- Selpercatinib is being positioned in "adults with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment" and "people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy"
- For patients for *RET*-fusion positive TC in the UK, selpercatinib is positioned as an alternative treatment option to BSC in patients with advanced or metastatic DTC who were not responsive to radioactive iodine and who have previously received systemic therapy such as lenvatinib or sorafenib, and in patients with other subtypes of TC whose only option is BSC.
- For patients with *RET*-mutant MTC in the UK, selpercatinib is positioned as an alternative therapy to cabozantinib for untreated adult patients with progressive, unresectable locally advanced or metastatic MTC, as well as an alternative to BSC for patients who have who have been previously treated with or are ineligible for cabozantinib

B.1.3.1 Disease overview

Thyroid cancer is characterised by abnormal growth and proliferation of the cells in the thyroid gland, a small gland at the base of the neck. Thyroid cancer is usually asymptomatic and is often discovered incidentally via imaging studies (e.g. computed tomography [CT] scans and magnetic resonance imaging [MRI]) performed for another reason, or when patients present with a lump, a persistent hoarse voice, a sore throat and/or difficulty swallowing.[6] The thyroid is part of the endocrine system, secreting hormones to regulate a variety of vital bodily functions including metabolism, heart rate, central and peripheral nervous systems among others.[28] It is made up primarily of two types of cell: follicular cells, which produce thyroid hormones (tri-iodothyronine [T3] and thyroxine [T4]); and nonfollicular C cells, which produce calcitonin to regulate levels of calcium in the blood.[29]

There are five major histological subtypes of thyroid cancer (papillary, follicular, Hürthle cell anaplastic and medullary), depending on whether the cancer arises in the follicular or nonfollicular cells.[14, 29] Papillary, follicular, Hürthle cell and anaplastic thyroid cancers form in the follicular cells, whilst MTC forms in the nonfollicular cells and is associated with additional symptoms, such as persistent diarrhoea or flushing of the face due to dysregulation of calcitonin.[6, 14]

Thyroid cancer has been associated with specific genetic variations that either activate oncogenes or turn off tumour suppressor genes. *RET* fusions, alterations, or point mutations can occur in specific histological subtypes such as MTC and papillary thyroid cancer (PTC) resulting

in oncogenic activtion.[14] In *RET*-fusion positive PTC patients (accounting for 25% of all cases, though this varies significantly based on etiological factors), *RET* alterations are most typically acquired during a person's lifetime.[11] In MTC, nearly all patients with hereditary MTC (accounting for approximately 25% of all cases) have a mutation of the *RET* gene, while about 50% of sporadic MTC cases carry a *RET* mutation.[11] Other oncogenic mutations have been implicated in papillary, follicular and anaplastic thyroid cancers, include in genes such as *TRK*, *RAS*, *BRAF*, *PPARG* and *p53*.[30]

Disease classification and prognosis

Thyroid cancer is associated with generally good prognosis, with a five-year survival in the UK of 87% and a 10-year survival of 84%, though this is dependent on the subtype of thyroid cancer. Metastatic thyroid cancers are associated with a higher mortality, with a one-year survival of 100% for Stage I thyroid cancer patients and only 77% for Stage IV (metastatic) patients.[5]

Papillary and follicular thyroid cancer are classified as differentiated thyroid cancers (DTC) and account for around 90% of all thyroid cancers.[6] PTC is the most common subtype, accounting for approximately 80–85% of thyroid malignancies in Europe, and are associated with an excellent prognosis profile, with a five-year survival in men of around 90% and 95% in women. Mortality is associated with the low percentage of cases which metastasise.[6] Follicular thyroid cancer (FTC) is the second most common type, comprising approximately 5–10% of all thyroid cancers and is associated with a slightly higher mortality, with a five-year survival of 90% in both men and women.[6]

Hürthle cell cancers are a rare type of thyroid cancer accounting for approximately 4% of thyroid cancers.[7] Hürthle cell cancers are usually grouped with follicular thyroid cancers as they have some similarities, but affected thyroid tissue is histologically distinct and tumours grows more aggressively.[31] Hürthle cell thyroid cancer tends to affect more women than men.[7]

Anaplastic, or undifferentiated, thyroid cancers account for 1–3% of all thyroid cancers and are associated with a higher mortality due to their relatively rapid growth. Five-year survival for anaplastic thyroid cancer is only 10% in both men and women.[6]

Medullary thyroid cancer (MTC) is a rare cancer, accounting for approximately 3% (adult) to 10% (paediatric) of thyroid cancers.[8] It is associated with a higher mortality rate than DTC, with a five-year survival of 75% in men and 90% in women.[6] The two forms of MTC, sporadic and hereditary, are associated with different disease risk levels and several types of *RET* mutations are known to contribute to oncogenicity.[3] Sporadic *RET* mutations correlate with a more aggressive disease phenotype,[11] while hereditary MTC severity ranges depending on the specific mutation.[11]

Distant metastases occur in 4–15% of thyroid cancer patients, with the more aggressive forms tending towards a higher chance of metastases and the lungs being the most commonly affected organ.[9] Metastases to central nervous system (CNS) are unusual in TC, occurring in around 1% of patients with DTC and MTC and can cause acute disabling symptoms and a marked reduction of patients' survival.[9] For patients with DTC, median survival estimates ranging from 7.1–19 months have been reported in patients with brain metastases and higher survival times reported for patients treated with multikinase inhibitors (MKIs).[32]

RET alterations and prognosis in TCs

The *RET* oncogene was first discovered in 1985, with subsequent analysis of human tumours revealing that oncogenic RET fusion proteins, termed RET/PTC, are a feature of approximately 20-40% of PTCs, with these estimates varying globally and due to etiological factors.[3, 33] CCDC6-RET (also named RET/PTC1) is the most common, accounting for approximately 60% of *RET*-associated PTC, with NCOA4-RET (also named RET/PTC3) representing approximately 30% and PRKAR1A-RET (RET/PTC2) representing 10%. The remaining *RET/PTC* family members are extremely rare.[33]

Relative tumour aggressiveness has also been associated with different RET/PTC family members, although these findings remain controversial. Expression of the NCOA4-RET (RET/PTC3) fusion has been associated with the relatively aggressive solid histologic PTC variant, whereas CCDC6-RET (RET/PTC1) expression has been linked to the more indolent classic variant.[12, 13] Furthermore, RET/PTC fusions are less common in the indolent follicular variant of PTC relative to other histologic subtypes.[3] However findings refuting these data have also been reported, and there is therefore no consensus on whether *RET*-fusion positive TC is associated with a worse prognosis.[26, 34]

While most MTCs are sporadic and affect adult populations, a subset are familial and occur in the frame of inherited cancer syndromes called multiple endocrine neoplasia type 2 (MEN2) syndromes and may have an early onset.[14] The disease is further classified as two subtypes MEN2A and MEN2B, based on disease severity and associated phenotypes, with the less common and clinically more severe MEN2B subtype associated with earlier disease onset and more aggressive disease.[3] For patients with the MEN2B syndrome, the mutation of highest risk is the M918T, which is associated with the earliest onset and most aggressive phenotypes. In individuals with other mutations including the most common MEN2A mutation, C634R and the MEN2B A883F mutations, prognosis is also considered poor. The remaining, so-called 'moderate risk' *RET* mutations, may be associated with later or more variable age of onset.[3] Somatic mutations of *RET* (mainly M918, but also including E768 and V804) and are found in a subset of sporadic MTC cases and correlate with a poor prognosis versus *RET* wild type tumours.[3, 14]

Epidemiology

The World Health Organization reports thyroid cancer to be one of the top 10 cancers worldwide. The 5-year prevalence (all ages) of thyroid cancer in the UK was estimated to be 19,138 (28.7/100,000) in 2018.[35] In the UK, thyroid cancer is the twentieth most common cancer, accounting for 1% of all new cancer cases with approximately 3,700 new cases every year between 2015–2017 according to Cancer Research UK.[5] Over the last three decades, the incidence of thyroid cancer has increased by 164% and is projected to rise by 74% between 2014 to 2035.[5] Incidence rates for thyroid cancer in the UK are highest in people aged 65 to 69, and incidence is higher in males than females (1 in 332 UK males and 1 in 170 UK females will be diagnosed with thyroid cancer in their lifetime).[5]

Epidemiology data by histologic subtype and *RET* status are limited for *RET* fusion-positive TC. The most common *RET* alterations found in PTC occur as fusions between *RET* and CCDC6 and NCOA4. RET fusions are identified in about 5–40% of PTC tumours, with the incidence varying considerably in different patient series and by geography,[3, 10, 36-38] with an overall average of around 25%.[11] RET fusions are uncommon in thyroid cancer subtypes other than PTC. FTC,

the other major type of differentiated thyroid cancer, is generally negative for *RET* fusions. Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) may derive from pre-existing differentiated carcinomas, including PTC, and therefore a subset may inherit *RET* fusions.[39] In an analysis of a number of large databases (more than 60,000 tumour samples), *Landa et al.* (2016) found *RET* fusions in 2.32% (n=560) and 7.2% (n=500) of PTC cases, 0.93% (n=107) of ATC cases, and 4.47% (n=134) PDTC cases.[40] Similarly, in a recent study, 5.9% of PDTC but no ATC harboured *RET* rearrangements, suggesting that *RET* fusion-positive PTCs rarely progress to ATC.[41]

Of the approximately 25% of MTC cases that are hereditary (occurring as inherited MEN2 cancer syndromes), almost 100% are associated with mutations of the *RET* gene.[11] The more common subtype, MEN2A, represents >95% of cases, with the majority of mutations arising from substitutions of cysteine residues in the RET extracellular domain (C609, C611, C618, C620, C634). MEN2B represents the remainder, with a strong association with the more clinically severe M918T mutation.[3] MTC arises sporadically in about 75% of cases and *RET* somatic mutations, mainly M918T but also including E768 and V804, occur in about 40–50% of sporadic MTC.[11]

Symptoms and health-related quality-of-life impact of TC

The humanistic burden of *RET*-altered thyroid cancer is not well described, and there is a large data gap in the literature, with the majority of humanistic burden studies conducted in patients with MTC and PTC regardless of *RET* status. As discussed above, *RET* mutations are associated with a worse prognosis for patients with MTC and, whilst there is not yet consensus, some evidence suggest that *RET* fusions may be associated with worse prognosis for patients with DTC. Therefore, whilst there is a lack of evidence for the clinical and humanistic burden of *RET*-altered progressive, advanced or metastatic thyroid cancer specifically, the burden of disease is likely to be comparable or worse than thyroid cancer patients as a whole.

According to a survey of 110 patients with thyroid cancer across eight countries, the aspects of quality of life of most concern were fatigue, pain, fear of recurrence of disease or second surgery, quality of sleep and sudden attacks of tiredness, physical and mental exhaustion, employment, and lumps in the neck.[16]

PTC is usually diagnosed in asymptomatic patients during medical evaluations for other reasons. Lumps in the neck are the most common primary symptom in symptomatic patients, followed by difficulty swallowing or breathing, pain or tenderness around the neck or ears, and change in voice quality. More subtle symptoms include throat clearing and cough.[42] Patients with PTC have poorer health-related quality of life (HRQoL) than the general population, as shown by a prospective observational study of 186 patients with PTC who had undergone thyroidectomy compared with 186 healthy volunteers.[15] The patient expert consulted as part of TA535 indicated that patients with radioactive iodine-refractory DTC subtypes experience debilitating symptoms such as pain and fatigue that can impact severely on their quality of life.[21] It is likely that patients with who do not respond to, are contraindicated to or do not tolerate treatment with a MKI have equally severe, if not worse HRQoL outcomes.

MTC presents similarly to PTC, with the most common primary presentation of sporadic MTC is a palpable neck mass, followed by neck lump, neck pain, hoarseness, coughing, dysphagia and shortness of breath. However, due to the additional dysregulation of calcitonin signalling,

additional side effects often occur, including severe diarrhoea, Cushing syndrome, facial flushing, bone pain, lethargy and weight loss.[17] Severe diarrhoea may be debilitating and can lead to problems with nutrition. Distant metastases may result in additional symptoms including spinal cord compression, bone fracture, bronchial obstruction and pain.[18] Debilitating symptoms associated with MTC (for example, severe diarrhoea) may lead to workplace absence and lost productivity.[19]

Economic burden

The economic burden of *RET*-altered thyroid cancer is not well described, and there is a large data gap in the literature. However, thyroid cancer as a whole is a costly, resource-intensive disease, and costs and use of healthcare resources increases with advanced disease. In a US study, approximately 54% of all patients diagnosed with thyroid cancer had at least one thyroid cancer-related hospitalisation during 12-month follow-up, with an average of 3 days' hospital stay.[43] For all patients (N=6,823), the all-cause total health care cost per patient per year (PPPY) was $17,112; patients with MTC had a considerably higher cost at $24,977 PPPY, and cost for those with any advanced thyroid cancer was highest at $46,910.[43] The overall cost-of-care burden of thyroid cancer in the US was estimated at $1.6 billion in 2013 (patients who received diagnoses after 1985) and between $3.1 billion and $3.5 billion expected cost in 2019.[44]

Thyroid cancer also has a considerable economic burden on patients. Employment is a frequent issue reported by patients with thyroid cancer, as patients are relatively young and the disease and its treatment affect their ability to work.[16] In a US study, patients with thyroid cancer were reported to have a higher risk of bankruptcy than other patients with more aggressive forms of cancer.[45] In Israel, the income of patients with thyroid cancer, 2 and 4 years after diagnosis, has been shown to be lower than in the general population, likely due to patients working only part time or having reduced physical functioning.[46]

Mortality

Whilst the prognosis is favourable for newly-diagnosed thyroid cancer patients (1- and 5-year overall survival is 91.4% and 87.4%, respectively),[5] prognosis is considerably worse for patients who are at an advanced stage of disease. The 5-year survival rate is 78% for metastatic PTC, 63% for metastatic FTC, 39% for metastatic MTC and only 4% for metastatic anaplastic thyroid cancer.

Mortality for *RET*-altered thyroid cancer is not well described. As described above, there is no consensus on whether *RET*-fusion positive TC is associated with a worse prognosis.[26, 34] However, somatic mutations of *RET* correlate with a poor prognosis versus *RET* wild type tumours.[3, 14] A study of 100 sporadic MTC patients with a 10.2-year mean follow-up found a positive correlation between the presence of the somatic *RET* mutations and the persistence of the disease (p=0.0002).[47] Survival curves for MTC patients also showed a significantly lower percentage of surviving patients in the group with *RET* mutations (p=0.006).[47] Survival estimates for advanced *RET* M918T-positive MTC patients are available from the EXAM trial, where median OS was 44.3 months for patients receiving cabozantinib and 18.9 months for patients receiving placebo.[24]

B.1.3.2 Clinical pathway of care

Treatment guidelines for thyroid cancer are available from the UK National Multidisciplinary Guidelines[20] and the British Thyroid Association[30], with NICE due to publish guidelines on the treatment of thyroid cancer in April 2022.[48] Currently, the only treatments that have been appraised by NICE for the treatment of progressive, locally advanced, or metastatic thyroid cancer are MKIs. These include lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535),[21] vandetanib for treating MTC (TA550)[23] and cabozantinib for treating MTC (TA516).[22]

Thyroid cancer diagnostic pathway

TC is usually diagnosed in asymptomatic patients during medical evaluations for other reasons. Thyroid nodules or neck masses are the most common primary symptom in symptomatic patients. Other symptoms patients may experience at diagnosis include difficulty swallowing or breathing, pain or tenderness around the neck or ears, and change in voice quality. More subtle symptoms include throat clearing and cough. Any diagnosis associated with change in voice, swallowing, breathing, or pain requires prompt and thorough evaluation.[42]

Ultrasonography is routinely used to evaluate thyroid nodules. The initial diagnosis of TC is made with ultrasound-guided fine needle aspiration to sample cells from the thyroid or neck lymph nodes. Aspiration is generally done on all thyroid nodules large enough to be felt. Results can be insufficient for a differential diagnosis to determine the underlying histology of TC and to discover atypical cells of undetermined significance.[42] Anaplastic thyroid cancers tend to be more aggressive, and many patients present with a history of a rapidly enlarging thyroid mass in a long-standing goitre. Diagnosis can be established by fine needle aspiration or core biopsy.[20]

Various additional tests can be reviewed to confirm a differential diagnosis, including imaging studies (computed tomography scans, magnetic resonance imaging tests, and positron emission tomography/computed tomography scans) and blood tests (thyroid-stimulating hormone [TSH], thyroglobulin, thyroglobulin antibodies, and T3 and T4 tests).[49] These tests in combination will determine the histology, size, stage and extension of the tumour, which in turn will determine the appropriate treatment strategy.[20]

RET testing in the UK

Confirmation of *RET*-testing will be required in order to determine eligibility for selpercatinib. In England, key oncogenic drivers previously used single gene fluorescence in-situ hybridisation (FISH) testing, performed on biopsy samples sequentially increasing the time taken to make a molecular diagnosis. However, the current transition to next generation sequencing (NGS), completed in Genomic Hubs, will mean a panel of genetic mutations, rearrangements and fusions (including *RET*-fusions) can be identified.[27] This will expedite the diagnostic process and allow clinicians to use targeted therapies, like selpercatinib, with fewer barriers.

Thyroid cancer treatment pathway

As the long-term prognosis for patients treated effectively for DTC is usually favourable, with an overall 10-year survival rate of 84% in the UK,[5] the objective of treatment is to balance the risk of recurring disease with avoiding exposure to unnecessary surgeries or side-effects of treatments in patients with a good prognosis.[30] Following initial diagnosis and staging, where the size and extension of the tumour is evaluated, patients will typically either undergo a partial or full thyroidectomy. Hürthle cell cancers tend to be more aggressive, and should be treated by total

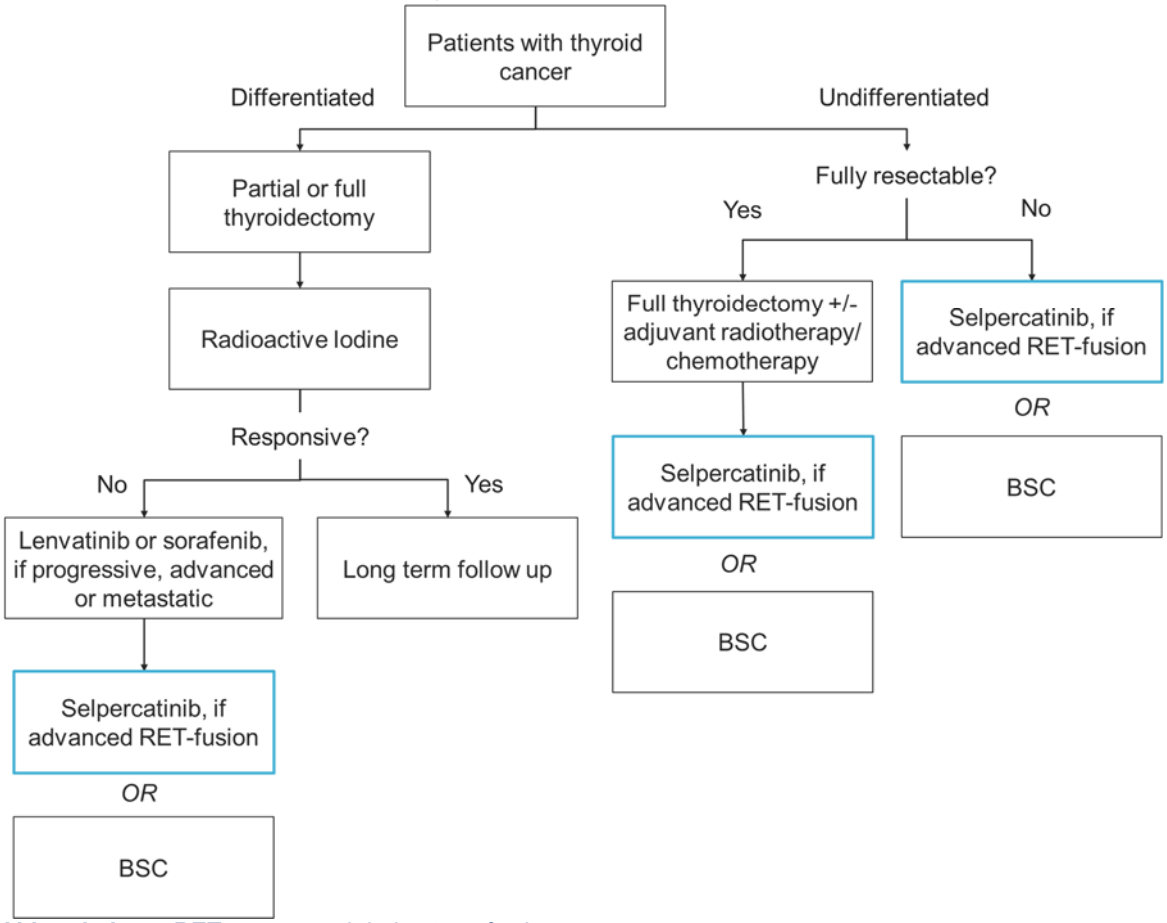
thyroidectomy.[20] The majority of patients with a tumour more than 1 cm in diameter, who have undergone total or near-total thyroidectomy, have I^{131} (radioactive iodine) ablation.[20] Patients who develop local, regional or metastatic disease (5–20% of patients) not amenable to surgery should be treated with radioactive iodine therapy.[20]

Around 5% to 15% of people with DTC develop radioactive iodine refractory DTC.[50] In the UK, lenvatinib and sorafenib are the only treatments recommended for patients with DTC who are classified as progressive, advanced or metastatic who were not responsive to radioactive iodine, if they are tyrosine kinase inhibitor naïve (TA535).[21] In a systematic literature review of these treatments, median overall survival (OS) was estimated to be between 32 and 41.6 months for patients receiving lenvatinib, and between 23 and 39.4 months for sorafenib.[50] At present there are no *RET*-specific treatments available for use in the UK.

The long-term prognosis for anaplastic (undifferentiated) TC is considerably worse, therefore total thyroidectomy may be curative for very small cancers, and in more advanced disease, surgery may be of benefit only if full resection can be achievable. External beam radiotherapy and chemotherapy may be used as adjuvant treatments in patients undergoing resection and no evidence of distant disease. 'Debulking' surgery, whereby tumour mass is reduced but not totally resected, should be avoided when complete resection cannot be achieved. Palliative chemoradiation may be of some value in selected cases. BSC has a principal role in management of these patients.[20]

The proposed treatment pathway and positioning of selpercatinib for adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment is outlined in Figure 3.

Figure 3: Treatment pathway and proposed positioning of selpercatinib in patients with advanced RET fusion-positive thyroid cancer



Abbreviations: RET; rearranged during transfection

Unmet need in thyroid cancer

MKIs are often associated with several off-target effects, resulting in a high rate of adverse events. In the SELECT trial which assessed the efficacy of lenvatinib for treating progressive, locally advanced or metastatic DTC, adverse events Grade ≥3 were reported in 85% of patients in patients treated with lenvatinib (n=261), compared to 30% in patients treated with placebo (n=131). Dose interruptions (82%), reductions (68%) and discontinuation (16.5%) were also higher in patients treated with lenvatinib than placebo (18%, 5% and 5% respectively). [24, 25]

For patients who do not respond to, are contraindicated to or do not tolerate treatment with MKIs, there are no further safe and effective treatment options, and patients are treated palliatively with best supportive care (BSC). There is therefore an unmet need for safe and effective treatments in this patient group following MKI therapy.

For patients with undifferentiated subtypes of TC there are no safe and efficacious treatments available and patients are most often treated palliatively with BSC, representing a substantial unmet need.

Medullary thyroid cancer diagnostic pathway

MTC typically presents similarly to DTC, with a thyroid nodule or neck mass, difficulty swallowing or breathing, pain or tenderness around the neck or ears, and change in voice quality, throat clearing and cough. History, however, may reveal other symptoms such as flushing, loose stools or diarrhoea and is vitally important in determining a potential familial element due to the relatively high rates of hereditary MTC.[20]

For patients undergoing differential diagnosis, a similar process is used for DTC, whereby ultrasound guided fine needle aspiration may be sufficient to diagnose MTC. In addition, evaluation of blood and tumour calcitonin and carcinoembryonic antigen (CEA) levels can be done if the initial diagnosis is uncertain, as these will typically be higher in patients with MTC versus other thyroid malignancies.[20]

Confirmation of *RET*-testing will also be required in order to determine eligibility for selpercatinib in MTC patients. The current transition to NGS (as described above) is expected to facilitate identification of *RET* mutations, expediting the diagnostic process.

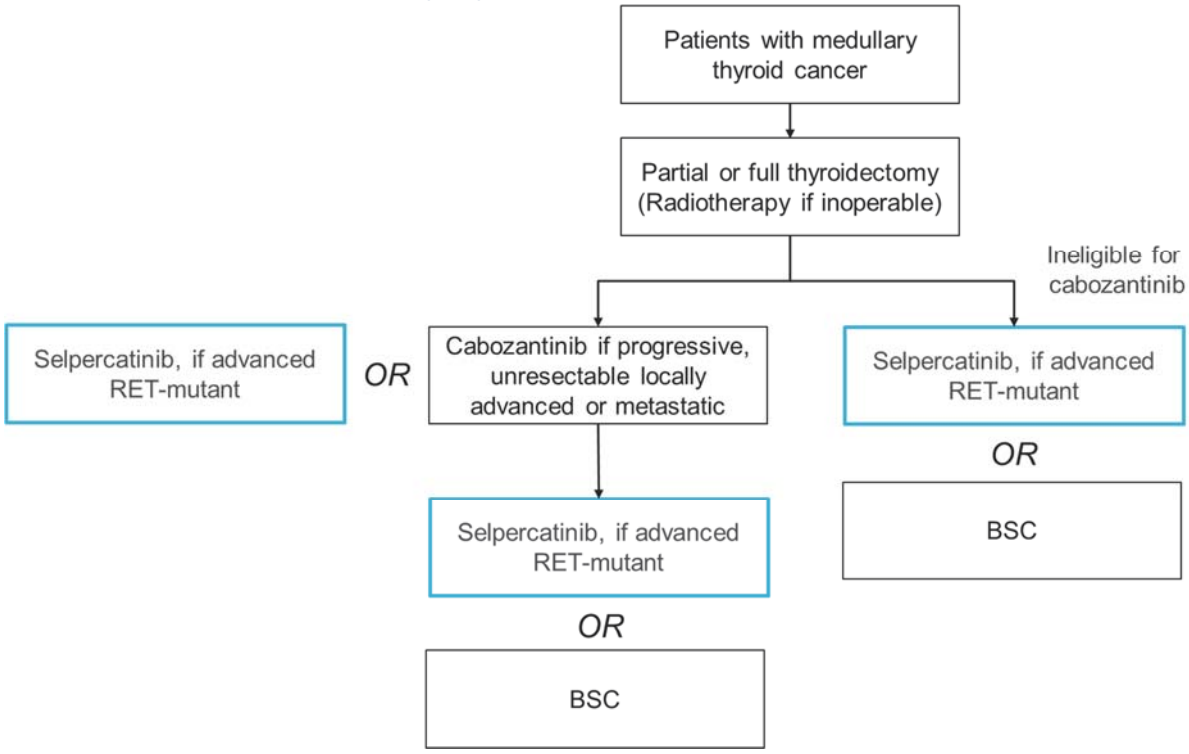
Medullary thyroid cancer treatment pathway

The long-term prognosis for patients with MTC is worse than that of DTC, but still remains favourable if treated effectively. Some patients may survive for many years even with a significant tumour burden, despite the poorer prognosis. This adds extra challenges when making decisions on the risk/benefit for persistent or recurrent disease when considering additional interventions.[30] Following diagnosis and staging, patients will typically undergo a partial or full thyroidectomy and, depending on the size of the tumour and the degree of nodal involvement, selective neck dissection. Radiotherapy may be used to control local symptoms in patients with inoperable disease.[20] Furthermore, prophylactic thyroidectomy should be offered to *RET*-positive family members.[20]

Cabozantinib,[22] but not vandetanib,[23] is recommended in the UK for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. In the EXAM trial, patients treated with cabozantinib showed a 5.5 month increase in median OS of 26.6 vs 21.1 months. However, this increase in overall survival is increased to 44.3 vs 18.9 months in patients with *RET* M918T-positive positive disease, demonstrating the benefit of targeting *RET* in this patient cohort. At present there are no *RET*-specific treatments available for use in the UK.

The proposed treatment pathway and positioning of selpercatinib for adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy is outlined in Figure 4.

Figure 4: Treatment pathway and proposed positioning of selpercatinib in patients with advanced RET-mutant medullary thyroid cancer



Abbreviations: RET; rearranged during transfection

Unmet need in medullary thyroid cancer

Cabozantinib is associated with a poor adverse event profile, leading to dose reductions in 82% of patients in the EXAM trial and 22% discontinuing treatment due to adverse events.[24, 25] According to a clinical expert experienced in the treatment of thyroid cancer, the significant toxicity associated with cabozantinib results in the majority of patients requiring a dose reduction within 6 months of treatment.[26] As a result, a subset of patients are not fit to receive first line cabozantinib, leaving them ineligible for treatment, with BSC representing their only treatment option. For patients who receive cabozantinib but who do not respond or who are unable to tolerate the side effect profile, there are no further safe and effective treatment options available, and patients are treated palliatively with BSC. There is therefore an unmet need for safe and effective treatment alternatives for patients who are naïve to systemic treatments, and for patients who have previously received cabozantinib.

As *RET* mutations are known to contribute to oncogenicity in MTC,[3] the highly selective targeting of the *RET* receptor allows for a potent anti-tumour response with minimal off target effects. Therefore, selpercatinib offers a safe and effective alternative to first line cabozantinib that specifically targets *RET* mutations to offer a less toxic regimen. Selpercatinib also provides an effective treatment option for those who are ineligible for first line cabozantinib, as well as those who do not respond or cannot tolerate cabozantinib, whose only other treatment option is BSC.

Positioning of selpercatinib

Selpercatinib is being positioned in “adults with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment ” and “people aged 12 years and over with advanced *RET*-mutant medullary thyroid cancer (MTC) who

require systemic therapy". NICE approval to use selpercatinib as a treatment to selectively inhibit *RET*-altered thyroid cancer in England and Wales would make it the first selective *RET* kinase inhibitor available to patients, representing a significant improvement in care for patients with *RET*-fusion positive thyroid cancer and medullary thyroid cancer. The evidence in support of the use of selpercatinib for these patients is based on the LIBRETTO-001 trial, a Phase 1/2 trial underpinning the conditional marketing authorisation application.

Due to the substantial inhibition of non-*RET* targets, MKIs are associated with drug-related adverse events that can limit chronic dosing and full on-target inhibition of RET.[10] With the high rate of adverse events, specific treatment strategies are required when using MKIs, which may add additional burden to the healthcare system through additional resource needed to manage these side effects.[24, 50] Therefore, with the highly specific and potent targeting of *RET* alterations, selpercatinib may offer an effective and side effect sparing treatment option in patients who progress following MKIs in *RET*-altered thyroid cancers, as a safe and effective alternative to cabozantinib for patients with *RET*-altered MTC, and as an effective treatment option for patients who are ineligible for cabozantinib due to its significant toxicity profile.

B.1.4 *Equality considerations*

There may be considerations relating to inequitable access to targeted treatments, due to regional variation in molecular testing practices. In England, the transition to NGS testing, completed at Genomic Hubs, means it will be possible to test for *RET* rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres. As such, this equality consideration is not expected to be a concern in this submission and highlights the urgency for NHS England to set up these services. No equality issues related to the use of selpercatinib in this indication have been identified or are foreseen.

B.2 Clinical effectiveness

Evidence for selpercatinib in *RET*-altered thyroid cancer

- The efficacy of selpercatinib in *RET* fusion-positive NSCLC has been demonstrated in LIBRETTO-001, a first in-human Phase I/II open-label trial

Efficacy

- The primary endpoint used in LIBRETTO-001 was objective response rate (ORR), defined as the proportion of patients with a best objective response (BOR) of confirmed complete response (CR) or partial response (PR) based on RECIST v1.1 and Independent Review Committee (IRC) assessment:
  - In the prior cabozantinib/vandetanib (treated) *RET*-mutant MTC population (integrated analysis set [IAS]), the ORR was [redacted]
  - In the cabozantinib/vandetanib naïve *RET*-mutant MTC population (untreated) (Supplemental analysis set 1 [SAS1]) the ORR was 72.7% (64/88; 95% CI 62.2, 81.7)[51]
  - In the previously treated *RET* fusion-positive TC population, the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9)[51]
- Key secondary outcomes assessed during LIBRETTO-001 included duration of response (DOR), PFS and OS by IRC assessment:

DOR

  - In the IAS *RET*-mutant MTC population, median DOR [redacted], with disease progression observed in only [redacted] of patients and median follow up of [redacted] months
  - In the SAS1 *RET*-mutant MTC population, median DOR 21.95 months (95% CI: NE, NE), with 4/64 progression events observed and median DOR follow-up of 7.79 months[51]
  - In the previously treated *RET* fusion-positive TC population, the median DOR was 18.43 (95% CI: 7.6, NE), with 6/15 events observed and median DOR follow-up of 17.51[51]

PFS

  - In the IAS *RET*-mutant MTC population, median PFS [redacted], with [redacted] alive and progression-free by IRC at the data cut-off
  - In the SAS1 *RET*-mutant MTC population, the median PFS by IRC was 23.56 months (95% CI: NE, NE), with 8/88 (9.1%) events observed and median follow-up of 11.07[51] months, with [redacted] patients alive and without documented disease progression
  - In the previously treated *RET* fusion-positive TC population, the median PFS by IRC was 20.07 months (95% CI: 9.4, NE), [redacted] events observed and median follow-up of 13.73 months, with [redacted] alive without documented disease progression[51]

OS

  - In the IAS *RET*-mutant MTC population, the median OS was not reached [redacted], with [redacted] of patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted]
  - In the SAS1 *RET*-mutant MTC population, the median OS was not reached [redacted]), with [redacted] patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted].

- In the previously treated *RET* fusion-positive TC population, the median OS was not reached [redacted], with [redacted] patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted].

- Patient reported outcomes were assessed from [redacted] patients with *RET*-mutant MTC using the European Platform of Cancer Research Quality of Life Questions C30 (EORTC QLQ-C30):
  - Of the [redacted] patients, [redacted] patients experienced definite improvement in the global health status/QoL subscale. Among patients with definite improvement, the median time to definite improvement was [redacted] months.
  - In line with clinical effectiveness measures, EORTC QLQ-C30 scores indicate a benefit to quality of life for advanced RET-mutant MTC patients receiving selpercatinib
- The results of LIBRETTO-001 demonstrate that treatment with selpercatinib results in a high and durable response rate for both pre-treated and untreated RET-mutant MTC and pre-treated RET fusion-positive TC patients and corresponds with benefits to patients' HRQoL

Safety

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (regardless of tumour type or treatment history) and specifically in those patients with *RET*-mutant MTC:
  - In the Overall Safety Analysis Set (OSAS) and the RET-mutant MTC Safety Analysis Set (SAS), permanent discontinuation of selpercatinib due to treatment-emergent adverse event (TEAE) were infrequent ([redacted] and [redacted] respectively), with no predominant pattern among the individual adverse events (AEs) reported
  - Grade 3 or 4 TEAEs were reported in [redacted] OSAS patients and [redacted] RET-mutant MTC SAS patients, irrespective of relatedness to selpercatinib. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication

Indirect Treatment Comparisons

- A matching-adjusted indirect comparison [MAIC] was conducted to compare the efficacy of selpercatinib in the any-line *RET*-mutant MTC population (IAS+SAS1) from the LIBRETTO-001 trial to cabozantinib and placebo in the EXAM trial. After weighting, the differences between treatments in PFS [redacted] versus cabozantinib ([redacted]; HR: [redacted]; 95% CI: [redacted]) and placebo ([redacted]; HR: [redacted]; 95% CI: [redacted]). After weighting, the differences between treatments in OS [redacted] versus cabozantinib ([redacted]; HR: [redacted]; 95% CI: [redacted]) and versus placebo ([redacted]; HR: [redacted]; 95% CI: [redacted]).
- A naïve indirect comparison was undertaken for the pre-treated *RET*-fusion population from LIBRETTO-001 to BSC. Acknowledging the limitations in the comparator data, evidence from the LIBRETTO-001 trial suggests that selpercatinib offers a considerable improvement in PFS compared with BSC. Median PFS was 20.07 (95% CI: 9.4, NE) months in the previously treated *RET* fusion-positive TC population (n=19) of the LIBRETTO-001 trial, compared with 3.6 (95% CI: 1.9, 3.7) in the pre-treated subgroup of the SELECT trial and 3.7 (95% CI: 3.5, 4.5) in the ITT population.

Innovation

- There are currently no targeted therapeutic options available on the NHS for *RET* altered TCs
- Selpercatinib offers a novel treatment approach and is the first treatment of its kind to demonstrate efficacy in *RET* altered TCs patients through highly selective targeting of the RET receptor
- For patients with RET-mutant MTC, cabozantinib is associated with significant toxicity, with 82% of patients requiring dose reductions and 22% discontinuing treatment due to adverse

events.[24] In contrast, in *RET*-mutant MTC patients treated with selpercatinib, dose reductions were seen in [redacted], with [redacted] of patients discontinuing treatment due to an AE
- For patients in the UK with RET-mutant MTC, selpercatinib may offer a safer and more effective treatment option than cabozantinib, as demonstrated by its markedly lower AE and discontinuation profile and higher ORR. Selpercatinib can also address the unmet need for patients who progress on or who are ineligible for cabozantinib due to its toxicity, who would otherwise be treated palliatively with BSC.
- Selpercatinib offers a safe and effective alternative to BSC in RET-fusion positive TC, extending survival for patients who are otherwise without effective treatment options.

Conclusion

- Clinical effectiveness and safety evidence from LIBRETTO-001 demonstrates that treatment with selpercatinib is well-tolerated and provides a clinically meaningful impact on the lives of patients with advanced *RET* altered TC. The high rates of durable response to selpercatinib treatment observed in LIBRETTO-001, paired with self-reported improvements in patients' quality of life, support the case for the use of selpercatinib in patients with *RET* altered TC who require systemic therapy in English clinical practice

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of selpercatinib in RET-altered solid tumours, including *RET* fusion-positive TC and *RET*-mutant MTC, namely 'as monotherapy for adults with advanced RET fusion-positive thyroid cancer (TC) who require systemic therapy and whose disease has progressed following prior systemic treatment' and 'people aged 12 years and over with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy'. The searches identified a total of 7,142 records, of which a total of 346 publications were ultimately included. No published evidence for selpercatinib was identified, but published data from comparators were identified to inform the indirect treatment comparison (ITC) and cost effectiveness analysis. Of these, 44 publications were identified that included patients with TC, of which 16 were primary reports, 11 of which were trials including patients with *RET*-altered tumours. Of the 16 primary reports, 11 were trials including patients with MTC, 3 included patients with PTC and 2 included patients with both MTC and PTC. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The main body of evidence for this submission is derived from the LIBRETTO-001 trial, which was used to support the conditional marketing authorisation application for selpercatinib in the TC and MTC indications. LIBRETTO-001 is an ongoing, multicentre, open-label, Phase I/II study to understand the pharmacokinetics (PK), safety, and maximum tolerated dose (MTD) for selpercatinib and to permit the preliminary assessment of efficacy and safety in patients with RET-altered solid tumours. It is the first in human Phase I/II study for selpercatinib. An overview of this trial is provided in Table 3.

The eligibility criteria for the LIBRETTO-001 trial was broader than the population of relevance for this submission, including patients ≥12 years old with locally advanced or metastatic solid tumours. A subset of patients in this study is in line with the population of relevance for this submission: 'as monotherapy for adults with advanced RET fusion-positive thyroid cancer (TC)

who require systemic therapy and whose disease has progressed following prior systemic treatment' and 'people aged 12 years and over with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy'.

Table 3: Clinical effectiveness evidence

Study	**LIBRETTO-001 (NCT03157128)**[52]		
Study design	A multicentre, open-label, Phase I/II study in patients with advanced solid tumours, with *RET activations*		
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), *RET*-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation) who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator, were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy, and an ECOG ≤2 or LPS ≥40% As of the 16th December 2019 data cut-off, enrolled patients included: • 226 patients with *RET*-mutant MTC • 27 patients with *RET* fusion-positive thyroid cancer		
Intervention(s)	Selpercatinib, once or twice daily, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study		
Comparator(s)	N/A		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use in the model	LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with *RET*-fusion positive TC who require systemic therapy and progressed on prior systemic therapy, and *RET*-mutant MTC patients who require systemic therapy.		
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • DOR • **PFS** • **OS** HRQoL: • EORTC QLQ-C30 Safety outcomes: • **AEs** • Changes from baseline in clinical safety laboratory and vital signs		
All other reported outcomes	• Best overall response • Clinical benefit rate • Best change in tumour size from baseline • CNS ORR		

	• CNS DOR • Time to any and best response • Determination of the safety and tolerability of selpercatinib • Characterisation of the pharmacokinetic properties

Abbreviations: AE: adverse event; BID: twice daily; BOR: best overall response; CBR: clinical benefit rate; CNS: central nervous system; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; LPS: Lansky Performance Score; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly LIBRETTO-001 CSR (17th June 2019 data cut-off)[52], Eli Lilly Data on File (16th December 2019 data cut-off)[52]

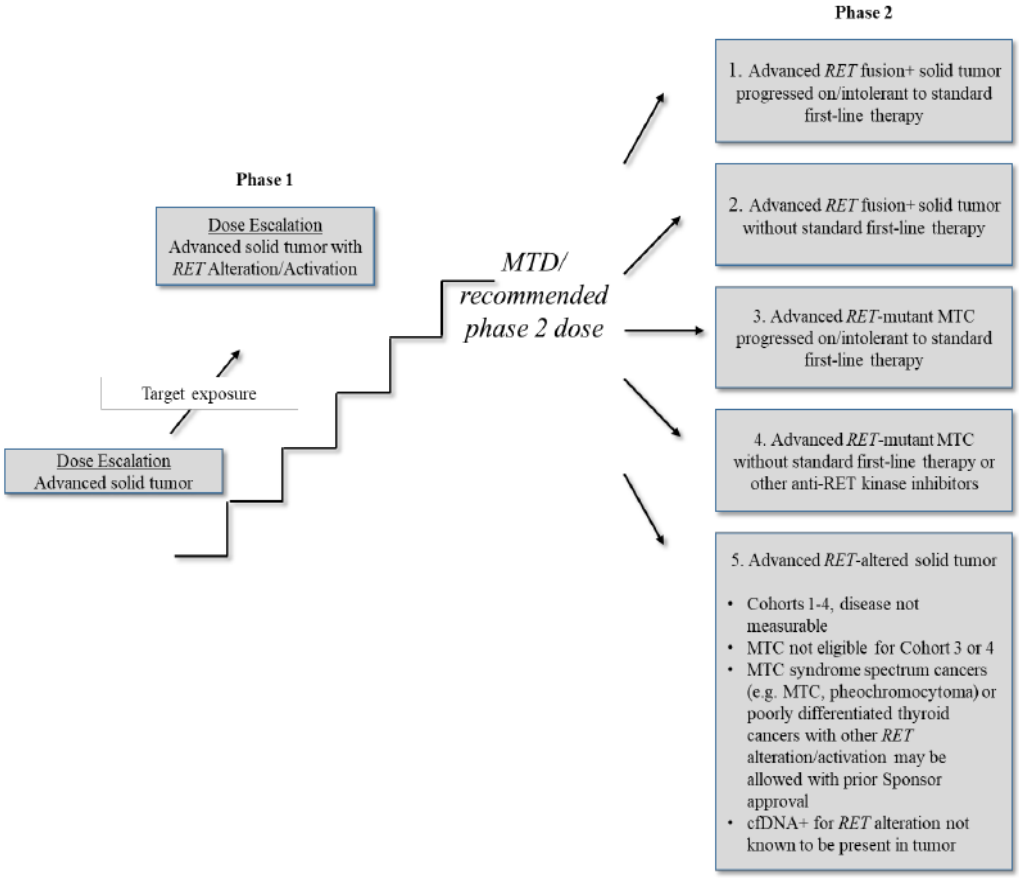
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

LIBRETTO-001

LIBRETTO-001 is an ongoing multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including *RET* fusion-positive solid tumours (e.g., non-small cell lung cancer [NSCLC], thyroid, pancreas, colorectal), *RET*-mutant MTC and other tumours with *RET* activation. The patient population includes patients as young as 12 years of age with a locally advanced or metastatic solid tumour, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy or declined standard therapy. Patients were screened for eligibility based on the criteria presented in Table 5, Section B.2.3.2. The study includes two phases: Phase I (dose escalation) in which patients were not selected based on *RET* alteration and Phase II (dose expansion), in which five cohorts of patients harbouring *RET* alterations were defined and in which the efficacy and safety of selpercatinib assessed. The study is currently in Phase II.[53] A schematic of the trial is presented in Figure 5. The most recent data cut-off for the interim analysis was 16th December 2019.

Figure 5. Study schema of the LIBRETTO-001 trial



Abbreviations: MTC: medullary thyroid cancer; MTD: maximum tolerated dose; cfDNA: cell free DNA; *RET*: rearranged during transfection.
Source: Eli Lilly LIBRETTO-001 CSR (17th June 2019 data cut-off) – Figure 1[52]

The primary objective of Phase I was to determine the MTD and the recommended Phase II dose (RP2D). During Phase I dose escalation, patients received selpercatinib dose levels that ranged from 20 mg once daily (QD) to 240 mg twice daily (BID), depending upon dose level assignment upon entry into the trial (total daily dose ranged between 20 and 480 mg).[54] A classical 3+3 dose escalation design was used, with 3 to 6 patients enrolled in each dose level cohort. [55] The starting dose of selpercatinib in oral capsule form was 20 mg QD for 1 Cycle. Cycles lasted 28-days. Escalation was to proceed through all dose levels or until the SRC and Sponsor determined that a suitable dose was achieved based on available data (safety, PK exposure, clinical activity).[54] Dose escalations were in increments of 100% above the previous dose level for the first 3 dose escalations. After the third dose increase, a modified Fibonacci dose escalation, where increments become smaller as the dose increases, was employed for any subsequent dose escalations, with increments of ~67%, ~50% and ~33%.[55] Additional dose escalations, if needed, were in increments of ~33%.[54] Each dose level after the starting dose represented the maximum dose to which patients were to be escalated, and no individual dose escalation was to be more than twice the dose at the previous level. Based on results from Phase I, the SRC selected an RP2D of 160 mg.[54]

Patients were subsequently enrolled into one of five Phase II cohorts to better characterise the safety and efficacy of selpercatinib in patients with specific abnormalities in *RET*. Classification into cohorts was based on tumour type, type of *RET* alteration and prior treatment (Table 4).

Table 4. LIBRETTO-001 patient cohorts

Patient cohort	Description
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy
Cohort 3	***RET*-mutant MTC** progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib
Cohort 4	***RET*-mutant MTC** without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity
Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample

Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RET: rearranged during transfection.

For Cohorts 1 to 4, evidence of a *RET* gene alteration in the tumour was required. *RET* fusion-positive TC patients were enrolled into Cohorts 1 and 2, whilst *RET*-mutant MTC patients were included in Cohorts 3 and 4 (Table 4). Individual patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity, or other reasons for treatment discontinuation.[54] Four weeks after the last dose (at least 28 days [+ a maximum of 7 days] after the last dose of study drug), all treated patients had a safety follow-up (SFU) assessment. Patients with documented PD could continue selpercatinib if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the Sponsor. The primary endpoint for the Phase II portion of the trial was overall response rate (ORR) using RECIST v1.1. Secondary oncological endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS), whilst the safety, tolerability and PK properties of selpercatinib were also considered.

In line with the decision problem for this submission, only results for the clinical effectiveness of selpercatinib in adults with advanced *RET* fusion-positive thyroid cancer (TC) who require systemic therapy and whose disease has progressed following prior systemic treatment and people aged 12 years and over with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy have been presented.

B.2.3.2 Trial methodology

A summary of the methodology and trial design of LIBRETTO-001 is presented in Table 5.

Table 5: Summary of LIBRETTO-001 trial methodology

Trial name	LIBRETTO-001
Location	A total of 84 investigational study sites across 16 countries worldwide have participated to date: United Kingdom, Canada, United States,

	Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy, Israel
Trial design	A multicentre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET-alterations
Eligibility criteria for participants	**Inclusion criteria** • At least 18 years of age (for countries and sites where approved, patients as young as 12 years of age could be enrolled) • Patients with a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy • For patients enrolled into the Phase II dose expansion, evidence of a *RET* gene alteration in tumour (i.e., not just blood), was required (a positive germline test for a *RET* mutation was acceptable for patients with MTC), see Table 9 • ECOG performance status of 0, 1, or 2 (age ≥16 years) or LPS ≥40% (age <16 years) with no sudden deterioration two weeks prior to the first dose of study treatment **Exclusion Criteria** • Phase II Cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment • Major surgery (excluding placement of vascular access) within four weeks prior to planned start of selpercatinib • Radiotherapy with a limited field of radiation for palliation within one week of the first dose of study treatment (with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least four weeks prior to the first dose of study treatment) • Any unresolved toxicities from prior therapy greater than NCI CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy • Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression (unless neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery) • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QTcF interval >470 msec on at least 2/3 consecutive ECGs and mean QTcF >470 msec on all 3 ECGs during Screening • Active uncontrolled systemic bacterial, viral, or fungal infection or clinically significant, active disease process, which in the opinion of the Investigator makes the risk:benefit unfavourable for the patient to participate in the trial. Screening for chronic conditions is not required • Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug

	• Uncontrolled symptomatic hyperthyroidism or hypothyroidism • Uncontrolled symptomatic hypercalcaemia or hypocalcaemia • Pregnancy or lactation • Active second malignancy other than minor treatment of indolent cancers
Method of study drug administration	Selpercatinib was administered in oral form, and was administered QD or BID, depending upon dose level assignment. A RP2D of 160 mg BID was selected during Phase I of the study.
Permitted and disallowed concomitant medication	**Permitted** Standard supportive medications used in accordance with institutional guidelines and Investigator discretion: • Haematopoietic growth factors to treat neutropoenia, anaemia, or thrombocytopaenia in accordance with ASCO guidelines (but not for prophylaxis in Cycle 1) • RBC and platelet transfusions • Anti-emetic, analgesic, and antidiarrheal medications • Electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels • Glucocorticoids (approximately 10 mg per day prednisone or equivalent, unless there was a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc. • Thyroid replacement therapy for hypothyroidism • Bisphosphonates, denosumab and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism • Hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone or luteinizing hormone-releasing hormone agonists) and breast cancer (e.g. aromatase inhibitors, selective estrogenic receptor modulators or degraders), that the patient was on for the previous 28 days **Disallowed** • Prior treatment with a selective RET inhibitor(s) • Concomitant systemic anti-cancer agents • Haematopoietic growth factors for prophylaxis in Cycle 1 • Therapeutic monoclonal antibodies • Drugs with immunosuppressant properties • Medications known to be strong inhibitors or inducers of CYP3A4 (moderate inhibitors/inducers could be taken with caution. If patients received strong CYP3A4 inhibitors/inducers, then the Sponsor was consulted to determine whether to stop selpercatinib or remove the patient from the study) • Herbal products, such as St John's wort, which could decrease the drug levels of selpercatinib • Investigational agents (other than selpercatinib) • No new, alternative systemic anticancer therapy was allowed prior to documentation of progressive disease • The concomitant use of PPIs was prohibited, and patients were to discontinue PPIs 1 or more weeks prior to the first dose of selpercatinib.

	• Histamine type-2 blocking agents were required be administered only between 2 and 3 hours after the dose of selpercatinib • Antacids e.g., aluminium hydroxide/magnesium hydroxide/simethicone or calcium carbonate, if necessary, was required to be administered 2 or more hours before and/or after selpercatinib
Primary outcome	**Phase I** Identification of the MTD, and the RP2D of selpercatinib for further clinical investigation. **Phase II** The primary endpoint was ORR based on RECIST 1.1 or RANO, as appropriate to the tumour type as assessed by IRC.
Secondary and exploratory outcomes	**Secondary endpoints** • Phase I: determination of the safety and tolerability of selpercatinib, characterization of the PK properties, and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST 1.1 or RANO • Phase II: BOR, DOR, CBR, CNS ORR, CNS DOR, PFS, OS, AEs, and changes from baseline in clinical safety laboratory values and vital signs, characterisation of pharmacokinetic properties **Exploratory endpoints** • Determination of the relationship between pharmacokinetics and drug effects (including efficacy and safety) • Evaluations of serum tumour markers • CEA and calcitonin (MTC), thyroglobulin (for patients with non-MTC thyroid cancer), and ACTH/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment with selpercatinib • Characterisation of *RET* gene fusions and mutations • Concurrently activated oncogenic pathways by molecular assays, including NGS from tumour biopsies and cfDNA • Collection of PROs data to explore disease-related symptoms and health related quality of life HRQoL
Pre-planned subgroups	The primary objective was analysed by several demographic variables for MTC patients enrolled in the PAS population (see Table 6, Section B.2.3.3 for a definition of this analysis set): • Age (≥65 versus <65) • Sex (male versus female) • Race (white versus other) • ECOG (0 versus 1–2) • Metastatic disease (yes versus no) The primary objective was also analysed by type of *RET* mutation and type of *RET* molecular assay used for MTC patients enrolled in the PAS population: • Mutation: o M918T o Extracellular cysteine mutation

	o V804M/L o Other • Molecular assay: o NGS on blood or plasma o NGS on tumour o PCR o Other The primary objective was also analysed by number of previous therapies or type of prior therapy received for MTC patients enrolled in the PAS population: • Number of prior therapies (1–2 versus 3) • Type of prior systemic therapy (prior cabozantinib versus prior vandetanib only versus prior cabozantinib and vandetanib)
Duration of study and follow-up	The study is ongoing. The first patient was treated on 9th May 2017. At the latest data cut-off of 16th December 2019, the median follow-up was [redacted] (for OS in patients in the IAS. See section B.2.3.3 for definition of IAS) Individual patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity, or other reasons for treatment discontinuation. Four weeks (28 days + a maximum of 7 days) after the last dose of study drug, all treated patients underwent a SFU assessment. All patients were also to undergo LTFU assessments every 3 months.

Abbreviations: ACTH: adrenocorticotropic hormone; AE: adverse event; ASCO: American Society for Clinical Oncology; BID: twice daily; BOR: best overall response; CBR: clinical benefit rate; CEA: carcinoembryonic antigen; cfDNA: circulating free DNA; CNS: central nervous system; CYP3A4: cytochrome P450 3A4; DOR: duration of response; ECGs: electrocardiograms; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL: health related quality of life; IRC: independent review committee; LPS: Lansky Performance Score; LTFU: long term follow-up; MTC: medullary thyroid cancer; NGS: next generation sequencing; NCI CTCAE: National Cancer Institute Common Terminology for Adverse Events; ORR: objective response rate; OS: overall survival; PD: disease progression; PFS: progression free survival; PPI: proton pump inhibitors; PRO: patient reported outcome; QD: once daily; QTcF: QT interval corrected for heart rate using Fridericia's formula; RANO: Response assessment in neuro-oncology criteria; RBC: red blood cell; RECIST: response evaluation criteria in solid tumours; RET: rearranged during transfection; RP2D: recommended Phase II dose; SFU: safety follow-up.
Source: Eli Lilly LIBRETTO-001 CSR (17th June data cut-off)[52], Eli Lilly Data on File (16th December 2019 data cut-off)[52]

B.2.3.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets

As discussed in Section 0, the eligibility criteria for the LIBRETTO-001 trial was broader than the population of relevance for this submission, including patients ≥12 years old with locally advanced or metastatic solid tumours. For the purposes of analysis, efficacy data sets were categorised into broad groupings of patients with *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive thyroid cancer, as shown in Figure 6. Definitions of the key study populations for *RET*-mutant MTC and *RET* fusion-positive patients included in the LIBRETTO-001 trial are presented in Table 6.

Figure 6: Enrolment and derivation of analysis sets in the LIBRETTO-001 trial

[1]*RET* fusion-positive other tumours: pancreatic cancer, rectal neuroendocrine cancer, salivary gland cancer, carcinoid, colon, small intestine, and xanthogranuloma. [2]Other solid tumours that do not fit the other disease cohorts. [3]Prior systemic therapy other than platinum-based chemotherapy. [4]Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 or Phase II Cohort 5. [5]Previously treated *RET* fusion-positive thyroid cancer defined as ≥1 prior systemic therapy in addition to radioactive iodine, if indicated. [6]Systemic therapy-naïve *RET* fusion-positive thyroid cancer defined as 0 prior systemic therapy other than radioactive iodine, if indicated.
Abbreviations: cabo: cabozantinib; IAS: integrated analysis set; MTC: medullary thyroid cancer; n: number of patients within category; NSCLC: non-small cell lung cancer; PAS: primary analysis set; *RET*: rearranged during transfection; SAS: supplemental analysis set; vande: vandetanib.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Table 6: Analysis set definitions

Trial name	LIBRETTO-001
***RET*-mutant MTC**	
Primary analysis set (PAS) (n=55)	The first *RET*-mutant MTC patients enrolled in Phase I and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET*-mutation prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* mutation co-occurring with another oncogenic driver, as determined at the time of study enrolment by local testing, were included. 2. Measurable disease[a] by RECIST 1.1 by investigator assessment 3. Received 1 or more lines of prior therapy of cabozantinib or vandetanib 4. Received 1 or more doses of selpercatinib

	The PAS provides evidence for the clinically meaningful efficacy of selpercatinib in patients with *RET*-mutant MTC who have received prior systemic therapy.	
Integrated analysis set (IAS) (n=124)	• All *RET*-mutant MTC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1–4 • Included all PAS patients and those treated after the 55th patient but on or before the data cut-off This IAS provides further evidence for the efficacy of selpercatinib in patients with *RET*-mutant MTC who have received prior systemic therapy in a larger number of patients, providing increased confidence in the PAS results.	
Supplementary analysis set (SAS)	• All other RET-mutant MTC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date. • **SAS1:** met PAS criteria 1, 2, and 4 • **SAS2:** met PAS criteria 1 and 4 • SAS assignment was non-overlapping, thus, SAS1/2 are mutually exclusive with each other.	SAS1 (Cabozantinib and vandetanib naïve) (n=88) • Could have received therapies other than cabozantinib or vandetanib SAS2 (Non-measurable disease) (n=14) • No measurable disease[b]
***RET* fusion-positive TC**		
Previously treated (n=19)	Patients who received a prior systemic therapy other than radioactive iodine	
Systemic therapy naïve (n=8)	Patients who did not receive any prior systemic therapy other than radioactive iodine	
Safety set		
Overall safety analysis set ([redacted])	Patients of the total LIBRETTO-001 patient population that received at least one dose of selpercatinib at the 16th of December data cut-off	
MTC safety analysis set ([redacted])	*RET*-mutant MTC patients in the LIBRETTO-001 patient population that received at least one dose of selpercatinib at the 16th of December data cut-off	

[a] Patients without measurable disease who were enrolled in Phase I dose escalation were included in the PAS. [b] Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later).
Abbreviations: BID: twice daily; CLIA: Clinical Laboratory Improvement Amendments; IAS: integrated analysis set; MTC: medullary thyroid cancer; PAS: primary analysis set; RECIST 1.1: Response Evaluation Criteria in Solid Tumours, Version 1.1; RET: rearranged during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Summary of clinical data cut-off dates

An interim analysis was conducted for 531 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 17th June 2019 data cut-off.

The results presented and analysed in this submission are based on a pre-planned analysis of efficacy and safety data from a 16th December 2019 data cut-off, unless noted otherwise. The

16th December 2019 data cut-off provides an additional 6-months follow-up for safety and efficacy information for the 531 patients originally enrolled in LIBRETTO-001 as of 17th June 2019 data cut-off, as well as safety information for additional patients enrolled since the initial interim analysis ([redacted] patients in total). As of 16th December 2019, [redacted] of responders in the *RET*-mutant MTC PAS had reached 6 months of follow up from the date of onset of initial response.

The efficacy evaluable dataset includes data up until 16th December 2019 for the 531 patients who had been treated with selpercatinib as of 17th June 2019. Of these patients, [redacted] were treated at the RP2D of 160 mg twice daily. Efficacy data for new patients enrolled into LIBRETTO-001 between 18th June 2019 and 16th December 2019 are not included in this discussion.

The safety evaluable data set includes all [redacted] patients treated with selpercatinib as of the 16th December 2019 data cut-off.

Statistical methods

Table 7: Statistical methods for the primary analysis of LIBRETTO-001

Trial name	LIBRETTO-001
Hypothesis objective	Phase I • The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib Phase II • The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	• Efficacy analyses per starting dose may not provide dose–response information, given that intra-patient dose escalation was allowed during Phase I. Therefore, efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyses • The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the investigator are presented in Appendix L • For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response • Best overall response was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e. the crude proportion of patients with best overall response of CR or PR) • Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions • The estimate of the ORR was accompanied by 2-sided 95% exact binomial confidence intervals (CI)
Sample size, power calculation	**Phase I** • Three to six patients were to be enrolled in each dose cohort based on a 3+3 design. Each patient was to participate in only a single dose cohort for the purpose of DLT evaluation (however, after completion of the DLT evaluation period, intra-patient dose escalation was allowed, provided that the patient was tolerating their current dose, and the dose level

	to which the patient was escalated to had already been evaluated, had a DLT rate of <33%, and was declared safe by the SRC) • A starting sample size of at least three patients per dose cohort, expanding to six patients in the event of a marginal DLT rate (30%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e. observing two or more patients with DLT). If a true DLT rate of 50% was assumed, then there would be an 89% chance that dose escalation would be halted in a given cohort • During Phase I, selected dose cohorts previously declared safe by the SRC could be expanded to a total of approximately 15 patients to further investigate the tolerability, PK and biological activity of selpercatinib • The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1–8), a total of approximately 120 patients would be enrolled in Phase I **Phase II** • For Cohort 1 (patients with *RET* fusion-positive solid tumours who progressed on or were intolerant to standard first-line therapy for their cancers), a true ORR of ≥50% was hypothesised when selpercatinib was administered to patients with such malignancies. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%. Ruling out a lower limit of 30% was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly defined patient populations who have failed prior therapies • For Cohort 2 (patients with *RET* fusion-positive solid tumours without prior standard first-line therapy), a true ORR of ≥55% was hypothesised when selpercatinib was administered to such patients. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35% • For Cohort 3 (patients with *RET*-mutant MTC who progressed on or were intolerant to vandetanib and/or cabozantinib), a true ORR of ≥ 35% was hypothesised when selpercatinib was administered to such patients. A sample size of 83 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% was considered clinically meaningful in patients who have failed prior MKI therapy (e.g., cabozantinib) and currently have limited treatment options for their advancing disease

	• For Cohort 4 (patients with *RET*-mutant MTC who are MKI-naïve), a true ORR of ≥ 50% was hypothesised when selpercatinib was administered to such patients. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%. • Notwithstanding the statistical considerations above, if approved by the SRC, enrolment beyond the above sample sizes in each of Cohorts 1 through 5, was allowed, in order to accommodate enrolment demand and allow for the characterization of AEs that may occur with low frequency • With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% was 77.9% and 95.2%, respectively. Up to ~150 patients in Cohort 1 would be allowed to accommodate enrolment of other *RET* fusion-positive solid tumours
Data management, patient withdrawals	Data censoring conditions for DOR, OS and PFS were as described below. If a patient met more than one of these conditions, then the scenario that occurred first was used for the analysis. **DOR and OS** DOR and OS were right censored for patients who met one or more of the following conditions: • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression o Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or experienced documented disease progression after missing two or more consecutively scheduled disease assessment visits o Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit • Alive and without documented disease progression on or before the data cut-off date o Censored at the date of the last evaluable disease assessment **PFS** PFS was right censored for patients who met one or more of the following conditions: • No postbaseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event) o Censored at the date of the first dose of selpercatinib • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression o Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits o Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit

	• Alive and without documented disease progression on or before the data cut-off date o Censored at the date of the last evaluable disease assessment

Abbreviations: AE: adverse event; CI: confidence interval; DLT: dose limiting toxicity; DOR: duration of response; MTD: maximum tolerated dose; ORR: objective response rate; OS: overall survival; RET: rearranged during transfection; PFS: progression-free survival; PK: pharmacokinetic; RP2D: recommended Phase II dose; SRC: Safety Review Committee.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib in the first line and second line setting for *RET* fusion-positive NSCLC patients. Definitions for these outcome measures are presented in Table 8.

Table 8. Definitions for outcome measures used in LIBRETTO-001

Outcome measure	Definition
Primary outcome	
Objective response rate	ORR was defined as the proportion of patients with BOR of confirmed CR or confirmed PR based on RECIST v1.1. Best overall response was defined as the best response designations for each patient recorded between the date of the first dose of selpercatinib and the data cut-off, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery Definitions of response by RECIST v1.1 are as follows:[57] • **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm • **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters • **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression) • **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
Secondary outcome	
Duration of response	DOR was calculated for patients who achieved either a CR or PR. For such patients, DOR was defined as the number of months from the start date of CR or PR (whichever response was observed first) to the first date that recurrent or progressive disease was objectively documented. If a patient died, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death was used to denote the response end date
Progression free survival	PFS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented progressive disease, as per RECIST v1.1 or death (whatever the cause)
Overall survival	OS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause)

EORTC QLQ-C30	The EORTC QLQ-C30 is a validated instrument that assesses HRQoL in adult cancer patients. It includes a total of 30 items and is composed of scales that evaluate physical (5 items), emotional (4 items), role (2 items), cognitive (2 items) and social (2 items) functioning, as well as global health status (2 items). Higher mean scores on these scales represent better functioning. There are also 3 symptom scales measuring nausea and vomiting (2 items), fatigue (3 items) and pain (2 items), and 6 single items assessing financial impact and various physical symptoms. Higher mean scores on these scales represent better functioning or greater symptomology. EORTC QLQ-C30 subscale scores range from 0 to 100 Descriptive analyses reported median/quartile, mean/standard deviation and mean change/standard error from baseline for each subscale at each study visit. A clinically meaningful difference was defined as 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[58] Patients with "improvement" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients with "worsening" were defined as those who demonstrated a decrease by ≥10-points from their baseline score. A definite change (improvement or worsening) was defined as an improvement or worsening, respectively, as defined above without any further change in score ≥10 points

Abbreviations: BOR: best overall response; CR: complete response; DOR: duration of response; EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours.

B.2.3.4 *RET* testing

For patients being enrolled into a specific Phase II dose expansion, evidence of a *RET* gene alteration in tumour (i.e., not just blood) as defined in Table 9, was required. However, a positive germline DNA test for a *RET* gene mutation as defined in Table 9 was acceptable in the absence of tumour tissue testing for patients with MTC.

Table 9: Definition of *RET* Alterations

***RET* mutation**[a]	Previously reported activating RET gene mutation excluding synonymous, frameshift, or nonsense mutations. For MTC, RET gene mutation not known to be activating, negative, or unknown could be enrolled during Phase I, and with Sponsor approval, to Cohort 5 of Phase II.
***RET* fusion**[a]	By PCR or NGS (FISH as the only molecular result was acceptable for Phase I dose escalation and Cohort 5 but not Cohorts 1 and 2 of Phase II
***RET* mutation**[a] **or *RET* fusion**[a]	Phase II: no other known validated driver alteration(s)[b]

[a] According to laboratory with CLIA, ISO/IEC, CAP, or similar certification, so long as a written Molecular Pathology Report is available and clearly asserts the presences of the referenced *RET* alteration. [b] Dual driver alterations were only restricted from Cohorts 1 through 4.

Abbreviations: CAP: College of American Pathologists; CLIA: Clinical Laboratory Improvement Amendments; FISH: Fluorescence in Situ Hybridization; ISO/IEC: International Organization for Standardisation/Independent Ethics Committee; MTC: medullary thyroid cancer; NGS: next generation sequencing; PCR: polymerase chain reaction.

RET alteration status and other oncogenic alteration types for the Overall Safety Analysis Set (OSAS), as of the 17th June 2019 interim data cut-off (N=531) are summarised by Phase II cohort in Table 10.

As expected, the presence of documented *RET* alteration was dictated by the enrolment requirements for the specific cohorts (outlined in Figure 5), and was [redacted] for Cohorts 1 through 4 and was [redacted] for Cohort 5 (Table 4). RET alteration type, again as expected by enrolment requirements, was a RET fusion for all patients in Cohorts 1 and 2, and was a RET mutation in Cohorts 3 and 4. The RET alteration type for Cohort 5 was RET fusion for [redacted] of patients, RET mutation in [redacted] of patients and was recorded as "other" in 0.9%. The assay that was most frequently used to assess RET alterations was NGS on Tumour (used in [redacted] and [redacted] in Cohorts 1, 2, 3, 4, and 5, respectively); other assay types included NGS on blood or plasma, polymerase chain reaction (PCR), Fluorescence In Situ Hybridization (FISH), and other.

Table 10: *RET* alteration status by Phase II cohort (Overall Safety Analysis Set, 17th June 2019 data cut-off)

Status	*RET* fusion-positive solid tumour		*RET*-mutant MTC		Cohort 5 n=[redacted]
	With standard therapy	Without standard therapy	Prior Cabozantinib/ vandetanib-	Cabozantinib/ vandetanib-naïve	
	Cohort 1 n=[redacted]	Cohort 2 n=[redacted]	Cohort 3 n=[redacted]	Cohort 4 n=[redacted]	
Documented *RET* alteration (n, %)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* Alteration type (n, %)**					
Fusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KIF5B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCDC6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCOA4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mutation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M918T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V804 M/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extracellular Cysteine Mutation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* alteration, type of assay (n, %)**					

NGS on Tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NGS on Blood or Plasma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FISH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FISH: Fluorescence In Situ Hybridization; PCR: polymerase chain reaction; MTC: medullary thyroid cancer; NGS: next generation sequencing.
Source: Eli Lilly LIBRETTO-001 CSR (17th June data cut-off)[52]

B.2.3.5 Baseline characteristics

A summary of patient demographics and other baseline characteristics is provided below of the 226 patients in the RET fusion-positive TC and RET-mutant MTC efficacy population.

RET-mutant medullary thyroid cancer

Baseline characteristics are presented below for the overall *RET*-mutant MTC populations, as well as the PAS, IAS and SAS1/2 analysis sets, as defined in B.2.3.3.

A summary of baseline characteristics in patients with *RET*-mutant MTC is provided in (Table 11). The median age of the population across all patients with *RET*-mutant MTC was [redacted] years and encompassed a wide range [redacted]. For the overall population, [redacted] were between the ages of [redacted] and [redacted] years, with similar numbers for the IAS and SAS1 ([redacted] and [redacted] respectively). There were more males than females. The majority ([redacted]) of *RET*-mutant MTC patients were white. Body weight had a median of [redacted] kg and ranged from [redacted] to [redacted] kg. The median BMI was [redacted] kg/m^2 and likewise displayed a wide range from [redacted] to [redacted] kg/m^2. Most patients had a baseline Eastern Cooperative Oncology Group (ECOG) of [redacted]

The median time from diagnosis was [redacted] months. Most patients in the IAS and SAS1 [redacted] respectively) had metastatic disease at enrolment. Next generation sequencing (NGS) on tumour samples was the most common method of determining *RET* mutation status. As expected with MTC patients, the median calcitonin [redacted] was elevated and ranged from [redacted] pg/ml. Similarly, the median CEA was [redacted] ng/ml ranging from [redacted] ng/ml. These features were similar across the other analysis sets.

In the overall patient population [redacted] had progressive disease at baseline and [redacted] had stable disease. In the IAS [redacted] had progressive disease at baseline and [redacted] had stable disease. In the SAS1 [redacted] had progressive disease at baseline and [redacted] had stable disease, while [redacted] had an unknown disease state at baseline.

The median time from diagnosis for all *RET*-mutant MTC patients was [redacted] months. The most common mutation was M918T, followed by extracellular cysteine mutations.

RET-mutant MTC IAS patients were a heavily pre-treated population, with [redacted] receiving at least three prior systemic regimens. As per the IAS definition, [redacted] had received at least 1 prior line of cabozantinib or vandetanib with the median number of prior systemic therapies being [redacted] ([redacted]). SAS1 patients were comparatively less treated, with [redacted] receiving no prior systemic treatments and [redacted] receiving three or greater (Table 12).

Table 11: Baseline demographics and disease characteristics of patients with *RET*-mutant MTC in the LIBRETTO-001 trial

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=124	SAS1 Cabozantinib /vandetanib-naïve N=88	SAS2 Non-measurable Disease N=14	Total N=226
Age, years					
Median	57.0	[redacted]	58.0	[redacted]	[redacted]
Range	17–84	[redacted]	15–82	[redacted]	[redacted]
Overall age group, n (%)					
<18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18–44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45–64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)					
Male	36 (65.6)	[redacted]	58 (65.9)	[redacted]	[redacted]
Female	19 (34.5)	[redacted]	30 (34.1)	[redacted]	[redacted]
Race, n (%)					
White	49 (89.1)	[redacted]	75 (85.2)	[redacted]	[redacted]
Black	1 (1.8)	[redacted]	1 (1.1)	[redacted]	[redacted]
Asian	0	[redacted]	4 (4.5)	[redacted]	[redacted]
Other/Missing	5 (9.1)	[redacted]	8 (9.1)	[redacted]	[redacted]
Ethnicity, n (%)					
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body weight (kg)					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height (cm)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body mass index, kg/m^2					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG, n (%)					
0	11 (20.0)	[redacted]	43 (48.9)	[redacted]	[redacted]

1	41 (74.5)	[redacted]	42 (47.7)	[redacted]	[redacted]
2	3 (5.5)	[redacted]	3 (3.4)	[redacted]	[redacted]
Stage at initial diagnosis, n (%)					
I–III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis, months					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of metastatic disease, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis of metastatic disease, months					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of diarrhoea at baseline, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcitonin (pg/ml)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CEA (ng/ml)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour burden (at least one measurable lesion per Investigator), n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEA: carcinoembryonic antigen; ECOG: Eastern Cooperative Oncology Group; IAS: Prior Platinum Chemotherapy; MTC: medullary thyroid cancer; PAS: Primary Analysis Set; RET: rearranged during transfection; SAS1: Treatment-naïve; SAS2: Prior Other Systemic Therapy; SAS3: Non-measurable Disease.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth et al. (2020)[51]

Table 12: Prior cancer-related treatments for *RET*-mutant MTC patients in the LIBRETTO-001 trial

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) N=55	**IAS** Prior cabozantinib /vandetanib N=124	**SAS1** Cabozantinib/ vandetanib-naïve N=88	**SAS2** Non-measurable Disease N=14	**Total** N=226
Received prior systemic therapy, n (%)					

Yes	55 (100.0)	[redacted]	[redacted]	[redacted]	[redacted]
No	0	[redacted]	[redacted]	[redacted]	[redacted]
Type of prior systemic therapy, n (%)					
MKI	55 (100.0)	[redacted]	7 (8.0)	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other MKIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radioactive Iodine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxane Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Systemic Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic regimens, n (%)					
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1–2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic regimens					
Median	2.0	[redacted]	0.0	[redacted]	[redacted]
Range	1–8	[redacted]	0–2	[redacted]	[redacted]
Best response to last systemic treatment, n (%)					
Partial response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer-related surgery, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS: Primary Analysis Set; IAS: Prior Platinum Chemotherapy; SAS1: Treatment-naïve; SAS2: Prior Other Systemic Therapy; SAS3: Non-measurable Disease.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth et al. (2020)[51]

RET fusion-positive thyroid cancer

Baseline characteristics are presented below for the *RET* fusion-positive TC study populations (previously treated and systemic therapy naïve), as defined in Section B.2.3.3.

A summary of *RET* fusion-positive TC histological subtypes is provided in Table 13. A total of 27 patients with *RET* fusion-positive TC were treated with selpercatinib. Of the 27 patients with *RET* fusion-positive TC, 19 patients received a prior systemic therapy other than radioactive iodine (RAI; hereafter referred to as "previously treated") and represented four different thyroid histological subtypes including: papillary (n=13), poorly differentiated (n=3), anaplastic (n=2), and Hürthle cell (n=1). The other 8 patients (all papillary) received no other prior systemic therapy other than RAI (hereafter referred to as "systemic therapy naïve").[51]

A summary of the baseline demographics and disease characteristics of these patients can be found in Table 14 and Table 15, respectively. For *RET* fusion-positive thyroid cancer patients, the median time from diagnosis was [redacted] months. All patients had metastatic disease at enrolment, [redacted] were diagnosed as Stage 4, and [redacted] had CNS metastasis at baseline (Table 15). Next generation sequencing (NGS) on tumour samples was the most common method of determining *RET* fusion status. The most common fusion partner was KIF5B, followed by CCDC6 and then NCOA4.

A summary of the prior cancer-related treatments for these patients can be found in (Table 16). Of *RET* fusion-positive TC patients [redacted] had received RAI as a prior therapy. Of these patients, [redacted] had received at least one prior systemic therapy other than RAI, and [redacted] received at least three prior regimens, with a median of [redacted]. In the overall *RET* fusion-positive TC patient population [redacted] had progressive disease at baseline and had [redacted] stable disease.

Table 13: Histology and prior therapy in patients with *RET* fusion-positive TC

Histology, n (%)	Previously treated[a] N=19	Systemic therapy naïve[b] N=8
Papillary	13 (68.4)	[redacted]
Poorly differentiated	3 (15.7)	[redacted]
Anaplastic	2 (10.5)	[redacted]
Hürthle cell	1 (5.3)	[redacted]

[a]≥1 systemic therapy in addition to RAI, [b]No prior systemic therapy other than RAI
Abbreviations: RAI: radioactive iodine; RET: rearrange during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth et al. (2020)[51]

Table 14: Baseline demographics of patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	Previously treated[a] N=19	Systemic therapy naïve[b] N=8	*RET* fusion-positive TC N=27
Age, years			
Median	54.0	[redacted]	[redacted]
Range	25–88	[redacted]	[redacted]
Overall age group, n (%)			
18–44 years	[redacted]	[redacted]	[redacted]
45–64 years	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			

Male	9 (47.4)	[redacted]	[redacted]
Female	10 (52.6)	[redacted]	[redacted]
Race, n (%)			
White	14 (73.7)	[redacted]	[redacted]
Black	1 (5.3)	[redacted]	[redacted]
Asian	2 (10.5)	[redacted]	[redacted]
Other/Missing	2 (10.5)	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Height (cm)			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Body weight (kg)			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Body mass index, kg/m2			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Baseline ECOG, n (%)			
0	5 (26.3)	[redacted]	[redacted]
1	12 (63.2)	[redacted]	[redacted]
2	2 (10.5)	[redacted]	[redacted]
Smoking history, n (%)			
Never smoked	[redacted]	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

[a]≥1 systemic therapy in addition to RAI, [b]No prior systemic therapy other than RAI
Abbreviations: ECOG: Eastern Cooperative Oncology Group; RAI: radioactive iodine; RET: rearrange during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth et al. (2020)[51]

Table 15: Disease characteristics of *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC N=27**
Primary tumour type, n (%)	
Papillary thyroid	[redacted]
Poorly differentiated thyroid	[redacted]

Anaplastic thyroid	[redacted]
Hurthle cell thyroid	[redacted]
Stage at diagnosis, n (%)	
I–IIIC	[redacted]
IV	[redacted]
IVA	[redacted]
IVB	[redacted]
IVC	[redacted]
Missing	[redacted]
Time from diagnosis, months	
Median	[redacted]
Range	[redacted]
History of metastatic disease, n (%)	
Yes	[redacted]
No	[redacted]
Time from diagnosis of metastatic disease, months	
Median	[redacted]
Range	[redacted]
At least 1 measurable lesion by investigator, n (%)	
Yes	[redacted]
No	[redacted]
Sum of diameters at baseline by investigator, mm	
Median	[redacted]
Range	[redacted]
CNS metastases at baseline by investigator, n (%)	
Yes	[redacted]
No	[redacted]

Abbreviations: CNS: central nervous system; RET: rearrange during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Table 16: Prior cancer-related treatments for *RET* fusion-positive TC patients in the LIBRETTO-001 trial

Characteristic	*RET* fusion-positive TC N=27
Received prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Type of prior systemic therapy, n (%)	
MKI	[redacted]
Cabozantinib	[redacted]
Vandetanib	[redacted]
Sorafenib	[redacted]

Lenvatinib	[redacted]
Other MKIs	[redacted]
Chemotherapy	[redacted]
Platinum chemotherapy	[redacted]
Radioactive iodine	[redacted]
Anti-PD1/PD-L1 therapy	[redacted]
Taxane chemotherapy	[redacted]
Other systemic therapy	[redacted]
Number of prior systemic regimens, n (%)	
0	[redacted]
1–2	[redacted]
≥3	[redacted]
Prior systemic regimens	
Median	[redacted]
Range	[redacted]
Best response to last systemic treatment, n (%)	
Partial response	[redacted]
Stable disease	[redacted]
Progressive disease	[redacted]
Not Evaluated	[redacted]
Unknown	[redacted]
Prior radiotherapy, n (%)	[redacted]
Prior cancer-related surgery, n (%)	[redacted]

Abbreviations: RAI: radioactive iodine; RET: rearrange during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

B.2.3.6 Participant disposition

RET-mutant medullary thyroid cancer

Table 17 presents the patient disposition of the *RET*-mutant MTC efficacy population. Of the 226 patients with *RET*-mutant MTC, [redacted] patients ([redacted]) were still on treatment as of the 16 December 2019 data cut-off. In the IAS, of 124 patients with *RET*-mutant MTC, [redacted] patients ([redacted]) were still on treatment and [redacted] patients ([redacted]) stayed on treatment post-progression at the discretion of the investigator. Of the 88 in the SAS1, [redacted] patients ([redacted]) were still on treatment. For all patients with *RET*-mutant MTC, the most common reason for discontinuation was disease progression ([redacted]).

Table 17: Patient disposition of *RET*-mutant MTC patients in the LIBRETTO-001 trial

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=124	SAS1 Cabozantinib /vandetanib-naïve N=88	SAS2 Non-measurable Disease N=14	Total N=226

Treatment ongoing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated post-progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status continuing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS: Primary Analysis Set; IAS: Integrated Analysis Set; SAS1: cabozantinib/vandetanib-naïve; SAS2: non-measurable disease.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

RET fusion-positive thyroid cancer

Table 18 presents the patient disposition for the *RET* fusion-positive TC efficacy population. Of the 27 patients with RET fusion-positive TC, [redacted] patients ([redacted]) were still on treatment as of 16th December 2019 data cut-off.

Table 18: Patient disposition of *RET* fusion-positive TC patients in the LIBRETTO-001 trial

	***RET* fusion-positive TC N=27**
Treatment Ongoing, n (%)	[redacted]
Discontinuation, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Non-compliance	[redacted]
Withdrawal of consent	[redacted]
Treated post-progression, n (%)	[redacted]
Study status continuing, n (%)	[redacted]
Study status discontinued, n (%)	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

B.2.4 *Quality assessment of the relevant clinical effectiveness evidence*

The LIBRETTO-001 trial was assessed for risk of bias and generalisability in line with NICE requirements. Overall the results of the LIBRETTO-001 trial may be considered at low risk of bias, however some points are inconclusive as the clinical trial is currently ongoing, as summarised in Table 19. The trial had a clearly focussed issue, the exposure and the outcome were both accurately measured to minimise bias, the results were deemed precise, the results were believable and the results are generalisable to the local population.

Table 19: Quality assessment of the LIBRETTO-001 trial

Study ID: LIBRETTO-001	
Reference: Wirth LJ, Cabanillas ME, Sherman E, Solomon B, Leboulleux S, Robinson B, et al. Clinical activity of Loxo-292, a highly selective RET inhibitor, in patients with retaltered thyroid cancers. Thyroid. 2018;28:A171.[59]	
Oxnard G, Subbiah V, Park K, Bauer T, Wirth L, Velcheti V, et al. Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with RET Fusion+ Non-Small Cell Lung Cancer. Journal of Thoracic Oncology. 2018;13(10):S349-S350.[60]	
Wirth L, Sherman E, Drilon A, Solomon B, Robinson B, Lorch J et al. LBA93 Registrational results of LOXO-292 in patients with RET-altered thyroid cancers. Ann Oncol, Volume 30, Issue Supplement_5, October 2019[61]	
Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer. https://ClinicalTrials.gov/show/NCT03157128	
Study Question	**Grade (yes/no/unclear)**
1. Did the study address a clearly focused issue?	Yes. The population was clearly defined and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of LOXO-292 in patients with advanced solid tumours including RET fusion-positive solid tumours, MTC, and other tumours with RET activation. This is abstract only so only CT.gov has information on inclusion and exclusion. The primary endpoint is MTD and secondary endpoints include safety, ORR, and DOR.
2. Was the cohort recruited in an acceptable way?	Cannot tell. Abstract only but clear inclusion and exclusion criteria outlined on CT.gov. However, it is an open-label, single-arm study which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes. This was a prospective study with an appropriate study design with validated tools for outcome assessment and data collection. All patients were classified using the same criteria.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by a RECIST assessment and assessed by an IRC. Adverse events were not assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it is an open-label, single-arm study.
5A. Have the authors identified all important confounding factors?	Cannot tell. Abstract only.

List the ones you think might be important, that the author missed.	
5B. Have they taken account of the confounding factors in the design and/or analysis?	Cannot tell. Abstract only.
6A. Was the follow up of subjects complete enough?	Cannot tell. This is an ongoing trial.
6B. Was the follow up of subjects long enough?	Cannot tell. This is an ongoing trial.
7. What are the results of this study?	LOXO-292 was well-tolerated and had marked antitumor activity in RET-fusion+ NSCLC patients, including those with resistance to prior MKIs and brain metastases from the initial results resented.
8. How precise are the results?	The results were precise. RECIST assessment was used on all scans to determine the ORR with an IRC. Adverse events will need to be assessed using CTCAE in the future.
9. Do you believe the results?	Yes. However, the study is ongoing and abstract only.
10. Can the results be applied to the local population?	Yes. These results can be applied to other TC and NSCLC patients with RET-altered tumours.
11. Do the results of this study fit with other available evidence?	Cannot tell. No targeted therapy is approved for patients with RET-altered tumours but the results are similar to vandetanib which also selectively targets RET signalling.
12. What are the implications of this study for practice?	The results from this small single-arm study show LOXO-292 as a potential effective therapy for TC and NSCLC patients with RET-altered tumours.

Abbreviations: CT.gov: clinical trials.gov; CTCAE: common terminology criteria for adverse events; DOR: dose response rate; IRC: independent review committee; MKI: multikinase inhibitors; MTC: medullary thyroid cancer; MTD: maximum-tolerated dose; ORR: objective response rate; RECIST: response evaluation criteria in solid tumours; RET: rearrangements and/or mutations during transfection.

B.2.5 *Clinical effectiveness results of the relevant trials*

The analysis sets presented in this section relevant to the submission are based on a blinded central independent review committee (IRC) assessment of the LIBRETTO-001 trial. The analysis sets presented are only those relevant to the decision problem. Results based on investigator assessment are available in Appendix L.

The results presented and analysed in this section are based on the 16th December 2019 data cut-off, unless noted otherwise.

The 16th December 2019 data cut-off provides efficacy information on the 531 patients enrolled in LIBRETTO-001 as of 17th June 2019. As of 16th December 2019, [redacted] of responders in the *RET*-mutant MTC PAS had reached 6 months of follow up from the date of onset of initial response.

The efficacy evaluable dataset includes data up until 16th December 2019 for the 531 patients who had been treated with selpercatinib as of 17th June 2019. Of these patients, [redacted] were treated

at the RP2D of 160 mg twice daily. Efficacy data for new patients enrolled into LIBRETTO-001 between 18th June 2019 and 16th December 2019 are not included.

B.2.5.1 *RET*-mutant medullary thyroid cancer

Objective response rate by RECIST v1.1 (primary endpoint)

Objective response rate (ORR) was defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. BOR was defined as the best response designation for each patient recorded between the date of the first dose of selpercatinib and the data cut-off, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery.

IRC assessed BOR and ORR for *RET*-mutant MTC are presented for the PAS, IAS and SAS1 groups, summarised in Table 20. For the PAS, the ORR was 69.1% (38/55; 95% CI: 55.2, 80.9) by IRC assessment, for the IAS it was [redacted] and for the SAS1 it was 72.7% (64/88; 95% CI 62.2, 81.7).[51] As such, across all three analysis sets, the majority of patients treated with selpercatinib experienced at least a partial response, reflecting the anticipated resultant high efficacy levels conferred by targeting the RET oncogenic driver.

Waterfall plots illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment are shown below for the PAS (Figure 7), IAS (Figure 8) and SAS1 (Figure 9), demonstrating the majority of patients showing >25% reduction in the sum of diameters of their tumour.

Table 20: Best overall response and objective response rate for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=124	SAS1 Cabozantinib/vandetanib-naïve N=88
No. of eligible patients[a], n	[redacted]	[redacted]	[redacted]
Best overall response, n (%)			
Complete response	5 (9.1)	[redacted]	10 (11.4)
Partial response	33 (60.0)	[redacted]	54 (61.4)
Stable disease	14 (25.5)	[redacted]	20 (22.7)
Progressive disease	1 (1.8)	[redacted]	2 (2.3)
Not evaluable	2 (3.6)	[redacted]	2 (2.3)
Objective response rate (CR + PR)			
n (%)	38 (69.1)	[redacted]	64 (72.7)
95% CI	55.2, 80.9	[redacted]	(62.2, 81.7)

[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per *RET*-mutant MTC SAP), i.e., all patients treated on or before 17 December 2018.
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set IRC: Independent Review Committee; MTC: medullary thyroid cancer; No.: number; PAS: Primary Analysis Set; PR: partial response; RET: rearranged during transfection; SAP: statistical analysis plan; SAS1: Treatment-naïve.

Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 7: Waterfall plot of best change in tumour size in *RET*-mutant MTC (PAS)

Seven subjects are not shown due to 5 having non-target lesions only, and 2 patients discontinued treatment prior to first post-baseline assessment.
Abbreviations: CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 8: Waterfall plot of best change in tumour size in *RET*-mutant MTC (IAS)

Eleven subjects are not shown due to 5 having non-target lesions only, and 6 patients do not have post-baseline target lesion measurement.
Abbreviations: CR: complete response; NE: not estimable; PD: progressive disease; PR: partial response; SD: stable disease.
Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 9: Waterfall plot of best change in tumour size in *RET*-mutant MTC (SAS1)

Eight subjects are not shown due to six patients having non-target lesions only (though assessed otherwise by the investigator and thus included in SAS1), and 2 do not have post-baseline target lesions measurement.
Abbreviations: CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.
Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Duration of response

Duration of response (DOR) was defined as the number of months from the start date of CR or PR (whichever response status was observed first) and subsequently confirmed, to the first date that recurrent or progressive disease was objectively documented. If a patient died, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death was used to denote the response end date.

The DOR of the PAS, IAS and SAS1 groups are summarised in Table 21. For the PAS, the median DOR by IRC was not reached, (95% CI: 19.1, Not estimable [NE]), with [redacted] events observed and median DOR follow-up of 14.06 months.[51] There were [redacted] patients who were in response for at least [redacted] months as assessed by IRC. For the [redacted] responding IAS patients, the median DOR by IRC was not reached, with [redacted] events observed and median DOR follow-up of [redacted] months. For the SAS1 group, the median DOR was reached at 21.95 months (95% CI: NE, NE), with 4/64 progression events observed and median DOR follow-up of 7.79 months.[51] There were [redacted] patients in response for at least 12 months as assessed by IRC. Kaplan–Meier plots of DOR for PAS, IAS and SAS1 are presented in Figure 10, Figure 11 and Figure 12, respectively. This durable response may provide a meaningful therapeutic benefit to patients, with progression typically associated with a significant drop in quality of life.

It is important to note that median DOR was not reached by the 17th of December 2020 data cut-off date in the PAS and IAS groups due to a low number of events and the large number of patients still on treatment and in response. Note that in the SAS1 group, median DOR estimates are highly unreliable due to data immaturity, as evidenced by the inability to evaluate a confidence interval.

Table 21: Duration of response for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=124	SAS1 Cabozantinib/vandetanib-naïve N=88
Responders (n)	38	[redacted]	64
Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)			
Median	NE	[redacted]	21.95[a]
95% CI	19.1, NE	[redacted]	NE, NE
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of duration of response			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)			
Median	14.06	[redacted]	7.79
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)[b]			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
Response status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no prior disease progression)	[redacted]	[redacted]	[redacted]
Censored	32 (84.2)	[redacted]	60 (93.8)
Probability (%) of remaining in response (Kaplan–Meier estimate)			
6 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a]Note that these median estimates are highly unreliable due to data immaturity, as evidenced by the inability to evaluate a confidence interval. [b]Includes censored patients who have not yet progressed
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IAS: prior platinum chemotherapy; NE: not estimable; PAS: Primary Analysis Set; PD: disease progression; SAS1: treatment-naïve.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 10: Kaplan–Meier plot of duration of response in *RET*-mutant MTC (PAS)

Abbreviations: DOR: duration of response; No.: number.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 11: Kaplan–Meier plot of duration of response in *RET*-mutant MTC (IAS)

Abbreviations: DOR: duration of response; No.: number.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 12: Kaplan–Meier plot of duration of response in *RET*-mutant MTC (SAS1)

Abbreviations: DOR: duration of response; No.: number.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Progression free survival

Progression free survival (PFS) is defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression (PD) or death (whatever the cause). Unless specified otherwise, the analytical methods described for DOR were used for PFS.

PFS for the PAS, IAS and SAS1 groups is summarised in Table 22. For the PAS, median PFS by the IRC was not reached, however the majority (were alive without documented disease progression by IRC assessment at the data cut-off.[51] For the IAS, median PFS by the IRC , with alive and progression-free by IRC at the data cut-off. For the SAS1, the median PFS by IRC was 23.56 months (95% CI: NE, NE), with 8/88 (9.1%) events observed and median follow-up of 11.07 months, with patients alive and progression-free for at least 12 months as assessed by IRC (Note, however, that these median estimates are not mature, as evidenced by the inability to evaluate a CI).[51] This indicates a durable PFS benefit that will maintain patient quality of life. Kaplan–Meier plots of PFS for the PAS, IAS and SAS1 are shown in Figure 13, Figure 14 and Figure 15 respectively.

Table 22: Progression free survival for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=124	SAS1 Cabozantinib/ vandetanib-naïve N=88[a]
Reason censored (n, %)			
Alive without documented disease progression			

Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)			
Median[b]	NE	[redacted]	23.56
95% CI	24.4, NE	[redacted]	NE, NE
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	82.3	[redacted]	92.4
95% CI	68.7, 90.4	[redacted]	82.1, 96.8
Duration of follow-up (months)			
Median	16.69	[redacted]	11.07
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of progression-free survival (n, %)[c]			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
Progression status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	42 (76.4)	[redacted]	80 (90.9)
Probability (%) of being progression-free (Kaplan–Meier estimate)			
6 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per *RET*-mutant MTC SAP), i.e., all patients treated on or before 17 December 2018. [b]Note that these median estimates are highly unreliable due to data immaturity, as evidenced by the inability to evaluate a confidence interval. [c]Includes censored patients who have not yet progressed.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IAS: Prior Platinum Chemotherapy; PD: disease progression; PAS: Primary Analysis Set; SAS1: Treatment-naïve.
Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 13: Kaplan–Meier plot of progression free survival in *RET*-mutant MTC (PAS)

Abbreviations: PFS: progression free survival.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 14: Kaplan–Meier plot of progression free survival in *RET*-mutant MTC (IAS)

Abbreviations: PFS: progression free survival.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 15: Kaplan–Meier plot of progression free survival in *RET*-mutant MTC (SAS1)

Abbreviations: PFS: progression free survival.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Overall survival

Overall survival is defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who were alive or lost to follow-up as of the data cut-off date were right-censored. The censoring date was determined from the date the patient was last known to be alive.

OS for the PAS, IAS and SAS1 groups is summarised in Table 23. For the PAS, median OS was not reached , with of patients still alive after a median follow-up of months. At 12 months, the OS rate was . For the IAS, the median OS was not reached , with of patients still alive and median follow-up of months. At 12 months, the OS rate was For the SAS1, the median OS was not reached), with patients still alive and median follow-up of months. At 12 months, the OS rate was . Kaplan–Meier plots of OS for PAS is shown in Figure 16 demonstrating the vast majority of patients are alive at the 16th December data cut-off.

Table 23: Overall survival for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) **N=55**	**IAS** Prior cabozantinib /vandetanib **N=124**	**SAS1** Cabozantinib/ vandetanib-naïve **N=88**
Duration of overall survival (months)			
Median			
95% CI			
Minimum, maximum			
Rate (%) of OS			

12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Survival status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IAS: Prior Platinum Chemotherapy; NE: not evaluable; PD: progressive disease; PAS: Primary Analysis Set; SAS1: Treatment-naïve.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Figure 16: Kaplan–Meier plot of overall survival in *RET*-mutant MTC (PAS)

Abbreviations: OS: progression free survival.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

EORTC-QLQ-C30

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (Version 3.0) is a well-validated instrument that assesses health related quality of life (HRQoL) in adult cancer patients. It includes a total of 30 items and is composed of scales that evaluate physical (5 items), emotional (4 items), role (2 items), cognitive (2 items), and social (2 items) functioning, as well as global health status (2 items). Higher mean scores on these scales represent better functioning. There are also 3 symptom scales measuring nausea and vomiting (2 items), fatigue (3 items), and pain (2 items), and 6 single items assessing financial impact and various physical symptoms. Higher mean scores on these symptom scales represent greater symptomology.

EORTC QLQ-C30 subscale scores range from 0 to 100. Descriptive analyses reported median/quartile, mean/SD, and mean change/standard error (SE) from baseline for each

subscale at each study visit. A clinically meaningful difference was defined as 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology. Patients with "improvement" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients with "worsening" were defined as those who demonstrated a decrease by ≥10-points from their baseline score. A definite change (improvement or worsening) was defined as an improvement or worsening, respectively, as defined above without any further change in score ≥10 points.

As of the 16th December 2019 data cut-off, EORTC-QLQ-C30 data were available from [redacted] patients with *RET*-mutant MTC. The mean baseline score for global health status/QoL subscale was [redacted] (standard deviation, SD=[redacted]). Of the [redacted] patients, [redacted] patients experienced definite improvement in the global health status/QoL subscale. Among patients with definite improvement, the median time to definite improvement was [redacted] months. The mean baseline score for physical, emotional, cognitive, and social function subscales were each [redacted] points while that for role functioning subscale was [redacted] points at baseline.

Of the [redacted] patients, the proportion of patients experiencing definite improvement in QLQ-C30 subscales is as follows: physical (n=[redacted]), emotional (n=[redacted]), role (n=[redacted]), cognitive (n=[redacted]), and social (n=[redacted]). The proportion of patients experiencing definite worsening in QLQ-C30 subscales is as follows: [redacted] (physical functioning), [redacted] (emotional functioning), [redacted] (role functioning), [redacted] (cognitive functioning), and [redacted] (social functioning). The proportion of patients with any clinically meaningful improvement or worsening is reported in Table 25 by cycle.

QLQ-C30 subscale scores and proportion improving/worsening

A summary of the baseline QLQ-C30 symptom subscale scores for patients with *RET*-mutant MTC and the proportion of patients showing improvement or worsening in scores can be found in Table 24, and in Table 25 by cycle.

Table 24: Baseline scores of the symptom subscales of the EORTC-QLQ-C30 and proportion showing improvement/worsening in *RET*-mutant MTC patients

Subscale	*RET*-mutant MTC [redacted]		
	Baseline score, mean (SD)	Proportion (%) showing improvement	Proportion (%) showing worsening
Nausea and vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; RET: rearranged during transfection; SD: standard deviation.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Table 25: Proportion of patients with *RET*-mutant MTC with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		*RET*-mutant MTC [redacted]			
		Cycle 3	Cycle 5	Cycle 7	Cycle 9
Global Health Status/QoL	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Symptom subscales					
Nausea & vomiting	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Pain	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Constipation	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

The proportion of patients with no change, reported as "stable", are not included in this table.
Abbreviations: EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MTC: medullary thyroid cancer; QoL: quality of life; RET: rearranged during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Bowel diaries

A modified version of the Systemic Treatment-Induced Diarrhoea Assessment Tool (mSTIDAT) was given to *RET*-mutant MTC patients only. The bowel diary (mSTIDAT) was completed weekly during cycle 1, and on day 1 of each cycle thereafter.

As of the 16th December 2019 data cut-off, mSTIDAT data were available from [redacted] patients with RET-mutant MTC. Overall compliance was very high for the bowel diary; [redacted] of all diaries were completed as instructed and adherence was [redacted] at each scheduled visit.

At baseline, [redacted] patients reported having diarrhoea on the mSTIDAT, of whom most reported it as moderate or severe ([redacted] and [redacted], respectively). By cycle 3, [redacted] patients with baseline diarrhoea reported having none while by cycle 7, [redacted] patients with baseline diarrhoea reported having none. Those who continued to report diarrhoea, the severity was reported as minimal by [redacted] at cycle 3 and [redacted] at cycle 7.

More than [redacted] of patients who reported diarrhoea on the mSTiDAT reported a reduction in diarrhoea [redacted] during the study treatment period. Among those [redacted] patients, the average time to first reduction was [redacted] months. There were [redacted] patients who experienced worsening of diarrhoea during the study. A summary of average scores for mSTIDAT items measuring the impact of bowel habits and diarrhoea on daily living and quality of life among patients who reported diarrhoea at baseline is presented in Table 26.

Table 26: Modified STIDAT – impact of bowel habits and diarrhoea on daily living and quality of life in patients with *RET*-mutant MTC who reported diarrhoea at baseline (N=99)

Modified STIDAT Items (Scale range: 0-10)	Baseline		Cycle 3		Cycle 5		Cycle 7		Cycle 9	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Bowel habits affecting ability to perform work or daily activities of living	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bowel habits affecting energy level	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bowel habits affecting mood	[redacted]									
Diarrhoea affecting family life	[redacted]									
Diarrhoea affecting social life	[redacted]									
Diarrhoea affecting overall quality of life	[redacted]									

B.2.5.2 *RET* fusion-positive thyroid cancer

Objective response rate by RECIST v1.1 (primary endpoint)

ORR for the *RET* fusion-positive TC patients is summarised in Table 27. For patients with previously treated *RET* fusion-positive TC (n=19), the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9) by IRC.[51] For patients with systemic therapy naïve *RET* fusion-positive thyroid cancer (n=8), the ORR was [redacted]. A waterfall plot illustrating the best overall change in tumour size per RECIST 1.1 based on IRC assessment is shown below in Figure 17, demonstrating the majority of patients achieved at least a partial response, reflecting a similarly high response rate to the larger *RET*-mutant MTC population and the high efficacy levels conferred by targeting *RET* fusion-positive TC.

Table 27: Best overall response and objective response rate for *RET* fusion-positive TC in the LIBRETTO-001 trial

	Previously treated[b] N=19	Systemic therapy naïve[c] N=8	*RET* fusion-positive TC N=27
No. of eligible patients[a], n	19	[redacted]	[redacted]
Best overall response, n (%)			
Complete response	1 (5.3)	[redacted]	[redacted]
Partial response	14 (73.7)	[redacted]	[redacted]
Stable disease	4 (21.1)	[redacted]	[redacted]
Progressive disease	0	[redacted]	[redacted]
Not evaluable	0	[redacted]	[redacted]
Objective response rate (CR + PR)			
n (%)	15 (78.9)	[redacted]	[redacted]
95% CI	(54.5, 93.9)	[redacted]	[redacted]

[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP), i.e., all patients treated on or before 17th December 2018. [b]≥1 systemic therapy in addition to RAI. [c]No prior systemic therapy other than RAI. [4]Investigator assessments of stable disease include unconfirmed partial responses.
Abbreviations: CI: confidence interval; CR: complete response; PR: partial response; RAI: radioactive iodine.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 17: Waterfall plot of best change in tumour burden in *RET* fusion-positive TC patients with ≥6 months follow-up

Abbreviations: CR: complete response; PR: partial response; SD: stable disease.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Duration of response

DOR for *RET* fusion-positive TC patients is summarised in Table 28. For previously treated *RET* fusion-positive thyroid cancer patients, the median DOR was 18.43 months by IRC (95% CI: 7.6, NE), with [redacted] events observed and median DOR follow-up of 17.51 months and [redacted] in response for at least 12 months.[51] By Kaplan–Meier estimate, the probability of remaining in response at 6- and 12- months was [redacted] and [redacted], respectively (Figure 18). All systemic therapy naïve *RET* fusion-positive thyroid cancer responders were still in response by IRC assessment, demonstrating similarly meaningful durations in patients to those seen in the *RET*-mutant MTC patient group.

Table 28: Duration of response rate for *RET* fusion-positive TC

	Previously treated[a] N=19	Systemic therapy naïve[b] N=8	*RET* fusion-positive TC N=27
Responders	15	[redacted]	[redacted]
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)			
Median	18.43	[redacted]	[redacted]
95% CI	7.6, NE	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]

Rate (%) of duration of response			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)			
Median	17.51	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
Response status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	9 (60.0)	[redacted]	[redacted]

[a]≥1 systemic therapy in addition to RAI. [b]No prior systemic therapy other than RAI.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not evaluable; PD: disease progression; RAI: radioactive iodine.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 18: Kaplan–Meier plot of duration of response in *RET* fusion-positive TC

[redacted]

Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Progression-free survival

The PFS of the *RET* fusion-positive TC patients is summarised in Table 29. For the previously treated *RET* fusion-positive thyroid cancer patients followed for at least 6 months from first dose,

the median PFS by IRC was 20.07 months (95% CI: 9.4, NE), with [redacted] progression-free for at least 12 months, [redacted] events observed and median follow-up of 13.73 months.[51] By Kaplan–Meier estimate, the probability of being progression-free at 6- and 12- months was [redacted] and 64.4% (95% CI: 37.0, 82.3), respectively (Figure 19), indicating a durable PFS benefit.[51] [redacted] systemic therapy naïve *RET* fusion-positive thyroid cancer patients were progression free.

Table 29: Progression free survival for *RET* fusion-positive TC

	Previously treated[b] N=19	Systemic therapy naïve[c] N=8	*RET* fusion-positive TC N=27
No. of eligible patients[a], n	[redacted]	[redacted]	[redacted]
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)			
Median	20.07	[redacted]	[redacted]
95% CI	9.4, NE	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	64.4	[redacted]	[redacted]
95% CI	37.0, 82.3	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Observed duration of progression-free survival (n, %)			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
Progression status (n %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no prior disease progression)	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]

[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per *RET*-mutant MTC SAP), i.e., all patients treated on or before 17th December 2018.[b]≥1 systemic therapy in addition to RAI. [c]No prior systemic therapy other than RAI. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not estimable; PD: progressive disease; RAI: radioactive iodine.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

Figure 19: Kaplan–Meier plot of progression free survival in *RET* fusion-positive TC

Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Overall survival

The OS of the *RET* fusion-positive TC patients is summarised in Table 30. Overall, the median OS was not reached [redacted], with the majority [redacted] of patients still alive after a median follow-up of [redacted] months. At 12 months, the OS rate was [redacted]. For previously treated *RET* fusion-positive thyroid cancer patients, the median OS was not reached [redacted], with [redacted] patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted].

For systemic therapy naïve *RET* fusion-positive thyroid cancer patients, the median OS was not reached [redacted], with [redacted] of patients still alive after a median follow-up of [redacted] months. At 12 months, the OS rate was [redacted].

Table 30: Overall survival for *RET* fusion-positive TC

	Previously treated[a] N=19	Systemic therapy naïve[b] N=8	*RET* fusion-positive TC N=27
Duration of Overall Survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate (%) of Overall Survival			
12 months or more	[redacted]	[redacted]	[redacted]

95% CI	[redacted]	[redacted]	[redacted]
Duration of Follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Survival Status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]

[a]≥1 systemic therapy in addition to RAI. [b]No prior systemic therapy other than RAI.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not estimable; RAI: radioactive iodine.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

EORTC-QLQ-C30

As of the 16th December 2019 data cut-off, no EORTC-QLQ-C30 data were available from patients with *RET* fusion-positive TC.

B.2.6 *Subgroup analysis*

Response rate and duration of response were analysed by several demographic variables in the PAS group, using IRC assessment, to identify any differences in the efficacy of selpercatinib in these subgroups. ORR was consistent across all subgroups and the DOR for all subsets was not reached.

Table 31: ORR and DOR by demographics based on IRC assessment (PAS, *RET*-mutant MTC)

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	55	38	69.1 (55.2, 80.9)	[redacted]
Age				
<65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	36	[redacted]	[redacted]	[redacted]
Female	19	[redacted]	[redacted]	[redacted]
Race				
White	49	[redacted]	[redacted]	[redacted]
Other	6	[redacted]	[redacted]	[redacted]
ECOG				
0	11	[redacted]	[redacted]	[redacted]
1–2	44	[redacted]	[redacted]	[redacted]
Any metastatic disease				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.

Abbreviations: DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; NR: not reached; ORR: objective response rate; PAS: primary analysis set; PR: partial response.
Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

ORR and DOR by type of *RET* mutation are presented in Table 32. In patients with M918T, the ORR was [redacted] ([redacted]). In patients with a V804M or V804L gatekeeper mutation, the ORR was [redacted]). In patients with an extracellular cysteine mutation, the ORR was [redacted]. In patients with other *RET* mutations, the ORR was [redacted], which appeared to be higher than for the other subsets, potentially due to small patient numbers. The DOR in patients with M918T was [redacted] months. The DOR for all remaining subsets was not reached.

The ORR and DOR by type of molecular test are also presented in Table 32. In patients tested with NGS on tumour tissue, the ORR was [redacted]. Only [redacted] patients were tested with NGS on blood/plasma, one was a responder. In patients tested with polymerase chain reaction (PCR), the ORR was [redacted]). The DOR for all subsets was not reached. ORR was broadly consistent across all subgroups and the DOR for all subsets was not reached, with the exception of patients with the *RET* M918T mutation.

Table 32: ORR and DOR by *RET* mutation type and type of molecular assay based on IRC assessment (PAS, *RET*-mutant MTC)

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	55	38	69.1 (55.2, 80.9)	[redacted]
***RET* Mutation Type**				
M918T	33	[redacted]	[redacted]	[redacted]
Extracellular Cysteine Mutation	7	[redacted]	[redacted]	[redacted]
V804M/L[a]	5	[redacted]	[redacted]	[redacted]
Other	10	[redacted]	[redacted]	[redacted]
Type of *RET* Molecular Assay				
NGS on Blood or Plasma	[redacted]	[redacted]	[redacted]	[redacted]
NGS on Tumour	[redacted]	[redacted]	[redacted]	[redacted]
PCR	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

[a]Patient has either V804M or V804L mutation
'*' denotes where some data have been censored.
Abbreviations: DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; NR: not reached; ORR: objective response rate; PAS: primary analysis set; PR: partial response.
Sources: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

ORR and DOR by number of prior therapy or type of prior therapy are presented in Table 33. In patients with 1–2 prior therapies, the ORR was [redacted]). In patients with 3 or more prior therapies, the ORR was [redacted]). In patients who had prior cabozantinib and no vandetanib, the ORR was [redacted]). In patients that had prior vandetanib and no cabozantinib, the ORR was [redacted]. In patients that had both prior cabozantinib and vandetanib, the ORR was [redacted] ORR was broadly consistent across all subgroups and the DOR for all subsets was not reached,

Table 33: ORR and DOR by number and type of prior therapy based on IRC assessment (PAS *RET*-mutant MTC)

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	55	38	69.1 (55.2; 80.9)	[redacted]
Number of prior therapies				
1–2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Type of Prior Systemic Therapy				
Prior cabozantinib only	[redacted]	[redacted]	[redacted]	[redacted]
Prior vandetanib only	[redacted]	[redacted]	[redacted]	[redacted]
Prior cabozantinib and vandetanib	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: DOR: duration of response; IRC: Independent Review Committee; NE: not estimable; NR: not reached; ORR: objective response rate.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56], Wirth *et al.* (2020)[51]

B.2.7 *Meta-analysis*

A network meta-analysis (NMA) is a common method used to compare two or more interventions. As LIBRETTO-001 is a single arm trial, it is not possible to conduct a network meta-analysis or anchored indirect treatment comparison to estimate relative efficacy versus relevant comparators. As such, matched-adjusted, unanchored, indirect treatment comparisons and naïve indirect treatment comparisons versus studies investigating the efficacy of relevant comparators were explored, as reported in Section B.2.8.

B.2.8 *Indirect and mixed treatment comparisons*

- An SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of selpercatinib and potential comparators for the treatment of selpercatinib in *RET*-altered solid tumours, including *RET* fusion-positive TC and *RET*-mutant MTC

***RET*-mutant medullary thyroid cancer**

- In addition to the LIBRETTO-001 trial, two relevant trials were identified investigating comparator therapies (cabozantinib and vandetanib) at their recommended doses in patients with MTC: EXAM and ZETA.[24, 62-64]
- Only the LIBRETTO-001 and EXAM trials were considered in the feasibility assessment presented in this submission, as vandetanib is not a relevant comparator in UK clinical practice
- Matching-adjusted indirect comparisons (MAIC) were conducted for PFS and OS whereby outcomes in the LIBRETTO-001 trial were predicted using a propensity score weighting approach, in line with the methodology proposed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[65-67]
- Clinical effectiveness results were not reported separately for treatment-naïve and pre-treated patients in EXAM. Therefore, the any-line pooled population from the LIBRETT0-001 trial was used in the MAIC, providing a larger patient-level data set and more closely matching the characteristics of the *RET*-mutant subgroup of the EXAM trial

- For PFS, the unweighted curves for the *RET*-mutant population receiving cabozantinib (n=107) or placebo (n=62) in the EXAM trial digitised from Sherman *et al.* (2016) was compared to the weighted curve for the any-line LIBRETTO-001 population.[64] Baseline characteristics for the *RET*-mutant population were only available for patients receiving cabozantinib in EXAM, therefore the characteristics were assumed to be similar across the cabozantinib and placebo arms.
- No OS data were available from the EXAM trial for the *RET*-mutant subgroup. As such, the unweighted curves for the *RET* M918T-positive receiving cabozantinib (n=81) or placebo (n=45) in the EXAM trial digitised from Schlumberger *et al.* (2017) was compared to the weighted curve for the any-line LIBRETTO-001 population.[24] Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population and thus the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated.

- After weighting, the differences between treatments in PFS [redacted] versus cabozantinib ([redacted]; HR: [redacted]; 95% CI: [redacted]) and placebo ([redacted]; HR: [redacted]; 95% CI: [redacted]). After weighting, the differences between treatments in OS [redacted] versus cabozantinib ([redacted]; HR: [redacted]; 95% CI: [redacted]) and versus placebo ([redacted]; HR: [redacted]; 95% CI: [redacted]).

RET fusion-positive thyroid cancer

- In the absence of data for *RET* fusion-positive TC patients, two trials were identified that included a placebo arm that could be considered a reasonable proxy for BSC: DECISION and SELECT.[68, 69]
- The placebo arms of these trials represent the best available data for the efficacy of BSC in patients with *RET* fusion-positive TC who have received prior TKIs. However, these trials included predominantly first-line patients.
- PFS results from the SELECT trial are reported for the intention-to-treat population and a subgroup of patients who had received one prior TKI (hereafter referred to as the pre-treated subgroup)
  - The placebo arm of the SELECT ITT population was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC
  - OS data for BSC in the model was based on the rank preserving structural failure time (RPSFT)-adjusted OS data for patients receiving placebo in the ITT population
- Acknowledging the limitations in the comparator data, evidence from the LIBRETTO-001 trial suggests that selpercatinib offers a considerable improvement in PFS compared with BSC. Median PFS was 20.07 (95% CI: 9.4, NE) months in the previously treated *RET* fusion-positive TC population (n=19) of the LIBRETTO-001 trial, compared with 3.6 (95% CI: 1.9, 3.7) in the pre-treated subgroup of the SELECT trial and 3.7 (95% CI: 3.5, 4.5) in the placebo ITT population.

As discussed in Section 0, an SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of selpercatinib and potential comparators for the treatment of selpercatinib in *RET*-altered solid tumours, including *RET* fusion-positive TC and *RET*-mutant MTC.

As discussed in Section 0, 16 primary reports were identified in the clinical SLR that provided published data for potential comparators in thyroid cancer patients: 11 trials included patients with MTC, 3 included patients with PTC and 2 included patients with both MTC and PTC. Of the 16 included studies, three were Phase I/II, two were Phase II, five were Phase II randomised

controlled trials (RCTs), five were Phase III and one was Phase IV. Ten studies were open-label and the other six were double-blind. Seven were parallel-group study design. However, three trials provided the opportunity to crossover at progression and continue in an open-label trial (D4200C00097, DECISION and SELECT, see Appendix D). Nine were single-arm studies. Ten studies were multinational, one was from the UK and five were based in the US. Of the 16 studies, 11 included patients with *RET*-altered tumours. Full details of the methodology and results of the SLR are presented in Appendix D.

B.2.8.1 *RET*-mutant medullary thyroid cancer

For patients with advanced *RET*-mutant MTC that is untreated, the only treatment that is currently recommended in the UK is cabozantinib.[22] However, cabozantinib is associated with significant toxicity,[24, 25] and thus a proportion of patients may not be eligible for first-line systemic therapy, with BSC representing the only remaining treatment option. Vandetanib has also been appraised for this indication, but was not recommended.[23] Many patients who receive cabozantinib require dose reductions and discontinue treatment. Following cabozantinib, there are no further safe and effective treatment options are available and patients are treated palliatively with BSC.

No head-to-head trials are available comparing selpercatinib to relevant comparators, with evidence for the efficacy and safety of selpercatinib provided by the single-arm LIBRETTO-001 trial. Therefore, in order to estimate the comparative effectiveness of selpercatinib versus relevant comparators, the evidence identified in the SLR was reviewed for the purposes of conducting an ITC.

In addition to the LIBRETTO-001 trial, two relevant trials were identified investigating comparator therapies (cabozantinib and vandetanib) at their recommended doses in patients with MTC: EXAM and ZETA.[24, 62-64]

Feasibility assessment

Comparison of study characteristics and endpoints

Since vandetanib is not a relevant comparator in UK clinical practice, only the LIBRETTO-001 and EXAM trials were considered in the feasibility assessment presented in this submission. The characteristics of these trials and a summary of the key trial outcomes is presented in Appendix D. The definition and ascertainment of study endpoints were similar among the trials.

Comparison of baseline characteristics and prognostic factors

The baseline characteristics of the trial populations are presented in Appendix D. For the EXAM placebo arm, the baseline characteristics of the *RET*-mutant subgroups were not available. Key differences in the patient population characteristics include the following:

- The LIBRETTO-001 trial population is slightly older than the EXAM trial population
- The percentage of male patients in LIBRETTO-001 is slightly lower than in EXAM
- A higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the EXAM trial population

- The proportion of patients in the LIBRETTO-001 any-line MTC cohort with prior anticancer therapy was substantially higher than in the EXAM trial. The proportion of patients in the LIBRETTO-001 any-line MTC cohort with prior tyrosine kinase inhibitor therapy was substantially higher than in the EXAM trial
- The proportion of patients in the LIBRETTO-001 trial who never smoked was higher than in the EXAM trial

The populations appear to be similar for other reported characteristics.

Prognostic factors and predictive factors (treatment-effect modifiers) in patients with MTC were identified in the SLR and were validated with a clinical expert experienced in the treatment of thyroid cancer.[26] The findings are summarised in Appendix D, along with a comparison of the trial populations for each of these factors.

Many of the identified prognostic factors were not reported among the three trials. Based on the reported prognostic factors, outcomes in the LIBRETTO-001 trial may be expected to be somewhat worse than those in the EXAM trial, due to older age, worse performance status, and higher proportion of patients with prior therapy (i.e., lower proportion of treatment-naive patients). The proportion of patients who were female and who never smoked was higher in LIBRETTO-001; however, sex and smoking status were not identified as prognostic factors for MTC in the SLR, which was confirmed by clinical expert feedback.[26]

Given the LIBRETTO-001 trial does not include a control arm, it was not possible to conduct a network meta-analysis (NMA) or anchored indirect treatment comparison to estimate relative efficacy versus relevant comparators. As such, a matching-adjusted, unanchored, indirect treatment comparison versus the EXAM trial was explored to generate relative efficacy estimates versus cabozantinib and placebo (which can be considered a proxy for BSC).

Matching-adjusted indirect comparison (MAIC)

Methodology of the MAIC

The LIBRETTO-001 and EXAM trials included both treatment-naïve and pre-treated patients. In the LIBRETTO-001 trial, patients enrolled in the IAS (n=124) had received 1 or more lines of prior cabozantinib or vandetanib. Patients enrolled in the SAS1 (n=88) were cabozantinib and vandetanib naïve. Clinical effectiveness results are reported separately for these two analysis sets in Section B.2.5.1. In the *RET*-mutant subgroup of the EXAM trial (cabozantinib arm), 81/219 (37.0%) patients had received prior systemic therapy for MTC. However, clinical effectiveness results are not reported separately for treatment-naïve and pre-treated patients.

Therefore, an unanchored population-adjusted ITC was conducted using individual patient-level data from the any-line pooled population from the LIBRETTO-001 trial (IAS and SAS1; n=212) and summary evidence from the EXAM trial, as reported in Schlumberger *et al.* (2017) and Sherman *et al.* (2016).[24, 64] Specifically, matching-adjusted indirect comparisons (MAIC) were conducted for PFS and OS whereby outcomes in the LIBRETTO-001 trial were predicted using a propensity score weighting approach, in line with the methodology proposed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[65-67] The any-line pooled population from the LIBRETT0-001 trial was used rather than the IAS because the former provides a larger patient-level data set, more closely matches the characteristics of the EXAM trial population, and provides more information about the effect of line of therapy by which to adjust for the difference

between trials with regards to the proportion of pre-treated versus treatment-naïve patients. Due to similarities of baseline characteristics of the EXAM cabozantinib trial population and the any-line MTC population from LIBRETTO-001 all LIBRETTO-001 patients were included in the matched set and patient selection was not necessary.

The MAIC aimed to adjust for baseline characteristics with known or suspected associations with the efficacy outcomes that were reported in both the LIBRETTO-001 trial and EXAM trial publication. The variables included age, weight, ECOG performance score, sex, smoking status and *RET* M918T mutation status, since these were the available baseline characteristics for both the LIBRETTO-001 and EXAM trial.

To balance the baseline characteristics between LIBRETTO-001 and EXAM, the selected LIBRETTO-001 patients were assigned weights such that:

- Weighted mean baseline characteristics in LIBRETTO-001 patients exactly matched those reported for patients in EXAM
- The weight for each individual patient was equal to the patient's estimated odds (propensity) of being in LIBRETTO-001 versus EXAM

Weights meeting these conditions were obtained from a logistic regression model for the propensity of inclusion in the LIBRETTO-001 trial versus the EXAM study, with all matched-on baseline characteristics included as independent variables in the model.

Since only summary statistics for baseline characteristics were available from the EXAM study, the logistic regression model was estimated using the method of moments. Based on the method of moments estimate, the baseline means were exactly matched after weighting. The distribution of the weights was inspected for potential extreme values, which are indicative of poor overlap between the study populations in the distributions of patient characteristics.

For PFS, a hazard ratio (HR) and corresponding 95% CI were estimated from a weighted Cox proportional hazards (PH) model (with treatment indicator as the only covariate), incorporating the weights. For OS, a HR and corresponding 95% CI were estimated from a weighted Cox PH model (with treatment indicator and *RET* M918T status as covariates), incorporating the weights. A statistical test on the PH assumption was also performed. Stratified models of various distributions were applied in situations where the PH assumption did not hold.

- For PFS, the unweighted curves for the *RET*-mutant population receiving cabozantinib (n=107) or placebo (n=62) in the EXAM trial digitised from Sherman *et al.* (2016) was compared to the weighted curve for the any-line LIBRETTO-001 population.[64]
- No OS Kaplan–Meier data were available from the EXAM trial for the *RET*-mutant subgroup. As such, the unweighted curves for the *RET* M918T-positive receiving cabozantinib (n=81) or placebo (n=45) in the EXAM trial digitised from Schlumberger *et al.* (2017) was compared to the weighted curve for the any-line LIBRETTO-001 population.[24] Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population; in the EXAM study, HRs for PFS favoured the *RET* M918T-positive versus the *RET*-mutant subgroup (0.15 [95% CI: 0.08, 0.28] versus 0.23 [95% CI: 0.14, 0.38]).[24, 64] In contrast, HRs for PFS and OS numerically favoured the *RET*-mutant versus the *RET* M918T-positive subgroup in LIBRETTO-001 ([redacted] [95% CI: [redacted]]

versus [redacted] [95% CI: [redacted]]), indicating that selpercatinib is similarly or slightly less effective in the *RET* M918T-positive subgroup than the *RET*-mutant group.[26] As such, the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated.

Results of the MAIC

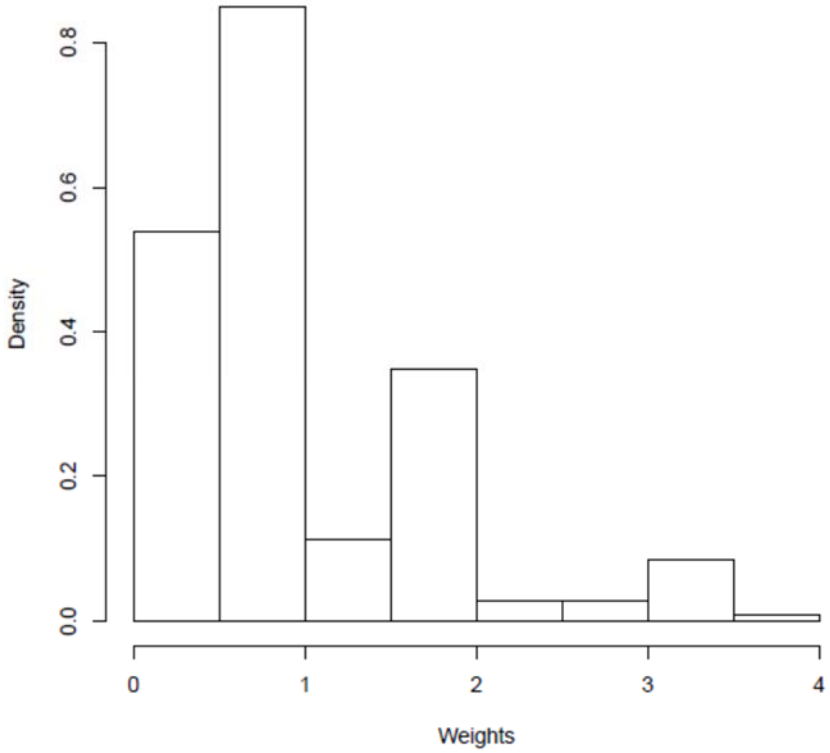
The comparison of baseline characteristics between the selected LIBRETTO-001 patients (N=226) and the *RET*-mutant EXAM patients (N=107) is presented in Table 34. Given the similarity between LIBRETTO-001 and EXAM trials, all LIBRETTO-001 patients were included in the matched set. After applying MAIC weights to the patients in LIBRETTO-001, all matched-adjusted baseline characteristics became exactly balanced between the two study populations. The effective sample size for LIBRETTO-001 after weighting (N_{eff}) was [redacted] and the distribution of weights is presented in Figure 20, indicating no evidence of extreme weights. Weights were rescaled so that they were relative to the original units weights of each individual, in line with the methodology proposed in NICE TSD18.[67] Rescaling had very limited impact on the results.

Table 34: Matching baseline characteristics between LIBRETTO-001 and EXAM before and after matching

Characteristic	Before matching		After matching and weighting
	LIBRETTO-001 any-line (N=212)	EXAM (N=107) *RET*-mutant cabozantinib	LIBRETTO-001 any-line (N_{eff}=[redacted])
Age, mean (SD)	[redacted]	55.00 (20, 86)[a]	[redacted]
Weight (kg), mean (SD)	[redacted]	74.00 (20.19)	[redacted]
ECOG-0 (%)	[redacted]	61.68	[redacted]
Sex (% male)	[redacted]	68.22	[redacted]
Smoking (% never)	[redacted]	51.40	[redacted]
RET M918T mutation status (%)	[redacted]	74.56	[redacted]

[a] Median (min, max)
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; SD: standard deviation; *RET*: rearranged during transfection.

Figure 20: Distribution of weights in the MAIC



Abbreviations: MAIC: matching-adjusted indirect comparison.

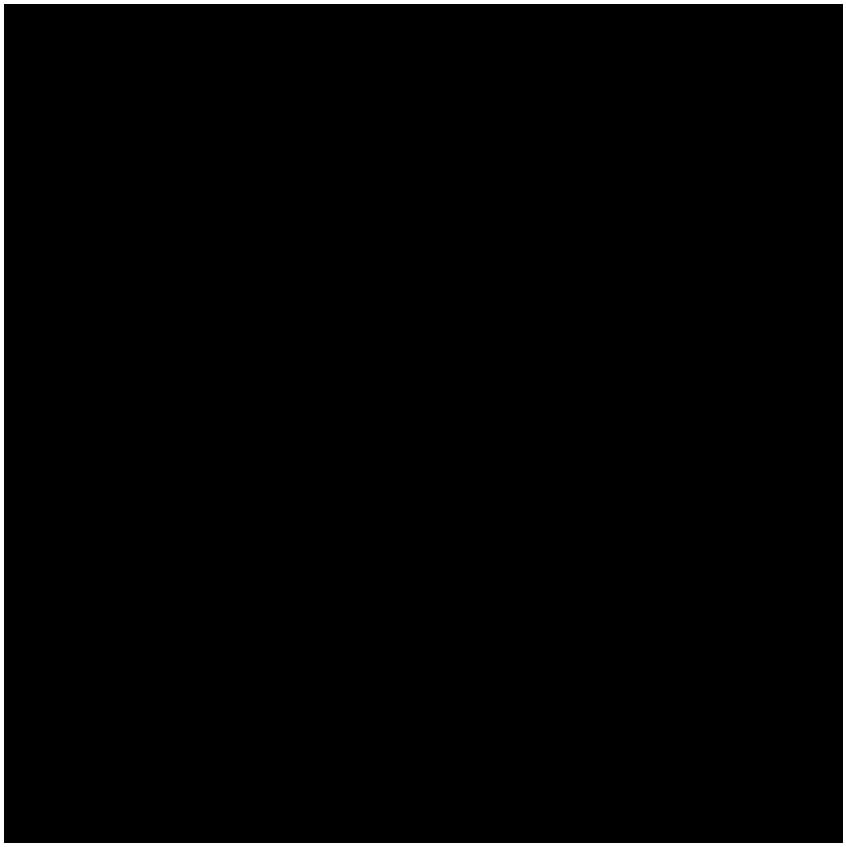
The weighted comparisons of efficacy outcomes between selpercatinib in the LIBRETTO-001 trial and cabozantinib and placebo in EXAM are presented in Table 35 (log-rank test and Cox regression model). After weighting, the differences between treatments in PFS [redacted] versus cabozantinib ([redacted]; HR [redacted]; 95% CI: [redacted]) and placebo ([redacted]; HR [redacted]; 95% CI: [redacted]). The differences between treatments in OS after weighting [redacted] versus cabozantinib ([redacted]; HR [redacted]; 95% CI: [redacted]) and placebo ([redacted]; HR [redacted]; 95% CI: [redacted]). However, the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated because the data for cabozantinib were for patients with *RET* M918T, and cabozantinib is known to be more effective in the M918T population. Kaplan-Meier plots for PFS and OS before and after weighting are presented in Figure 21 and Figure 22, respectively.

Table 35: Comparison of PFS and OS for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM) before and after matching

	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Selpercatinib versus cabozantinib				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib versus BSC (placebo)				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[redacted]	[redacted]	[redacted]

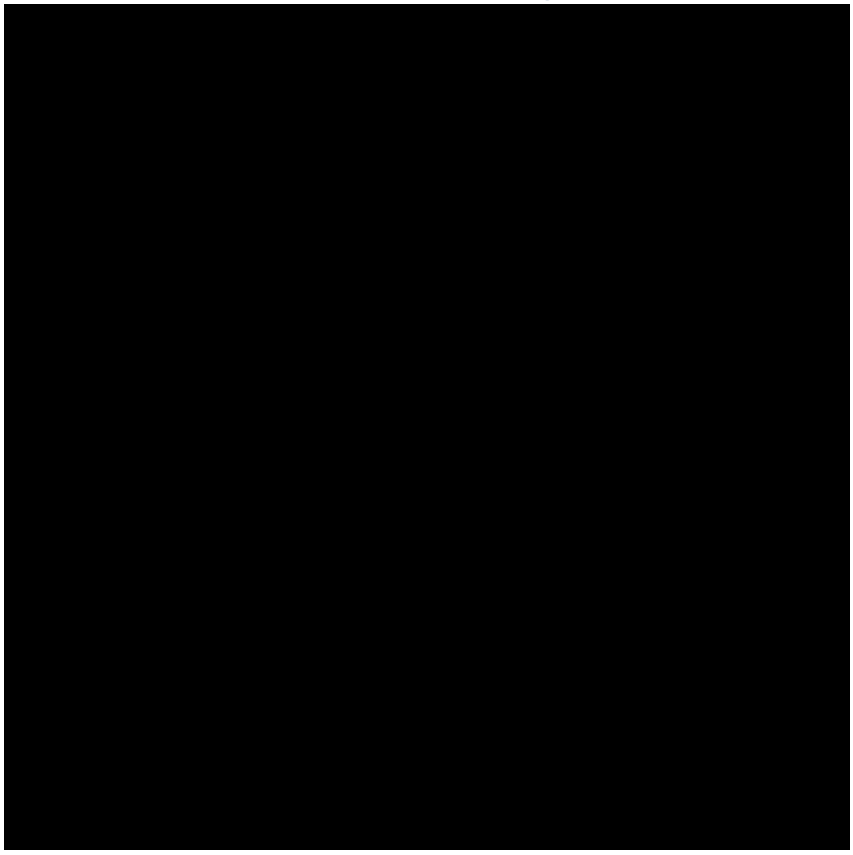
[a] The treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated because the data for cabozantinib were for patients with *RET* M918T. Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population.
Abbreviations: BSC: best supportive care; CI: confidence intervals; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

Figure 21: Progression-free survival (IRC assessment) for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM *RET*-mutant subgroup) before and after weighting



Test for PH assumption in PFS was rejected before and after matching for selpercatinib versus cabozantinib ($p<0.05$), but not for placebo ($p>0.05$).
Abbreviations: PFS: progression-free survival; IRC: independent review committee; Loxo: selpercatinib.

Figure 22: Overall survival for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM *RET* M918T-positive subgroup) before and after weighting



OS for cabozantinib is expected to be overestimated as the analyses use data for the *RET* M918T-positive population and cabozantinib is known to be more effective in this population than in the overall *RET*-mutation population (Kaplan-Meier OS data for the *RET*-mutant group in EXAM are not available).
Test for PH assumption in OS was not rejected before and after weighting (p>0.05) for selpercatinib versus cabozantinib or placebo.
Abbreviations: OS: overall survival; Loxo: selpercatinib.

B.2.8.2 *RET* fusion-positive thyroid cancer

For patients with advanced *RET* fusion-positive TC, lenvatinib and sorafenib are the only treatments recommended (for patients with DTC).[21] For patients who do not respond to, are contraindicated to or do not tolerate treatment with MKIs there are no further safe and effective treatment options, and patients are treated palliatively with best supportive care (BSC). For patients with other subtypes of TC (i.e. anaplastic and poorly differentiated) there are no suitable active treatment options except for BSC.

No head-to-head trials are available comparing selpercatinib to relevant comparators, with evidence for the efficacy and safety of selpercatinib provided by the single-arm LIBRETTO-001 trial. Therefore, in order to estimate the comparative effectiveness of selpercatinib versus relevant comparators, the evidence identified in the SLR was reviewed for the purposes of conducting an ITC.

No RCT data were identified in patients with *RET* fusion. As discussed in Section B.1.3.1 and confirmed by a clinical expert experienced in the treatment of thyroid cancer, the prognostic significance of *RET* fusion in TC is unclear.[26, 70] As such, it is unclear whether data for patients

with TC is generalisable to *RET* fusion-positive TC. In the absence of data for *RET* fusion-positive TC patients, two trials were identified that included a placebo arm that could be considered a reasonable proxy for BSC: DECISION and SELECT.[68, 69]

Both SELECT and DECISION were Phase III, double-blind, parallel-group RCTs. SELECT included adult patients with DTC (including a PTC sub-population) with evidence of radioactive iodine-refractory disease and DECISION included patients with locally advanced or metastatic radioactive iodine-refractory DTC progressing within the previous 14 months according to RECIST. Patients received lenvatinib 24 mg, orally QD, or sorafenib 400 mg, orally BID, in the SELECT and DECISION trials respectively, or a matching placebo. The placebo arms of these trials represent the best available data for the efficacy of BSC in patients with *RET* fusion-positive TC who have received prior TKIs.

The baseline characteristics of the SELECT and DECISION trials alongside the pre-treated *RET* fusion-positive TC from LIBRETTO-001 are presented in Appendix D. A comparison of the study populations based on inclusion and exclusion criteria shows that LIBRETTO-001 is similar to the SELECT trial in terms of disease classification criteria and ECOG scores. Key differences relate to the presence of *RET* fusions in the trials: 100% of patients are *RET*-fusion positive in LIBRETTO-001, while *RET* fusion status is unknown in the SELECT trial. SELECT only allowed patients with confirmed progressive DTC type whereas all subtypes of thyroid cancer are permitted in LIBRETTO-001. However, the majority of patients in LIBRETTO-001 have papillary form of thyroid cancer (68.4%) which is also the dominant form in the SELECT (51.9%). Another key difference is the number of patients who received prior systemic therapy. The SELECT trial included predominantly first-line patients: 100% of patients had received at least 1 prior therapy in LIBRETTO-001, compared with 20.6% in SELECT. However, in SELECT, the treatment effect on PFS in pre-treated patients (HR: 0.22; 95% CI: 0.12, 0.41) was consistent with the overall population (HR: 0.21; 95% CI: 0.16, 0.28). Subgroup data by line of therapy were not reported for OS in SELECT. Thus, it is unclear whether these data represent an overestimate of the efficacy of BSC in the population of interest for this submission. In addition, OS was confounded by crossover in both trials.

SELECT

PFS results from the SELECT trial are reported for the intention-to-treat population and a subgroup of patients who had received one prior TKI (hereafter referred to as the pre-treated subgroup), as shown in Table 36. Kaplan-Meier curves of PFS for lenvatinib versus placebo are presented in Figure 23A and B for the intention-to-treat population and pre-treated subgroup, respectively.

Table 36: PFS for lenvatinib and placebo in the SELECT trial

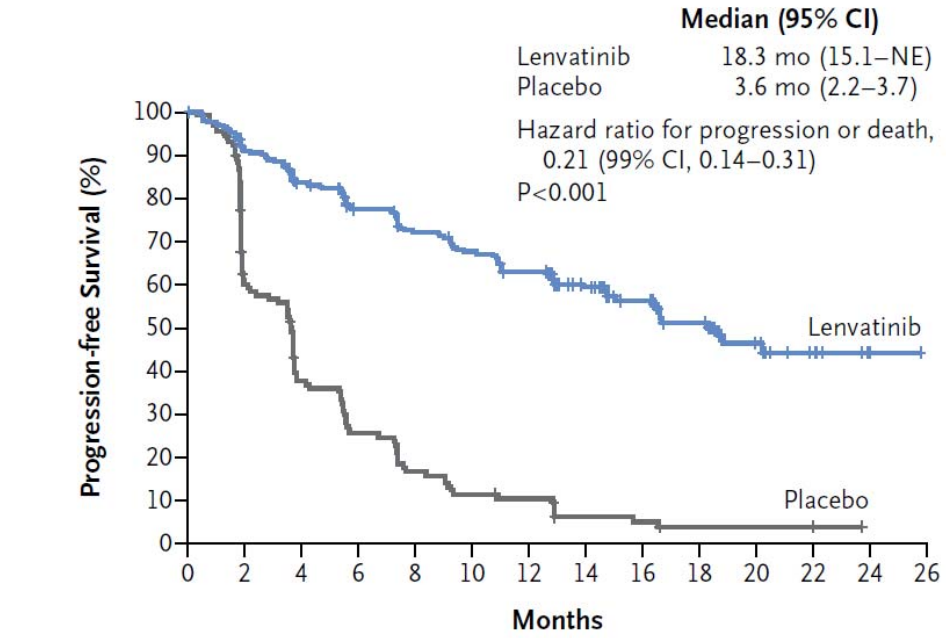
	Intention-to-treat		Pre-treated subgroup[a]	
	Lenvatinib (n=261)	**Placebo (n=131)**	**Lenvatinib (n=66)**	**Placebo (n=27)**
Median PFS (95% CI), months	18.3 (15.1, NE)	3.6 (2.2, 3,7)	15.1 (8.8, NE)	3.6 (1.9, 3.7)
HR (95% CI)	0.21 (0.14, 0.31)[a]		0.22 (0.12, 0.41)	
p-value	<0.001		<0.0001	

[a] Patients who had received 1 prior TKI.

Abbreviations: CI: confidence intervals; HR: hazard ratio; NE: not estimable; PFS: progression-free survival; TKI: tyrosine kinase inhibitor.
Source: Schlumberger *et al.* (2015)[68]

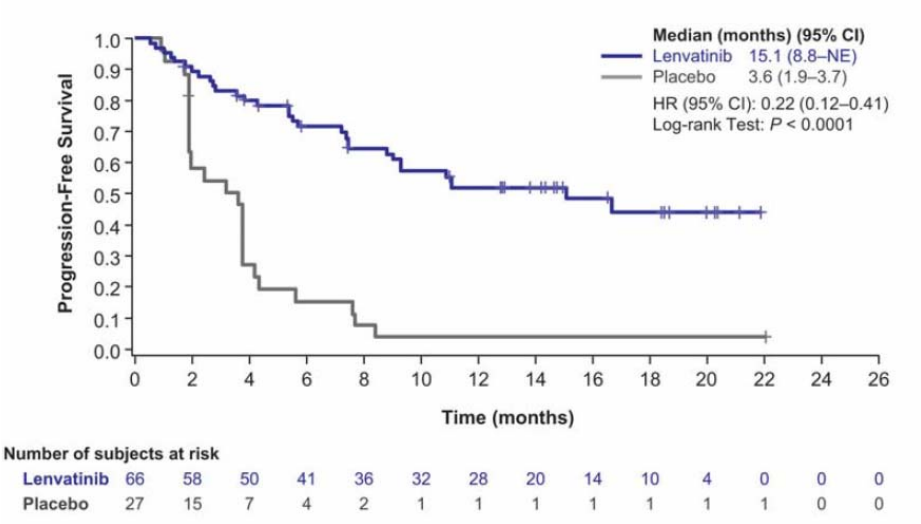
Figure 23: Kaplan–Meier curves of PFS for DTC patients receiving lenvatinib versus placebo in the SELECT trial

A) Intention-to-treat population



No. at Risk														
Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

B) Pre-treated subgroup[a]



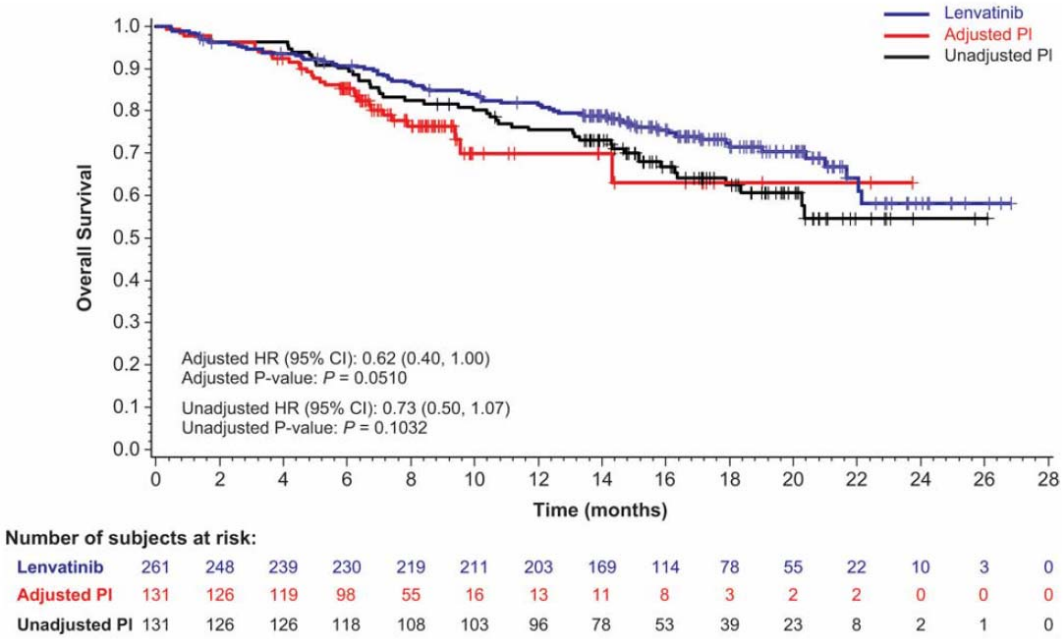
Number of subjects at risk														
Lenvatinib	66	58	50	41	36	32	28	20	14	10	4	0	0	0
Placebo	27	15	7	4	2	1	1	1	1	1	1	1	0	0

[a] Patients who had received 1 prior TKI.
Abbreviations: CI: confidence interval; HR: hazard ratio; NE: not estimable.
Source: Schlumberger *et al.* (2015)[68]

The majority of patients who received placebo crossed over to lenvatinib. Kaplan-Meier curves for OS before and after adjustment using a rank preserving structural failure time (RPSFT)

model, which were presented as part of TA535, are presented in Figure 24.[21] The HR after adjustment was 0.62 (95% CI: 0.40, 1.00; p=0.051). OS curves for the pre-treated subgroup were not reported.

Figure 24: RPSFT-adjusted and unadjusted Kaplan-Meier curves of OS for DTC patients receiving lenvatinib versus placebo in the SELECT trial



Abbreviations: CI: confidence interval; HR: hazard ratio; RPSFT: rank preserving structural failure time model.
Source: NICE TA535.[21]

DECISION

PFS and OS results from the DECISION trial are only reported for the intention-to-treat population, as shown in Table 37. Kaplan-Meier curves for PFS and OS for sorafenib versus placebo can be found in Figure 25A and B, respectively. Patients receiving placebo in DECISION were permitted to cross over to sorafenib, and thus the OS curve for placebo is subject to confounding. Median OS was not reached by the time of publication.

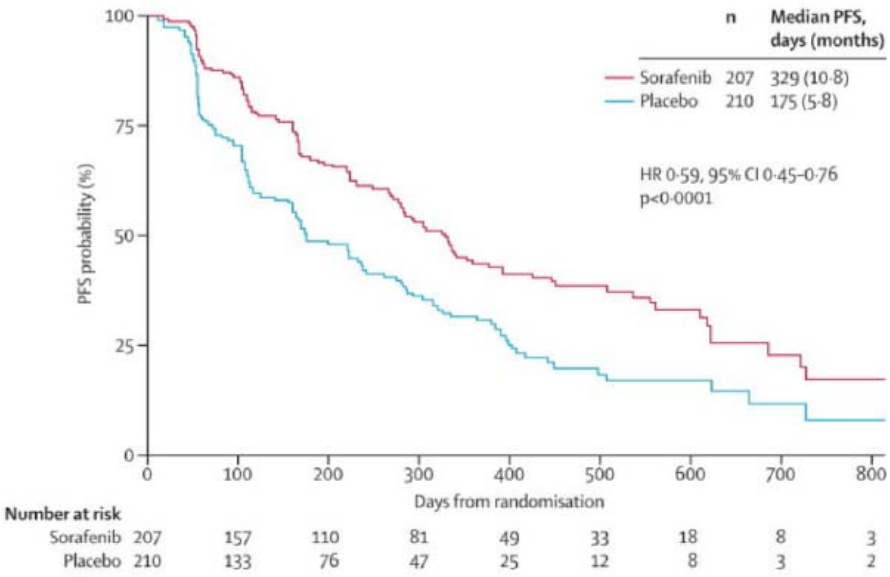
Table 37: Median PFS and median OS in the DECISION trial

	DECISION	
	Sorafenib (n=207)	Placebo (n=210)
Median PFS, months	10.8	5.8
HR (95% CI; p-value)	0.59 (0.45, 0.76; p<0.0001)	
Median OS, months	NR	NR
HR (95% CI)	0.80 (0.54, 1.19; p=0.14)	

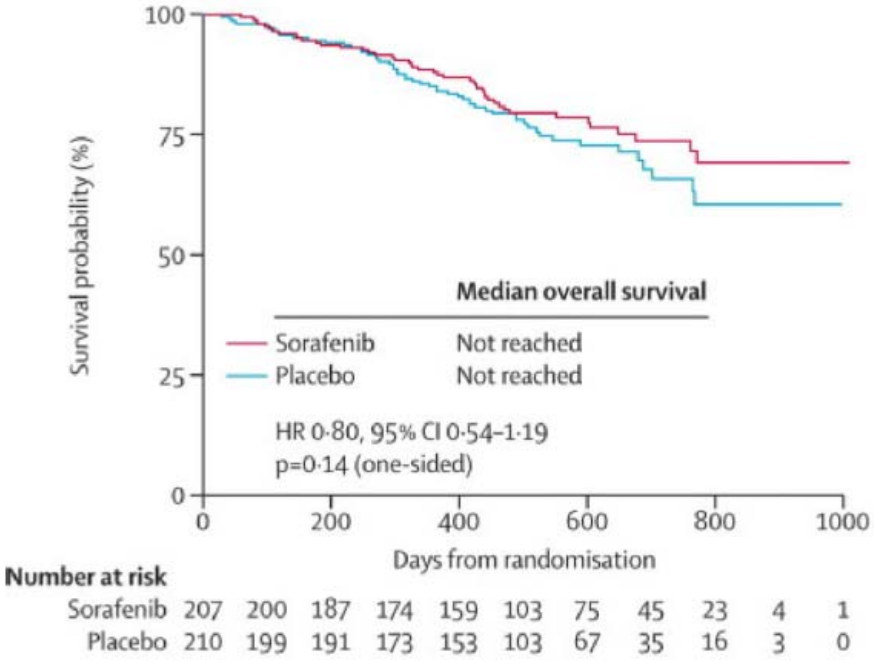
[a] 99% confidence interval reported.
Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression free survival.
Sources: Brose *et al.* (2014)[71]

Figure 25: Kaplan-Meier curves for sorafenib versus placebo in the DECISION trial

A) PFS



B) OS



Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression free survival.
Source: Brose *et al.* (2014)[71]

Naïve indirect comparison

The placebo arm of the SELECT study for lenvatinib was considered a suitable proxy for BSC in the UK in TA535. Clinical expert opinion suggests that lenvatinib is the dominant choice in practice and the overall trial population is more comparable to the target population of interest as at least 1 prior TKI was permitted in the study. As such, the placebo arm of SELECT was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC and was used to inform the efficacy of BSC in the economic model.

There are a number of differences between the SELECT trial and the LIBRETTO-001 trial populations: all patients in the LIBRETTO-001 trial were *RET* fusion-positive, whereas fusion status is unknown in the SELECT trial, and SELECT only allowed patients with confirmed progressive DTC type whereas all subtypes of thyroid cancer are permitted in LIBRETTO-001. The prognostic effect of these differences on the results is unclear, but it is unlikely to impact the direction of the effect favouring selpercatinib compared to BSC. Additionally, whilst the SELECT trial only included patients with DTC, since patients with other subtypes of TC have no suitable treatment options other than BSC, the placebo arm of the SELECT ITT population was also considered a suitable proxy for comparator efficacy for the other subtypes of TC within the *RET* fusion-positive TC population (e.g. anaplastic TC).

Acknowledging the limitations in the comparator data, evidence from the LIBRETTO-001 trial suggests that selpercatinib offers a considerable improvement in PFS compared with BSC. Median PFS was 20.07 (95% CI: 9.4, NE) months in the previously treated *RET* fusion-positive TC population (n=19) of the LIBRETTO-001 trial, compared with 3.6 (95% CI: 1.9, 3.7) in the pre-treated subgroup of the SELECT trial and 3.7 (95% CI: 3.5, 4.5) in the ITT population.

B.2.8.3 Uncertainties in the indirect and mixed treatment comparisons

RET-mutant MTC: Limitations of the MAIC for LIBRETTO-001 versus EXAM

- Only known baseline prognostic factors that were consistently reported in both studies were matched in the MAIC, and consequently other potential prognostic factors and effect modifiers were not accounted for in the MAICs. As with any comparison of non-randomised treatment groups, the MAICs are also subject to potential bias due to unobserved or unmeasurable confounding.
- No OS Kaplan–Meier data were available from the EXAM trial for the *RET*-mutant subgroup. As such, the unweighted curves for the *RET* M918T-positive receiving cabozantinib or placebo in the EXAM trial digitised from the Schlumberger *et al.* (2017) was compared to the weighted curve for the any-line LIBRETTO-001 population.[24] Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population, thus the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated. In addition, no baseline characteristics were reported for the *RET* M918T-positive subgroup, so the LIBRETTO-001 trial data was still matched and weighted to the *RET*-mutant cabozantinib arm (although M918T status was included as a covariate in the Cox PH model).
- Clinical effectiveness results are not reported separately for treatment-naïve and pre-treated patients in the *RET*-mutant subgroup of the EXAM trial. As such, subgroup analyses by line of therapy could not be conducted to estimate the relative efficacy of selpercatinib versus cabozantinib and BSC in treatment-naïve and pre-treated patients.
- Unweighted PFS and OS curves for the *RET*-mutant and *RET* M918T-positive subgroups of the EXAM trial, respectively, are based on small patient numbers, and thus are associated with considerable uncertainty.
- The PH assumption was violated for PFS before and after weighting for the comparison of selpercatinib versus cabozantinib, and thus stratified survival functions were also explored for extrapolation.

RET fusion-positive TC: Limitations of the naïve comparison for LIBRETTO-001 versus SELECT

Evidence for the efficacy of selpercatinib in pre-treated *RET* fusion-positive TC is available from the LIBRETTO-001 trial. However, there are a number of limitations with the available data:

- The pre-treated *RET* fusion-positive TC subgroup comprises on 19 patients, and thus PFS and OS data are subject to considerable uncertainty. OS data are particularly immature.
- The majority (13/19 [68.4%]) of these patients had PTC, and thus it is unclear whether this data can be generalised to other subtypes of TC within the *RET* fusion-positive TC population

The placebo arm of the SELECT ITT population was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC, given the availability of OS and PFS data for this population. However, there are a number of limitations with this source of evidence:

- The SELECT trial did not limit to patients with a *RET* fusion. Since the prognostic significance of *RET* fusion in TC is unclear, the data from SELECT may not be generalisable to the *RET* fusion-positive TC population.
- The SELECT trial only included patients with DTC, and thus it is not clear whether these data can be generalised to other subtypes of TC within the *RET* fusion-positive TC population (e.g. anaplastic TC). However, given prognosis is generally worse for the other TC subtypes,[20] data from the placebo arm of the SELECT ITT population likely represents an overestimate of the efficacy of BSC in these patients.
- Overall survival was confounded by crossover. Kaplan-Meier curves for OS that have been adjusted for crossover using a RPSFT model are available from TA535[21].

In addition, given the small number of patients enrolled in the pre-treated *RET* fusion-positive TC subgroup of the LIBRETTO-001 trial, a matching-adjusted indirect comparison was not considered feasible, and relative efficacy was based on a naïve indirect treatment comparison. As such, this comparison may be subject to considerable selection bias, due to the lack of randomisation, and confounding due to potential differences in patient populations.

Clinical evidence for comparators used in the cost-effectiveness analysis

The evidence available for each of the relevant comparators in this appraisal can be summarised as follows:

RET-mutant MTC: Selpercatinib, cabozantinib and BSC

- The *RET*-mutant subgroup of the EXAM trial represents the most relevant source of published evidence for cabozantinib and BSC from those studies identified in the SLR, providing summary PFS Kaplan–Meier data for 107 patients receiving cabozantinib and 62 patients receiving placebo (which can be considered a proxy for BSC).[64] These data were used to inform PFS for cabozantinib and BSC in the economic model.
- There were a number of differences in the patient population characteristics between the LIBRETTO-001 trial and the EXAM trial. As such, a MAIC was conducted to adjust for baseline

characteristics with known or suspected associations with the efficacy outcomes that were reported in both the LIBRETTO-001 trial and EXAM trial publication.

    - Clinical effectiveness results were not reported separately for treatment-naïve and pre-treated patients in EXAM. Therefore, the any-line pooled population from the LIBRETT0-001 trial was used in the MAIC, providing a larger patient-level data set and more closely matching the characteristics of the *RET*-mutant subgroup of the EXAM trial
    - Patient characteristics for all patients in the any-line MTC population from LIBRETTO-001 were matched to the cabozantinib arm of the *RET*-mutant subgroup of the EXAM trial (the only population with patient characteristics reported)
    - The weighted PFS and OS curves generated in the MAIC were used to inform PFS and OS for selpercatinib in the economic model

- No OS Kaplan–Meier data were available from the EXAM trial for the *RET*-mutant subgroup. However, OS Kaplan–Meier data are available for the *RET* M918T-positive subgroup of the EXAM trial for data in 81 patients receiving cabozantinib and 45 patients receiving placebo.[24] Clinical experts confirmed that placebo outcomes in the *RET* M918T-positive group may be similar to the *RET*-mutant group as a whole; in the EXAM study, median PFS in the placebo arm was similar in the *RET* M918T-positive and *RET*-mutant cohorts (17 weeks versus 20 weeks, respectively). As such, the OS curve for placebo (which can be considered a proxy for BSC) from the *RET* M918T-positive subgroup was used to inform OS for BSC in the model.
- The OS curve for cabozantinib from the *RET* M918T-positive subgroup of the EXAM trial was not considered generalisable to the *RET*-mutant subgroup, since cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population; in the EXAM study, HRs for PFS favoured the *RET* M918T-positive versus the *RET*-mutant subgroup ([redacted] [95% CI: [redacted]] versus [redacted] [95% CI: [redacted]]).[24, 64] As such, OS for cabozantinib in the model was estimated by applying the HR for cabozantinib in the *RET*-mutant subgroup to the OS survival functions for placebo (from the *RET* M918T-positive subgroup, as described above).

RET fusion-positive TC: Selpercatinib and BSC

- PFS and OS reported for the pre-treated *RET* fusion-positive TC patients in LIBRETTO-001 (n=19) were used to inform the efficacy of selpercatinib for pre-treated *RET* fusion-positive TC patients in the economic model
- The placebo arm of the SELECT trial was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC. Whilst PFS data are available for the pre-treated subgroup of SELECT, RPSFT-adjusted OS data are only available for the ITT population (n=131). As such, for consistency with the data informing OS, the placebo arm of the ITT population was used in to inform both OS and PFS for BSC in the model.

Full details of the approaches used to derive clinical inputs for the model are provided in B.3.3.2.

B.2.9 *Adverse reactions*

Summary of LIBRETTO-001 safety analysis

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (regardless of tumour type or treatment history) and specifically in those patients with RET-mutant MTC
- [redacted] percent of patients in the OSAS and [redacted] of patients in the RET-mutant MTC SAS received the proposed starting dose of 160 mg BID. Dose reductions were required in [redacted] of the OSAS and [redacted] of the RET-mutant MTC SAS, with the most common reason being AEs ([redacted] and [redacted] respectively)
- In the OSAS and the RET-mutant MTC SAS, permanent discontinuation of selpercatinib due to TEAEs were infrequent ([redacted] and [redacted], respectively), with no predominant pattern among the individual AEs reported
- In the OSAS, Grade 3 or 4 TEAEs were reported in [redacted] patients and [redacted] in the RET-mutant MTC SAS, irrespective of relatedness to selpercatinib. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication
- In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable and addressable toxicities. As a result, permanent discontinuation of selpercatinib due to TEAEs was infrequent in both the OSAS and RET-mutant MTC SAS, meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib
- Overall, selpercatinib was shown to be well tolerated across patient populations, and taking into account the clinical efficacy demonstrated in RET-mutant MTC patients, selpercatinib has demonstrated a positive risk: benefit ratio in this population

The following sections present treatment exposure and adverse event data from the overall safety analysis set (OSAS; n=[redacted]) and MTC safety analysis set (MTC SAS; n=[redacted]) analysis sets. All adverse events (AEs) from the time the informed consent form was signed until the end of the safety follow up period (28 ±7 days post last dose) were recorded in patients who received one or more doses of selpercatinib as of the 16 December 2019 data cut-off date.

B.2.9.1 Treatment duration and dosage

Following the Phase I dose escalation portion of the study, the Phase II dose of selpercatinib recommended for treatment is 160 mg twice daily (BID). Table 38 summarises the range of starting doses and average time on treatment for patients in the LIBRETTO-001 trial. The majority ([redacted] of the OSAS and [redacted] of the *RET*-mutant MTC SAS) received a starting dose of 160 mg BID, with a small proportion receiving either >160mg BID (200–240mg BID; [redacted] of the OSAS and [redacted] of the *RET*-mutant MTC SAS) or <160mg BID (20mg QD – 120mg BID; [redacted] of the OSAS and [redacted] of the *RET*-mutant MTC SAS). The proposed starting dose of 160 mg BID was received by [redacted] of patients in the OSAS, for [redacted] patients as a starting dose and for [redacted] patients as a protocol-specified dose adjustment.

Dose reductions were seen in [redacted] of the OSAS and [redacted] of the *RET*-mutant MTC SAS, with the most common reason being adverse events ([redacted] and [redacted] respectively). Dose interruptions were more common, with [redacted] of the OSAS and [redacted] of the *RET*-mutant

MTC SAS requiring interruption. The most common reason for interruption was adverse events ([redacted] and [redacted] respectively).

Table 38: Selpercatinib dosing (SAS)

	RET-mutant MTC N=[redacted]	Overall N=[redacted]
Starting dose, n (%)		
20 mg QD	[redacted]	[redacted]
20 mg BID	[redacted]	[redacted]
40 mg BID	[redacted]	[redacted]
60 mg BID	[redacted]	[redacted]
160 mg QD	[redacted]	[redacted]
80 mg BID	[redacted]	[redacted]
120 mg BID	[redacted]	[redacted]
160 mg BID (RP2D)	[redacted]	[redacted]
200 mg BID	[redacted]	[redacted]
240 mg BID	[redacted]	[redacted]
Time on treatment, months		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

Abbreviations: BID: twice daily; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; RP2D: recommended Phase II dose; QD: once daily; SAS: safety analysis set.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Table 39: Selpercatinib relative dose intensity (SAS)

	RET-mutant MTC N=[redacted]	Overall N=[redacted]
Relative dose intensity (%)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Category, n (%)		
≥90%	[redacted]	[redacted]
75–90%	[redacted]	[redacted]
50–75%	[redacted]	[redacted]
<50%	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RET rearranged during transfection; SAS: safety analysis set..
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Table 40: Selpercatinib dose modifications (SAS)

	RET-mutant MTC N=[redacted]	Overall N=[redacted]
Dose reduction, n (%)		

Any	[redacted]	[redacted]
For AE	[redacted]	[redacted]
Intra-patient dose escalation	[redacted]	[redacted]
For other reason	[redacted]	[redacted]
Dose interruption, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	[redacted]
For other reason	[redacted]	[redacted]
Dose increase, n (%)		
Any	[redacted]	[redacted]
Intra-patient escalation[a]	[redacted]	[redacted]
Reescalation[b]	[redacted]	[redacted]
Other reason	[redacted]	[redacted]

[a]Started at a lower dose during dose escalation that was subsequently increased. [b]Reescalation after a dose reduction
Abbreviations: AE: adverse event; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RET rearranged during transfection; SAS: safety analysis set.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

B.2.9.2 Summary of adverse events

For patients in the LIBRETTO-001 OSAS, the median time on treatment was [redacted] months, with a longest time on treatment of over [redacted] years. The median age of patients receiving selpercatinib was [redacted] years for the OSAS, and encompassed a wide range ([redacted]), with [redacted] patients younger than 18 years of age and [redacted] of patients in the 45–64 age group.

The majority of patients carried the three different tumour diagnoses of NSCLC ([redacted]), MTC ([redacted]), and *RET* fusion-positive thyroid cancer ([redacted]). Most patients had received prior cancer therapy: [redacted] had undergone surgery, [redacted] had received one or more systemic therapies and [redacted] had received radiotherapy.

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied, with a safety profile characterised by recognisable toxicities which can be monitored, reversed with dose interruption, or addressed through dose reduction or concomitant medication. A summary of safety trends is presented in Table 41. Permanent discontinuation of selpercatinib due to TEAEs were infrequent [redacted] deaths within 28 days of last dose were attributed to selpercatinib. All deaths were attributed to either disease progression ([redacted] patients), to an AE unrelated to drug, or to unknown reasons.

Table 41: Summary of safety trends (SAS)

	Incidence, n (%)	
	***RET*-mutant MTC N=[redacted]**	**Overall N=[redacted]**
Any AE		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Grade 3 or 4 AE		

	Incidence, n (%)	
	RET-mutant MTC N=	Overall N=
All		
Related to selpercatinib		
AE leading to treatment discontinuation		
All		
Related to selpercatinib		
SAE		
All		
Related to selpercatinib		
Fatal AE (none related to selpercatinib)		

Abbreviations: AE: adverse event; MTC: medullary thyroid cancer; RET rearranged during transfection; SAE: serious adverse event; SAS: safety analysis set.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

B.2.9.3 Treatment emergent adverse events

Most patients in the OSAS experienced at least 1 treatment-emergent adverse event (TEAE) during treatment. The most common TEAEs, defined as those reported in at least 20% patients in the OSAS were: dry mouth , diarrhoea , hypertension , AST increase (, ALT increase , fatigue , constipation , peripheral oedema , headache , nausea .

Overall the rates of adverse events between the *RET*-mutant MTC SAS and the OSAS were similar (Table 42).

Table 42: Common adverse events all grades (15% or greater in any Safety Analysis Set)

Preferred term	Maximum severity incidence, n (%)									
	RET-mutant MTC N=					Overall N=				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Dry mouth										
Diarrhoea										
Hyper-tension										
AST increased										
ALT increased										
Fatigue										
Consti-pation										

Oedema peripheral	[redacted]									
Headache	[redacted]									
Nausea	[redacted]									
Blood creatinine increased	[redacted]									
Abdominal pain	[redacted]									
Rash	[redacted]									
ECG QT prolonged	[redacted]									
Vomiting	[redacted]									
Cough	[redacted]									
Pyrexia	[redacted]									
Thrombo-cytopenia	[redacted]									
Arthralgia	[redacted]									
Hypo-calcaemia	[redacted]									

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; MTC: medullary thyroid cancer; RET rearranged during transfection.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

TEAEs Generally Consistent Across in NSCLC and MTC Patients

Selpercatinib safety was generally consistent across NSCLC and MTC patients with the following exceptions:

- The NSCLC population (relative to the MTC population) had a higher incidence of diarrhoea ([redacted] respectively), thrombocytopenia ([redacted]) and pyrexia ([redacted]).
- The MTC population (relative to the NSCLC population) had a higher incidence of hypertension ([redacted] respectively), fatigue ([redacted]), and abdominal pain ([redacted]).

As there is no known explanation for these differences, the pooled analyses (n = [redacted]) is considered the most comprehensive evaluation of selpercatinib.

B.2.9.4 Grade 3–4 adverse events

Grade 3 or 4 TEAEs were reported in [redacted] patients in the OSAS group, irrespective of relatedness to study drug (Table 43). The most common Grade 3–4 events in the OSAS were:

hypertension ([redacted]), ALT increase ([redacted]), AST increase ([redacted]), hyponatremia ([redacted]). There were [redacted] Grade 3–4 TEAEs considered by the investigator to be related to selpercatinib.

In the MTC SAS group, Grade 3 or 4 TEAEs were reported 168 (56.2%) patients, irrespective of relatedness to study drug (Table 43). The most common Grade 3–4 events were similar to those of the OSAS group: hypertension ([redacted]), ALT increase ([redacted]), AST increase ([redacted]), hyponatremia ([redacted]).

Table 43: Grade 3–4 adverse events in 2% or more patients (SAS)

Preferred term	Incidence, n (%)	
	RET-mutant MTC N = [redacted]	Overall N = [redacted]
1 or more Grade 3–4 AEs	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
ECG QT prolonged	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]

Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG: electrocardiogram; MTC: medullary thyroid cancer; RET rearranged during transfection; SAS: safety analysis set..
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

B.2.9.5 Adverse events of special interest

Based on predictions from the *RET*-related literature, the preclinical toxicology program, and primarily, experience with selpercatinib, three AEs of special interest (AESIs) were investigated in the LIBRETTO-001 trial: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase, drug hypersensitivity reaction, and hypertension. All of the identified AESIs were monitorable and reversible with successful dose modification strategies which allow the majority of patients who experience these events to continue safely on therapy.

ALT/AST increase and hypertension

A summary of ALT/AST and hypertension AESIs can be found in Table 44. The majority of ALT/AST TEAEs were related to selpercatinib and were Grade 1 or 2. Although ALT and AST TEAEs were the most common reasons for dose interruptions (ALT=[redacted]%; AST=[redacted]%) and reductions (ALT=[redacted]%; AST=[redacted]%), they led to permanent discontinuation in only [redacted] patients. No patients met the Hy's Law criteria of drug induced liver injury.

Of the [redacted] OSAS patients, [redacted] of patients had a reported chronic history of hypertension and [redacted] did not. The frequency of reported hypertension AEs was similar between these patients despite the difference in medical history. A minority of patients required dose interruption ([redacted] considered related) and/or reduction ([redacted] related). No patients discontinued therapy due to an AE of hypertension.

Table 44: ALT/AST and hypertension AESIs in the LIBRETTO-001 trial (OSAS)

Adverse event of special interest, n (%)	LIBRETTO-001 OSAS N=[redacted]	
	Any grade	Grade 3/4
AST increase	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
ALT increase	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Drug hypersensitivity reaction

Study drug-related drug hypersensitivity was defined as patients who early in their treatment course, experienced a constellation of symptoms or findings inclusive of maculopapular rash that was often preceded by fever and associated with arthralgias or myalgias. These were often followed by platelet decrease and/or transaminase increases or, less commonly, by a blood pressure decrease, tachycardia, and/or creatinine increase. A summary of hypersensitivity AESIs can be found in Table 45.

Table 45: Hypersensitivity AESIs in the LIBRETTO-001 trial (OSAS)

Adverse event of special interest	LIBRETTO-001 OSAS N=[redacted]
Drug hypersensitivity, n (%)	[redacted]
Singe event	[redacted]
Multiple events	[redacted]
Range	[redacted]
Median time to first onset, weeks	[redacted]
Range	[redacted]
Grade 3 hypersensitivity events, n (%)	[redacted]
Grade 4 hypersensitivity events	[redacted]
AEs deemed ‘serious’ attributed to selpercatinib	[redacted]
Dose interruptions or reductions	[redacted]
Dose discontinuations	[redacted]

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
Source: Eli Lilly Data on File (16th December 2019 data cut-off)[56]

Notable Event:QT Prolongation

Any grade ECG QT Prolonged was reported for [redacted] patients ([redacted]), with [redacted] ([redacted]%) considered related to selpercatinib. The majority of events were Grade 1 or Grade 2. One patient had an AE of QTcF prolongation that was deemed serious.

QTcF prolongation was manageable by selpercatinib dose interruptions ([redacted] patients) or reductions ([redacted] patients), while no action with drug was taken in [redacted] patients. No patients discontinued treatment due to QT prolongation.

Cardiac arrhythmia due to QT prolongation such as *torsades de pointes* can have a high impact on individual patients, as outcomes can be severe and, in some cases, could be fatal if severe events are not treated. To date, [redacted] clinically significant TEAE related to QT prolongation such as treatment emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, sudden death, or *torsades de pointes* have been observed.

QT prolongation events can be managed and reversed with successful dose modification strategies, allowing patients to continue safely on therapy.

B.2.10 *Ongoing studies*

The LIBRETTO-001 trial is ongoing. Additional data from this trial may become available during the course of the appraisal. A Phase III trial to investigate the efficacy and safety of selpercatinib versus standard treatment (cabozantinib or vandetanib) in adult patients with untreated RET-Mutant MTC (LIBRETTO-531; NCT04211337), is currently recruiting.

B.2.11 *Innovation*

RET-mutant MTC

Current treatment guidelines[18, 30, 72-74] for patients with MTC note that MTC does not respond well to conventional therapy, and patients with MTC report debilitating symptoms (e.g., severe diarrhoea), which may lead to workplace absence and lost productivity.[19] Cabozantinib is associated with significant toxicity. According to a clinical expert experienced in the treatment of thyroid cancer, the majority of patients will require a dose reduction within six months of treatment, and a considerable proportion of patients are not eligible to receive cabozantinib as a first-line systemic treatment.[26] In the EXAM trial, 82% of cabozantinib-treated patients had a dose reduction, and 46% underwent a second-level dose reduction, while 22% discontinued treatment with cabozantinib due to adverse events (compared to 9% versus placebo).[24]

Selpercatinib offers a novel treatment approach and is the first of its kind to demonstrate efficacy in MTC patients through highly selective targeting of the RET receptor. It demonstrated an ORR of 69.1% (38/55; 95% CI: 55.2, 80.9) in patients pre-treated with either cabozantinib or vandetanib (PAS) and 72.7% (64/88; 95% CI 62.2, 81.7) in patients who were cabozantinib or vandetanib-naïve (SAS1).[51] By comparison, in *RET*-mutant MTC patients, cabozantinib demonstrated an ORR of less than half that of selpercatinib of 31.7% (32/101) in the RET-mutant subgroup of the EXAM trial, while vandetanib demonstrated an ORR of 51.8% (57/110) in the RET-mutant subgroup of the ZETA trial.[24, 63] The results of the MAIC (Section B.2.8.1) indicated that selpercatinib was associated with a statistically significant improvement in PFS and OS

compared with cabozantinib (HRs of [redacted] and [redacted] for PFS and OS, respectively) and placebo (HRs of [redacted] and [redacted] for PFS and OS, respectively). Selpercatinib also offers a comparatively safer therapeutic option than cabozantinib. Grade 3–4 AEs were reported in [redacted] *RET*-mutant MTC patients treated with selpercatinib, dose reductions were seen in [redacted], with [redacted] of patients discontinuing treatment due to an AE.

As *RET* mutations are known to contribute to oncogenicity in MTC,[3] the highly selective targeting of the RET receptor allows for a potent anti-tumour response with minimal off target effects. Therefore, for patients in the UK with *RET*-mutant MTC, selpercatinib may offer a safer and more effective treatment option than cabozantinib, as demonstrated by its markedly lower AE and discontinuation profile and higher ORR. Selpercatinib can also address the unmet need for patients who progress on or who are ineligible for cabozantinib, who would otherwise be treated palliatively with BSC.

RET fusion-positive TC

For patients in the UK with progressive, advanced or metastatic differentiated thyroid cancer who are not responsive to radioactive iodine, the only treatments available are MKIs, lenvatinib and sorafenib.[21] For patients with undifferentiated (i.e. anaplastic) thyroid cancer, there are currently no safe an effective treatments and patients are treated primarily with BSC.

MKIs have non-selective mechanisms of action and thus can be associated with off-target effects, As a results, they are associated with a significant toxicity profile that frequently leads to dose reductions and discontinuations, subjecting patients to considerable side effect profiles.[24, 25] In the SELECT trial which assessed the efficacy of lenvatinib for treating progressive, locally advanced or metastatic DTC, adverse events Grade ≥3 were reported in 85% of patients in patients treated with lenvatinib (n=261), compared to 30% in patients treated with placebo (n=131). Dose interruptions (82%), reductions (68%) and discontinuation (16.5%) were also higher in patients treated with lenvatinib than placebo (18%, 5% and 5% respectively). Similar results have been reported for sorafenib (Grade 3–4: 64.3%; discontinuation: 18.8%).[75] As in the UK, lenvatinib or sorafenib cannot be used following another MKI (i.e. they cannot be used progressively) unless a patient had to discontinue a MKI within 3 months of starting due to toxicity.[21] As such, following progression or discontinuation on lenvatinib and sorafenib, there are no further effective treatments and advanced patients are treated palliatively with BSC.

Selpercatinib has also demonstrated efficacy in TC patients through highly selective targeting of the RET receptor. In patients with previously treated *RET* fusion-positive thyroid cancer (n=19), the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9) by IRC.[51] For patients with systemic therapy naïve *RET* fusion-positive thyroid cancer (n=8), the ORR was [redacted]. Selpercatinib also offers a considerable improvement in PFS compared with BSC: median PFS was 20.07 (95% CI: 9.4, NE) months in the previously treated *RET* fusion-positive TC population (n=19) of the LIBRETTO-001 trial[51] compared with 3.6 (95% CI: 1.9, 3.7) in the pre-treated subgroup of the SELECT trial and 3.7 (95% CI: 3.5, 4.5) in the placebo ITT population (see Section B.2.8.2). Selpercatinib offers a safe and effective alternative to BSC, extending survival for patients who are otherwise without effective treatment options.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings of the clinical evidence base

The efficacy and safety of selpercatinib has been demonstrated in the LIBRETTO-001 trial, an ongoing, multicentre, open-label, Phase I/II study to understand the pharmacokinetics (PK), safety, and maximum tolerated dose (MTD) for selpercatinib and to permit the preliminary assessment of efficacy and safety in patients with RET altered solid tumours. The primary efficacy endpoint of ORR showed a high rate of response in *RET*-mutant MTC patients, with the PAS demonstrating an ORR of 69.1% (38/55; 95% CI: 55.2, 80.9) by IRC assessment, the IAS demonstrating [redacted] and the SAS1 demonstrating 72.7% (64/88; 95% CI 62.2, 81.7).[51] In patients with previously treated *RET* fusion-positive thyroid cancer (n=19), the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9) by IRC.[51] For patients with systemic therapy naïve *RET* fusion-positive thyroid cancer (n=8), the ORR was [redacted].

The LIBRETTO-001 trial also found selpercatinib to have a tolerable safety profile, with Grade 3–4 AEs seen in [redacted] patients and [redacted] of patients discontinued due to AEs in the OSAS, with similar results seen in the MTC SAS (Grade 3–4: [redacted]; discontinued [redacted]), though due to small sample side the *RET* fusion-positive TC population was not analysed separately for safety.

In the context of current clinical practice within the NHS in England, this submission positions selpercatinib "as monotherapy in adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment" and "as monotherapy in adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy". This is narrower than the anticipated marketing authorisation in *RET*-fusion positive TC, and is in line with the full anticipated marketing authorisation in *RET*-mutant MTC for selpercatinib in these populations and specifies more clearly the intended population of interest than that indicated in the NICE draft scope. This submission therefore focussed on clinical and safety data relevant to these patient populations from the LIBRETTO-001 trial.

The results of the MAIC (Section B.2.8.1) indicated that selpercatinib was associated with a statistically significant improvement in PFS and OS compared with cabozantinib (HRs of [redacted] and [redacted] for PFS and OS, respectively) and placebo (HRs of [redacted] and [redacted] for PFS and OS, respectively) for patients with *RET*-mutant MTC. Similarly, based on a naïve comparison versus the pre-treated subgroup of the SELECT trial (see Section B.2.8.2), selpercatinib offers a considerable improvement in PFS compared with BSC in the previously-treated *RET* fusion-positive TC population: median PFS was [redacted] (95% CI: [redacted]) months for selpercatinib compared with 3.6 (95% CI: 1.9, 3.7) for placebo and 3.7 (95% CI: 3.5, 4.5) in the placebo ITT population (which can be considered a proxy for BSC).

Strengths and limitations of the clinical evidence base

The clinical evidence presented within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including selpercatinib, in *RET*-altered thyroid cancers.

Evidence for the efficacy and safety of selpercatinib is provided by the LIBRETTO-001 trial. However, this trial may not be fully generalisable to patients in UK clinical practice. Patients in the LIBRETTO-001 trial in the PAS and IAS are relatively heavily pre-treated, specifically with MKIs (including cabozantinib, vandetanib, sorafenib and lenvatinib) in comparison to patients in UK clinical practice. In the PAS, [redacted] of patients received 1–2 prior therapies, and [redacted] received ≥3 prior therapies. In the IAS, [redacted] of patients received 1–2 prior therapies, and [redacted] received ≥3 prior therapies. In UK practice, since cabozantinib is the only NICE approved MKI for the treatment of progressive, advanced or metastatic MTC, patients are comparatively unlikely to have received more than one MKI prior to selpercatinib. Therefore, the effect of this difference is expected to result in conservative estimations with respect to selpercatinib.

Another key limitation of the evidence base was that no head-to-head randomised clinical trial evidence was available for selpercatinib comparing efficacy to relevant comparators (i.e. cabozantinib and BSC in *RET*-mutant MTC and BSC in *RET*-fusion positive TC), with the single-arm LIBRETTO-001 trial representing the primary source of evidence for selpercatinib. As such, relative efficacy is based on unanchored population-adjusted and naïve indirect comparisons, which may be subject to selection bias and confounding. In addition, data for comparator therapies in the relevant population of interest are not available for all outcomes: for example, Kaplan–Meier OS data were not available for the *RET*-mutant subgroup of the EXAM trial, and thus data for the *RET* M918T-positive population had to be used to inform OS in its place. The limitations of these analyses have been described in full in Section B.2.8.3.

Furthermore, sample sizes are small across the LIBRETTO-001 and comparator trials, especially for *RET*-fusion positive TC patient population, and OS data are immature. This leads to uncertainty in the long-term estimates of treatment efficacy in the model. Further data cuts from the LIBRETTO-001 trial, evidence from the Phase III trial investigating the efficacy and safety of selpercatinib versus standard treatment (cabozantinib or vandetanib) in adult patients with untreated RET-Mutant MTC (LIBRETTO-531; NCT04211337) and collection of data via the systemic anticancer therapy (SACT) cohort may help resolve this uncertainty. As such, selpercatinib is positioned as a candidate for approval on the CDF in this submission.

B.2.12.1 End of life criteria

Selpercatinib should be considered as an end of life treatment for adult patients with *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment and for adults and people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy who have previously received or who are ineligible for cabozantinib, given (a) these patients have a short life expectancy, normally less than 2 years and (b) there is sufficient evidence to indicate that the selpercatinib offers an extension to life of at least an additional 3 months, compared with current NHS treatment.

Further details to support selpercatinib as an end of life treatment are provided below.

The treatment is indicated for patients with a short life expectancy, normally less than 24 months

Median OS data are not available for patients with *RET*-mutant MTC receiving cabozantinib. Median OS for patients receiving placebo in the *RET* M918T-positive subgroup of the EXAM trial was 44.3 months, however, as discussed in Section B.2.8.1, cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population. In the economic

model, OS for cabozantinib was estimated by applying the HR for cabozantinib versus placebo in the *RET*-mutant subgroup of the EXAM trial to the extrapolated Kaplan–Meier curve for the *RET* M918T-positive subgroup placebo arm. Median OS predicted by the model was [redacted] months, demonstrating the life expectancy for patients receiving cabozantinib is expected to be greater than 24 months, and selpercatinib should not be considered an end-of-life treatment for patients who would otherwise receive cabozantinib in current NHS practice.

Median OS data are not available for patients with *RET*-mutant MTC who have previously received or who are ineligible for cabozantinib. However, median OS for patients receiving placebo (which can be considered a proxy for BSC) in the *RET* M918T-positive subgroup of the EXAM trial was 18.9 months.[24] Clinical experts confirmed that placebo outcomes in the *RET* M918T-positive group may be similar to the *RET*-mutant group as a whole, and thus these data demonstrate that median survival for *RET*-mutant MTC patients is expected to be less than 24 months. Since the EXAM trial included both treatment-naïve and pre-treated patients, it is expected that survival for patients who have received prior cabozantinib is poorer than that reported in the EXAM trial. Median OS predicted by the model was [redacted] months for patients receiving BSC.

As discussed in Section B.2.8.2, no RCT data were identified in patients with *RET* fusion. In the economic model, OS for patients receiving BSC was based on RPSFT-adjusted OS data for patients receiving placebo (which can be considered a proxy for BSC) in the ITT population of the SELECT trial. Median OS for patients receiving placebo in the ITT population of the SELECT trial was not estimable (95% CI: 20.3, NE), but was predicted from the economic model to be [redacted] months. These data suggest that median survival for *RET f*usion-positive TC patients receiving BSC is less than 24 months. However, as discussed in Section B.1.3.1 and confirmed by a clinical expert experienced in the treatment of thyroid cancer, the prognostic significance of *RET* fusion in TC is unclear.[26, 70]

Results from the economic model predicted a mean undiscounted life years of [redacted] for *RET* fusion-positive TC patients receiving BSC and [redacted] for the *RET*-mutant MTC patients receiving BSC. Whilst predicted mean OS is greater than 24 months, predicted median OS is ≤24 months in both populations, indicating that the majority of patients have a short life expectancy (less than 2 years). A minority of patients with extended survival skew mean survival estimates. As such, selpercatinib should meet the NICE end of life criteria for these subgroups of the licensed indication under review.

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

There are no direct comparisons between selpercatinib and current clinical management. Median OS for selpercatinib was not estimable in the LIBRETTO-001 trial, but was predicted from the economic model to be [redacted] for the pre-treated *RET* fusion-positive TC population and [redacted] for the any-line MTC population.

Consequently, there is sufficient evidence to indicate that selpercatinib offers an extension of life of at least an additional 3 months compared with current NHS treatment. This is further supported by the economic model, where the undiscounted incremental life years gained (LYG) predicted by the model for selpercatinib compared with BSC was estimated to be [redacted] and [redacted]

RET fusion-positive TC patients and *RET*-mutant MTC patients, respectively, increments that are considerably greater than 3 months.

Given the potential long-term survival benefits with selpercatinib and the poor life expectancy for patients on BSC, the end of life criteria apply to these subgroups of the licensed indication under review.

Table 46: End of life criteria

Criterion	Data available			Reference in submission
	***RET* fusion-positive TC (BSC arm)**	***RET*-mutant MTC (BSC arm)**	**Source**	
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS: [redacted] months	Median OS: [redacted] months	Economic model prediction, based on *RET* M918T-positive subgroup of the EXAM trial[24]	B.2.8, B.3.3.2
	Mean undiscounted life years: [redacted]	Mean undiscounted life years: [redacted]		
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	[redacted] months (difference in median OS)	[redacted] months (difference in median OS)	Economic model prediction based on the LIBRETTO-001 trial	B.2.5, B.3.3.2
	Incremental life years gained: [redacted] ([redacted] months	Incremental life years gained: [redacted] ([redacted] months)		

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; NHS: National Health Service; *RET*: rearranged during transfection; TC: thyroid cancer.

B.3 Cost effectiveness

Summary of cost-effectiveness results

De novo cost-effectiveness model

- A de novo cost-utility model was developed to evaluate the cost-effectiveness of selpercatinib as "monotherapy in adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment" and "as monotherapy in adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy"
- The model adopted a partitioned survival approach with three health states: *progression free* (PF)*, progressed disease* (PD), and *death*
- Selpercatinib was compared to cabozantinib and BSC via a MAIC using data from the LIBRETTO-001 trial for selpercatinib survival inputs and the EXAM[24, 64] trial for comparator therapies for *RET*-mutant MTC
- Selpercatinib was compared to BSC via a naïve indirect comparison using data from the LIBRETTO-001 trial for selpercatinib survival inputs and the SELECT[68] trial for BSC for pre-treated *RET* fusion-positive TC
- Stratified and unstratified standard parametric and flexible approaches were used to extrapolate survival data for selpercatinib (OS, PFS) and comparator (OS and PFS) therapies
- Utility values for the PF and PD health states (for both MTC and TC populations) were derived from Fordham et al. (2015),[76] in line with previous technology appraisals (TA516[22] and TA535[21])
- Resource use and costs included in the model were based on information from the LIBRETTO-001 trial, previous technology appraisals (TA516[22] and TA535[21]) and appropriate published sources including the BNF and NHS National Cost Collection 2018/19[77]
- Feedback from UK clinicians was sought in order to validate assumptions and inputs included in the model

Base case cost-effectiveness results

- For *RET*-mutant MTC, under the base case assumptions, selpercatinib was associated with pairwise ICERs of [redacted] and [redacted] per QALY gained versus cabozantinib and BSC, respectively. For pre-treated *RET*-fusion TC selpercatinib was associated with an ICER of [redacted] per QALY gained versus BSC

Sensitivity and scenario analyses

- [redacted]. Results of the scenario analyses exhibit substantial variation when different extrapolations for the PFS and OS for *RET*-mutant MTC population, and specifically OS in the *RET* fusion-positive TC population are used. This can be attributed to the uncertainty in the clinical data underpinning these endpoints.
- As demonstrated by the DSA, in *RET*-mutant MTC, the most influential parameters driving the model for the comparison of selpercatinib with cabozantinib was the OS treatment-effects for cabozantinib. For the comparison of selpercatinib versus BSC in *RET*-mutant MTC and *RET* fusion-positive TC, health state utilities were the most influential parameters.

Conclusions

- Selpercatinib was not yet found to represent a cost-effective use of NHS resources when considered at list price, with ICERs above the £30,000 per QALY threshold versus cabozantinib in *RET*-mutant MTC and £50,000 per QALY threshold versus BSC in both populations
- [redacted]

B.3.1 *Published cost-effectiveness studies*

In the context of current clinical practice within the NHS in England, this submission positions selpercatinib as monotherapy in adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment, and as monotherapy in adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy.

A systematic literature review (SLR) was conducted to identify health-related quality of life, resource use and cost data to populate missing parameters for the cost effectiveness analysis. Full details of the SLR are provided in Appendix D. However, As thyroid cancer is a rare type of cancer, and there are no other selective *RET* kinase inhibitors currently available to patients, it was not considered necessary to conduct a SLR to identify relevant previous economic evaluations. The most pertinent economic evaluations relating to the treatment of these patients in UK clinical practice are those submitted as part of previous NICE technology appraisals (TAs), and thus a targeted literature review (TLR) was conducted to identify past NICE TAs for patients with TC and MTC.

Two relevant appraisals were identified relevant to this submission: cabozantinib for treating MTC (TA516),[22] and lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535).[21] A summary of these appraisals can be found in Table 47.

- TA516 evaluated the clinical and cost-effectiveness of cabozantinib and vandetanib within their marketing authorisations for treating unresectable locally advanced or metastatic MTC and estimated the incremental cost-effectiveness of cabozantinib and vandetanib compared with each other and BSC.
- TA535 evaluated the clinical and cost-effectiveness of lenvatinib and sorafenib within their marketing authorisation for treating progressive, locally advanced or metastatic DTC (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

Table 47: Summary list of published cost-effectiveness studies

Study, country, design	Patient population	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
TA516 (2018), UK, CUA	• Histologically confirmed, unresectable, locally advanced or metastatic MTC • Progression in the previous 14 months	• **Model type:** Partitioned survival model • **Health states:** 3 (progression-free, progressed and death) • **Cycle length:** 1 month • **Discount rate:** 3.5% • **Time horizon:** 20 years (lifetime)	2.28 versus 1.79 (Cabozantinib, BSC)	£88,527 versus £15,793 (Cabozantinib, BSC)	£150,874
TA535 (2018), UK, CUA	• Histologically/cytologically confirmed diagnosis of radioactive iodine-refractory (RR) DTC • Progression in past 12 months • 0 or 1 prior VEGF/VEGFR therapy • ECOG 0-2	• **Model type:** Partitioned survival model • **Health states:** 4 (stable disease, response, progressive and death) • **Cycle length:** 1 month (28 days) • **Discount rate:** 3.5% and half cycle correction • **Time horizon:** 33 years (scenarios: 5 and 10 year)	2.82 versus 1.60 (Lenvatinib, BSC)	£95,102 versus £15,195 (Lenvatinib, BSC)	£65,872
TA535 (2018), UK, CUA	• Locally advanced or metastatic RR-DTC • Progression in past 14 months • At least 1 measurable lesion by CT or MRI • ECOG 0-2	• **Model type:** Partitioned survival model • **Health states:** 3 (progression-free, progressed and death) • **Cycle length:** 1 month (28 days) • **Discount rate:** 3.5% and half cycle correction • **Time horizon:** 30 years	2.75 versus 2.22 (Sorafenib, BSC)	£63,188 versus £17,954 (Sorafenib, BSC)	£85,644

Abbreviations: BSC: best supportive care; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; NR: not reported; RR-DTC: radioactive iodine refractory differentiated thyroid cancer.
Source: NICE TA516,[22] NICE TA535.[21]

B.3.2 *Economic analysis*

The objective of this economic analysis was to assess the cost effectiveness of selpercatinib in adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy, and adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment. The base case population is considered to be relevant to UK clinical practice, reflecting the anticipated positioning for selpercatinib in the treatment pathway and the highest unmet clinical need.

A *de novo* cost-effectiveness analysis of selpercatinib versus comparators relevant to the decision problem for this submission was performed. The analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) over a lifetime time horizon of the patient cohort from the initiation of treatment. Sections B.3.2.1, B.3.2.2 and B.3.2.3 present the patient population, the model structure and the included interventions and comparators, respectively.

B.3.2.1 Patient population

The patient populations for the economic evaluation were:

- Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy
- Adults with advanced *RET* fusion-positive TC who require systemic therapy and who have progressed following prior systemic treatment

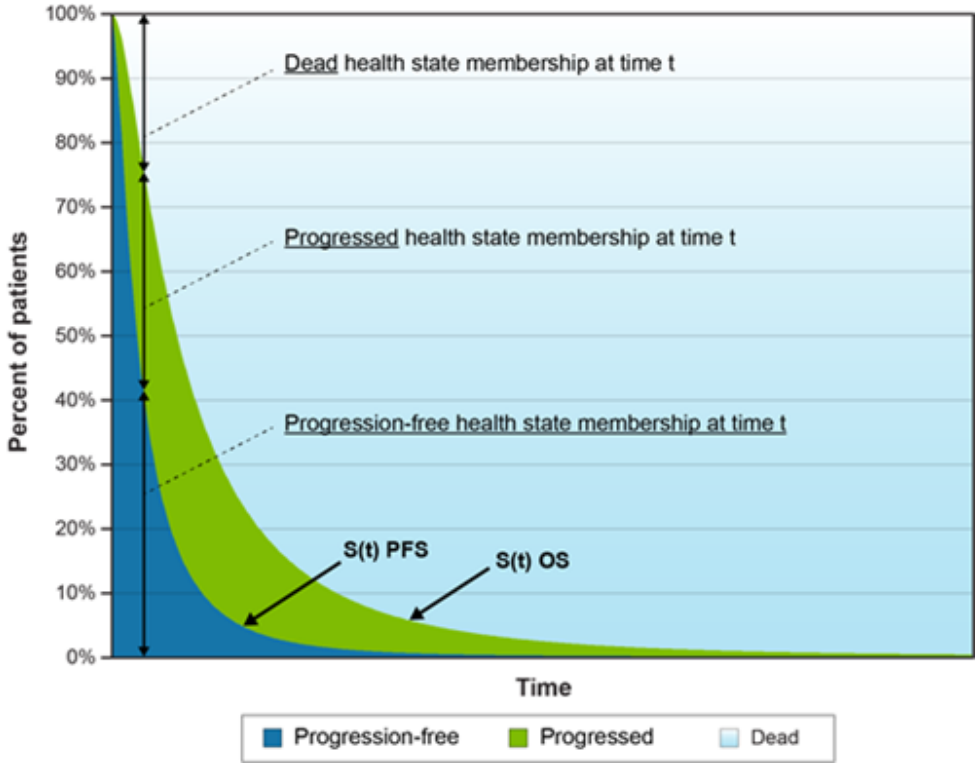
As set out in the decision problem in Section B.1.2 (Table 2), the *RET*-mutant MTC patient population considered in the model is in line with the full anticipated marketing authorisation for selpercatinib in MTC and the populations included in the LIBRETTO-001 trial, where patients with MTC had received 1 or more lines of prior cabozantinib or vandetanib (IAS; n=124) or were naïve to cabozantinib or vandetanib (SAS1; n=88). As discussed in Section B.2.8.3, data from the IAS and SAS1 were pooled to form the “any-line” population (n=212), which was used to inform the efficacy of selpercatinib in *RET*-mutant MTC patients in the model.

The *RET* fusion-positive TC population considered in the model is narrower than the full marketing authorisation for selpercatinib in TC, and is in line with the subgroup in the LIBRETTO-001 trial that received prior systemic therapy (n=19).

B.3.2.2 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of selpercatinib versus relevant comparators in adults and adolescents 12 years and older with advanced *RET*-mutant medullary MTC who require systemic therapy, and adults with advanced *RET* fusion-positive TC who require systemic therapy and who have progressed following prior systemic treatment. The developed model is a cohort-based partitioned survival model consisting of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death. A graphical depiction of the partitioned survival model approach is presented in Figure 26.

Figure 26: Partitioned survival model structure



The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific time point (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or the progressed health states beyond a specific time point (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership.
Abbreviations: OS: overall survival; PFS: progression-free survival.

Partitioned survival model

The partitioned survival model comprises three mutually exclusive health states: (i) PF, (ii) PD, and (iii) death. Cohorts of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy and adults with advanced *RET* fusion-positive TC who have progressed following prior systemic treatment were modelled to enter the partitioned survival model in the PF health state and to receive either selpercatinib or a comparator therapy. The proportion of patients in each heath state at each monthly model cycle was then determined for each therapy directly from cumulative survival probabilities from PFS and OS curves as follows:

- The proportion of patients occupying the PF state was calculated as the proportion alive and progression-free (based on PFS curve). All patients enter and occupy the PF state and are in stable disease as defined by the PFS measure assessed in LIBRETTO-001 and are not actively progressing. Patients incur costs of treatment, administration, medical monitoring and costs to manage Grade 3–4 adverse events while in this state. Patients also experience higher utility compared to progressed disease but also experience disutility based on the calculated rate of experiencing Grade 3–4 adverse events.
- The proportion of patients occupying the PD state was calculated as the proportion alive (based on OS curve) minus the proportion of patients alive and progression-free (based on PFS curve). Patients occupying the PD state have documented progressive disease as defined

and assessed in LIBRETTO-001 and receive subsequent treatment. Patients incur only health state costs following progression. The PD health state is associated with lower utility and no additional disutility or costs of managing Grade 3–4 adverse events are applied.

- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS curve). This is an absorbing state and a cost associated with palliative care is applied as a one-off upon death.

Patients were redistributed among the three health states at each model cycle.

The model structure does not allow for patients to improve their health state, which reflects the progressive nature of the condition. The death health state is an absorbing health state.

The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which facilitates the replication of within-trial data and means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with selpercatinib and comparator therapies. Importantly, the PFS and OS curves can be constructed from summary Kaplan–Meier data in the absence of patient-level data. Given the reliance on published summary data rather than patient-level data for comparator therapies, this was an important benefit of this model structure. Finally, as noted above, the partitioned-survival model structure has previously been used in NICE appraisals in TC (TA516 and TA535).[21, 22]

Features of the *de novo* analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Cost components considered included: drug and procedure acquisition costs for interventions and comparators, associated drug administration costs, cost of BSC, AE costs, other medical costs (by health state) and cost of end-of-life palliative care. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of selpercatinib versus each comparator was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) costs over a lifetime time horizon of the patient cohort from the initiation of treatment. A weekly cycle length was considered in the base case, and both costs and effects were discounted at 3.5% annually.[69] The economic analysis is conducted using the most recent estimates of resource use and treatment costs available from published sources (2018/2019). Costs quoted for other cost-years or in other currencies are inflated to the model cost-year and/or converted to UK, as applicable.

Table 48: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA516	TA535	Chosen values	Justification
Model structure	Partitioned survival model	Partitioned survival model	Partitioned survival model	Accurately reflect disease progression and the observed survival profile of patients treated with selpercatinib and comparator therapies and in line with precious appraisals
Time horizon	Lifetime horizon (20 years)	**Lenvatinib** Lifetime horizon (33.35 years) **Sorafenib** Lifetime horizon (30 years)	Lifetime horizon (25 years)	The reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
Cycle length	1 month (28 days) and half cycle correction	1 month (28 days) and half cycle correction	Weekly	Enables more accurate model predications. The cycle length was considered short enough that a half-cycle correction was not warranted.
Discount rate	3.5%	3.5%	3.5%	NICE reference case[69]
Source of utilities	Fordham *et al.* (2015)[76] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Fordham *et al.* (2015)[76] DECISION trial[71] **BSC** SD state: 0.77 Responsive state: 0.83 Progressive state: 0.64 **Lenvatinib** SD state: 0.76 Responsive state: 0.82 Progressive state: 0.64 **Sorafenib** SD state: 0.68 Responsive state: 0.74	Fordham *et al.* (2015)[76] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Health-state utility estimates reported by Fordham *et al.* (2015)[76] were accepted by the NICE appraisal committee in TA516 and TA535.

		Progressive state: 0.64		
Source of costs	• NHS Reference Costs • PSSRU • BNF	• NHS Reference Costs • PSSRU • BNF	• NHS National Cost Collection • PSSRU • BNF	Established sources of costs within the NHS. In line with the NICE reference case previous appraisals[21, 22, 69]
Resource use	• Expert opinion	• Expert opinion	Resource use was derived from prior appraisals[21, 22]	Resource use was not captured within the LIBRETTO-001 trial but prior NICE technology appraisals were considered a relevant source for resource use data.
Health effects measure	QALYs	QALYs	QALYs	NICE reference case[69]

Abbreviations: AE: adverse event; BNF: British National Formulary; PD: progressed disease; PF: progression-free; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; SD: stable disease.

B.3.2.3 Intervention technology and comparators

The intervention of interest is 160 mg selpercatinib administered orally twice daily in 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation. This is in line with the RP2D of the LIBRETTO-001 trial supporting the submission and the draft SmPC for selpercatinib.[1]

RET-mutant MTC

As discussed in Section B.1.3.2, cabozantinib,[22] but not vandetanib,[23] is recommended in the UK for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC (i.e. treatment naïve patients). For these patients, following a full thyroidectomy and/or radiotherapy, cabozantinib represents the only treatment option available. However, due its poor adverse event profile,[24, 25] treatment-naïve patients may not be eligible for cabozantinib due to tolerability concerns. Therefore, a proportion of these untreated patients may be treated with BSC, meaning the UK comparators for selpercatinib in untreated *RET*-mutant MTC patients are cabozantinib and BSC. For patients with progressive, unresectable locally advanced or metastatic MTC who progress or discontinue on cabozantinib, no further safe or effective treatment options are available in the UK, so patients are treated only with BSC. Furthermore, there are no *RET*-specific treatments licensed or available in the UK at present.

The dose for cabozantinib included in the model was 140 mg orally once daily until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation, and is aligned with the licensed indication for its use in MTC and the Phase III EXAM trial.[62, 78] In the model, BSC is assumed to consist of the routine care and monitoring described within the health-state costs presented in Section B.3.5.2. The placebo arm of the EXAM trial is considered a suitable proxy for BSC as determined in TA516. This was considered a suitable proxy for patients who received BSC at first-line (for patients not eligible to receive cabozantinib) or following

progression/discontinuation on cabozantinib, since patients presenting in this arm were either treatment-naïve or previously treated with a TKI, as per the inclusion criteria for the EXAM trial.[62]

***RET*-fusion positive TC**

Initially, patients classified as progressive, advanced or metastatic TC will typically receive a full or partial thyroidectomy and, if necessary, treatment with radioactive iodine (see Section B.1.3.2). Around 5% to 15% of people with DTC develop radioactive iodine refractory DTC.[50] The TKIs lenvatinib and sorafenib are the only treatments recommended for patients with DTC who are classified as progressive, advanced or metastatic who were not responsive to radioactive iodine if they are TKI naïve (TA535).[21] For patients who do not respond to, are contraindicated to or do not tolerate treatment with TKIs, there are no further safe and effective treatment options, and patients are treated palliatively with best supportive care (BSC). As above, BSC is assumed to consist of the routine care and monitoring described within the health-state costs presented in Section B.3.5.2.

As mentioned in section B.2.8.2, the placebo arm of the SELECT study for lenvatinib was considered a suitable proxy for BSC in the UK in TA535. Clinical expert opinion suggests that lenvatinib is the dominant choice in practice and the overall trial population is more comparable to the target population of interest as at least 1 prior TKI was permitted in the study. As such, the placebo arm of SELECT ITT population was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with pre-treated *RET* fusion-positive TC. Whilst the SELECT trial only included patients with DTC, since patients with other subtypes of TC have no suitable treatment options other than BSC, the placebo arm of SELECT ITT population was also considered a suitable proxy for comparator efficacy for the other subtypes of TC within the *RET* fusion-positive TC population (e.g. anaplastic or undifferentiated TC).

B.3.3 *Clinical parameters and variables*

The clinical evidence sources informing parameters for selpercatinib and comparators in the economic model are summarised in Table 49. Clinical data for selpercatinib for *RET*-mutant MTC and *RET* fusion-positive TC were derived from the relevant populations of the LIBRETTO-001 trial.[52, 56] Clinical data for cabozantinib and BSC in *RET*-mutant MTC were derived from the EXAM trial,[24, 62, 64] and clinical data for BSC in *RET* fusion-positive TC were derived from the SELECT trial.[68]

Table 49: Summary of clinical evidence sources informing parameters for selpercatinib and comparators in the economic model

Clinical parameter	Selpercatinib	Cabozantinib	BSC
***RET*-mutant MTC**			
Baseline characteristics	LIBRETTO-001 any-line population (IAS and SAS1; n=212)		
PFS	• Propensity score-weighted KM data for the LIBRETTO-001 any-line population (IAS and SAS1; n=[redacted])	• Unweighted KM data for the *RET*-mutant subgroup receiving cabozantinib (n=107) in the EXAM trial	• Unweighted KM data for the *RET*-mutant subgroup receiving placebo (n=62) in the EXAM trial

	• Matched to baseline characteristics of the *RET*-mutant population receiving cabozantinib in the EXAM trial	• Digitised from Sherman *et al.* (2016)[64]	• Digitised from Sherman *et al.* (2016) [64]
OS	• Propensity score-weighted KM data for the LIBRETTO-001 any-line population (IAS and SAS1; n=[redacted]) • Matched to baseline characteristics of the *RET*-mutant population receiving cabozantinib in the EXAM trial	• OS HR for cabozantinib versus placebo in the *RET*-mutant subgroup applied to the OS function for placebo (*RET*-M918T subgroup)	• Unweighted KM data for the *RET*-M918T subgroup receiving placebo (n=45) in the EXAM trial • Digitised from Schlumberger *et al.* (2017)[24]
Time-on-treatment	Assumed to be equivalent to PFS	Assumed to be equivalent to PFS	NA
AEs	LIBRETTO-001 MTC safety analysis set (n=[redacted])	Cabozantinib arm of the EXAM trial (n=214); Elisei *et al.* (2013)[62]	Placebo arm of the EXAM trial (n=109); Elisei *et al.* (2013)[62]
***RET* fusion-positive TC**			
Baseline characteristics	LIBRETTO-001 pre-treated subgroup (n=19)		
PFS	• KM data for LIBRETTO-001 pre-treated subgroup (n=19)	NA	• KM data for the ITT population receiving placebo (n=131) in SELECT • Digitised from Schlumberger *et al.* (2015)[68]
OS	• KM data for LIBRETTO-001 pre-treated subgroup (n=19)	NA	• RPSFT-adjusted KM data for patients receiving placebo in the ITT population of SELECT • Digitised from TA535
Time-on-treatment	Assumed to be equivalent to PFS	NA	NA
AEs	LIBRETTO-001 MTC safety analysis set (n=[redacted])	NA	Placebo arm of the SELECT trial (n=131); Schlumberger *et al.* (2015)[68]

Abbreviations: AEs: adverse events; BSC: best supportive care; IAS: integrated analysis set; ITT: intention-to-treat; KM: Kaplan-Meier; MTC: medullary thyroid cancer; OS: overall survival; OSAS: overall safety analysis set; PFS: progression-free survival; *RET*: rearranged during transfection; RPSFT: rank preserving structural failure time model; SAS1: supplementary analysis set 1; TC: thyroid cancer.

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort are provided in Table 50. Mean age and the percentage female were used alongside UK life tables to calculate the natural mortality of the general population. Mean age was also used to age-adjust utility values in the model.

These inputs were based on the baseline characteristics of patients who received selpercatinib in the pooled any-line *RET*-mutant MTC and pre-treated *RET* fusion-positive TC populations from the LIBRETTO-001 trial for the MTC and TC populations, respectively.

Table 50: Patient characteristics in the model

Model parameter	Value	Source
***RET*-mutant MTC**		
Mean age (SD)	[redacted]	LIBRETTO-001 any-line population (IAS and SAS1; n=212)
Sex (% female)	[redacted]	
***RET* fusion-positive TC**		
Mean age (SD)	[redacted]	LIBRETTO-001 pre-treated subgroup (n=19)
Sex (% female)	52.6%	

Abbreviations: IAS: integrated analysis set; MTC: medullary thyroid cancer; *RET*: rearranged during transfection; SAS1: supplementary analysis set 1; TC: thyroid cancer.

B.3.3.2 Survival inputs and assumptions

As described in Section B.3.2.2, the developed model is a cohort-based partitioned survival model consisting of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death. The proportion of patients in each heath state at each monthly model cycle was then determined for each therapy directly from cumulative survival probabilities from PFS and OS curves. As the follow-up periods for the relevant studies (LIBRETTO-001,[52] EXAM,[24, 62, 64] and SELECT[21, 68] trials – see Sections B.2.5 and B.2.8.1) were shorter than the model time horizon, extrapolation from the observed OS and PFS data was required.

For the purposes of survival analysis, pseudo patient-level data was derived from the published Kaplan-Meier curves and number of event information from the EXAM and SELECT trials using the algorithm described by Guyot *et al.* 2012.[79]

In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance on survival analyses, a range of standard parametric distributions (e.g. exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) and flexible models (i.e. spline models) were explored for extrapolation.[80] For the spline models, these were developed based on the algorithm by Royston and Parmar *et al.* (2002).[81] Stratified and unstratified one-, two-, three-knot Weibull spline models were explored using the FlexSurv package in R. The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were then estimated for each parametric function. Stratified models refer to models where all parameters can vary by treatment. These models relax the assumptions of PH or constant acceleration factors. The use of stratified models allows model fit statistics to be used to compare the model fit across all models (unlike models fitted separately to each treatment arm, wherein model fit cannot be compared across all models).

In determining the choice of survival model for the base case, consideration was given to the following, as per the recommendations provided in NICE DSU TSD14:[80]

- AIC and BIC goodness-of-fit statistics
- Visual inspection against the observed Kaplan-Meier curves
- Clinical plausibility for both short-term and long-term estimates of survival (as determined in TA516 and TA535 for comparator therapies)[21, 22]

Adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of patients alive being less than the proportion of patients alive and progression-free, could not occur (i.e. PFS was bound by OS as a minimum).

***RET*-mutant MTC**

As discussed in Section B.2.8.1, no head-to-head trials are available comparing selpercatinib to relevant comparators (cabozantinib and BSC, for those who cannot tolerate cabozantinib), with the single-arm, Phase I/II LIBRETTO-001 trial representing the primary source of clinical efficacy for selpercatinib. PFS and OS data are available from the LIBRETTO-001 trial for cabozantinib/vandetanib pre-treated and treatment-naïve *RET*-mutant MTC patients from the IAS (n=124) and SAS1 (n=88) analysis sets, respectively. However, whilst 37.0% of patients in the cabozantinib arm of the *RET*-mutant subgroup of the EXAM trial had received prior systemic therapy, results are not reported separately for treatment-naïve and pre-treated patients.

Therefore, an unanchored MAIC was conducted using individual patient-level data from the any-line pooled population from the LIBRETTO-001 trial (IAS and SAS1; n=212) and summary evidence from the EXAM trial, as reported in Schlumberger *et al.* (2017) and Sherman *et al.* (2016).[24, 64] The any-line pooled population from the LIBRETT0-001 trial was used rather than the IAS because the former provides a larger patient-level data set, more closely matches the characteristics of the EXAM trial population, and provides more information about the effect of line of therapy by which to adjust for the difference between trials with regards to the proportion of pre-treated versus treatment-naïve patients. Patient characteristics in LIBRETTO-001 were matched to the cabozantinib arm of the *RET*-mutant subgroup of the EXAM trial (the only population with patient characteristics reported).

- PFS and OS for selpercatinib in the model were based on the weighted PFS and OS curves generated in the MAIC, as shown in Figure 21 and Figure 22, respectively.
- PFS for cabozantinib and BSC in the model were based on published Kaplan-Meier data for PFS for patients receiving cabozantinib and placebo (which can be considered a proxy for BSC) in the *RET*-mutant subgroup of the EXAM trial, as shown in Figure 21.[64]
- No OS Kaplan–Meier data were available from the EXAM trial for the *RET*-mutant subgroup. However, OS Kaplan–Meier data are available for the *RET* M918T-positive subgroup of the EXAM trial for data 81 patients receiving cabozantinib and 45 patients receiving placebo.[24] Clinical experts confirmed that placebo outcomes in the *RET* M918T-positive group may be similar to the *RET*-mutant group as a whole. As such, the OS curve for placebo (which can be considered a proxy for BSC) from the *RET* M918T-positive subgroup, as shown in Figure 22, was used to inform OS for BSC in the model,.[24]

- The OS curve for cabozantinib from the *RET* M918T-positive subgroup of the EXAM trial was not considered generalisable to the *RET*-mutant subgroup, since cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population; in the EXAM study, HRs for PFS favoured the *RET* M918T-positive versus the *RET*-mutant subgroup ([redacted] [95% CI: [redacted]] versus [redacted] [95% CI: [redacted]]).[24, 64] As such, OS for cabozantinib in the model was estimated by applying the HR for cabozantinib in the *RET*-mutant subgroup to the OS function for placebo (from the *RET* M918T-positive subgroup, as described above) as the outcomes for the placebo arm in the *RET* M918T population are more likely to be generalisable to the *RET*-mutant population overall

Progression-free survival

A range of stratified and unstratified parametric functions were fitted to the weighted PFS curves for selpercatinib generated in the MAIC and the unweighted PFS curves for the *RET*-mutant population receiving placebo (n=62) and cabozantinib (n=102) in the EXAM trial (as shown in Figure 21; Section B.2.8.1). Table 51 summarises the AIC and BIC values for each survival model, and the long-term extrapolations of PFS are presented in Figure 27, Figure 28 and Figure 29 for selpercatinib, cabozantinib and BSC, respectively.

Table 51: Summary of goodness-of-fit data for stratified models for progression-free survival for selpercatinib, cabozantinib and BSC in *RET*-mutant MTC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; MTC: medullary thyroid cancer.

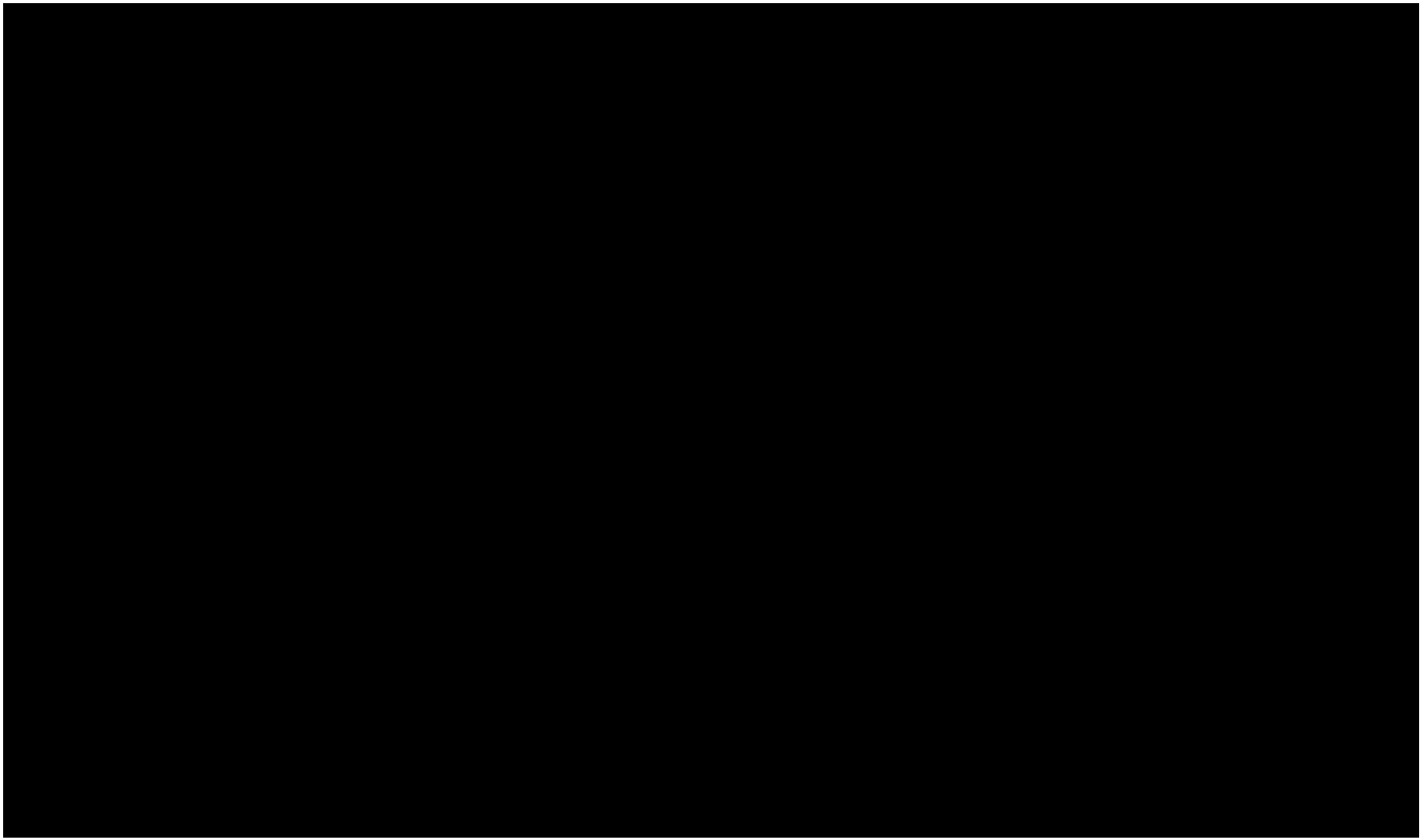
Statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit, clinical plausibility and external validation of the resulting clinical outcomes with the outcomes observed in the LIBRETTO-001 and EXAM trials.

PH tests were violated for PFS (Section B.2.8.1, Figure 21) therefore stratified, spline and accelerated failure time functions were considered across all treatment arms. All functions appeared to provide a very similar visual fit to the Kaplan–Meier data for cabozantinib and BSC, differing at the tail of extrapolations. The loglogistic was selected based on clinical feedback. The loglogistic function provided a good visual fit to the early KM-data and the longer tail accounted for a proportion of patients with extended PFS. This is aligned with the base case curve selected by the ERG in TA516. The loglogistic model was used to extrapolate PFS in the base case analysis is shown in Figure 30. Due to the lack of PFS maturity for selpercatinib a range of alternative survival functions are explored in scenario analyses.

Figure 27: Extrapolations of progression-free survival – Selpercatinib, *RET*-mutant MTC

Abbreviations: MTC: medullary thyroid cancer; PFS: progression-free survival.

Figure 28: Extrapolations of progression-free survival – Cabozantinib, *RET*-mutant MTC



Abbreviations: MTC: medullary thyroid cancer; PFS: progression-free survival.

Figure 29: Extrapolations of progression-free survival – BSC, *RET*-mutant MTC

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; *RET*: rearranged during transfection.

Figure 30: Log-logistic PFS curves for *RET*-mutant MTC

Abbreviations: BSC: best supportive care; KM: Kaplan–Meier.

Overall survival

OS data from the LIBRETTO-001 trial are particularly immature.[56] A range of parametric functions were fitted to the weighted OS curves for selpercatinib generated in the MAIC and the unweighted OS curve for the *RET* M918T0-positive subgroup receiving placebo (n=45) and cabozantinib (n=81) in the EXAM trial (as shown in Figure 22, Section B.2.8.1). Table 53 summarises the AIC and BIC values for each survival model, and the long-term extrapolations of OS are presented in Figure 31, Figure 32 and Figure 33 for selpercatinib, cabozantinib and BSC, respectively.

Whilst the OS Kaplan-Meier data for cabozantinib from the *RET* M918T-positive subgroup of the EXAM trial were explored in the survival analyses as described above, these data were ultimately not considered generalisable to the *RET*-mutant subgroup, since cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population. Clinical expert feedback confirmed that the outcomes for the placebo arm in the *RET* M918T population are more likely to be generalisable to the *RET*-mutation population overall. Therefore, due to the lack of data for *RET*-mutant patients for cabozantinib, to estimate OS for cabozantinib, survival functions were constructed by applying the OS HR versus placebo for the *RET*-mutant subgroup to the BSC (placebo) survival functions (only PH functions were explored). This is a common method for indirect comparison in oncology and was used for PFS by the Assessment Group in the appraisal of cabozantinib (TA516).[22] The HRs reported for the *RET*-mutant subgroup of the EXAM trial are presented in Table 52.

Table 52: Treatment effects for cabozantinib in *RET*-mutant MTC

Intervention	PFS	OS	Source
	HR versus placebo (95% CI)	HR versus placebo (95% CI)	
Cabozantinib versus placebo	0.23 (0.14, 0.38)[a]	0.79 (0.54, 1.17)	EXAM *RET*-mutant subgroup[24]

[a] Not used in the model because Kaplan-Meier data were available and survival functions were fitted to these data to avoid assuming PH.
Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.

Table 53: Summary of goodness-of-fit data for selpercatinib, cabozantinib and BSC overall survival in *RET*-mutant MTC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; MTC: medullary thyroid cancer.

As for PFS, statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit, clinical plausibility and external validation of the resulting clinical outcomes with the outcomes observed in the LIBRETTO-001 and EXAM trials.

Based on the *RET* M918T subgroup Kaplan-Meier data for cabozantinib and placebo from EXAM, PH were not violated. This assumption was considered to hold for the *RET* mutant population for EXAM. Therefore, unstratified PH functions were explored across treatment arms. Clinical feedback confirmed that a cluster of stratified and unstratified survival functions provided a good fit to the early KM-data for the placebo arm from EXAM with the stratified functions providing more plausible long-term survival rates for placebo and cabozantinib but potentially underestimating OS for selpercatinib. The Weibull may overestimate the survival for selpercatinib but may provide a more plausible relative difference compared to BSC and cabozantinib. On this basis and acknowledging the immature OS data for selpercatinib, the Weibull was chosen as the base case survival function as shown in Figure 34. A range of survival functions, including those which relax the PH assumptions, are explored in scenario analyses.

Figure 31: Extrapolations of overall survival – Selpercatinib, *RET*-mutant MTC

Abbreviations: MTC: medullary thyroid cancer; *RET*: rearranged during transfection.

Figure 32: Extrapolations of overall survival – Cabozantinib, *RET*-mutant MTC

Abbreviations: MTC: medullary thyroid cancer; *RET*: rearranged during transfection.

Figure 33: Extrapolations of progression-free survival – BSC, *RET*-mutant MTC

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; *RET*: rearranged during transfection.

Figure 34: Weibull OS curves for *RET*-mutant MTC

Abbreviations: BSC: best supportive care; KM: Kaplan–Meier.

RET fusion-positive TC

PFS and OS data are available for pre-treated *RET* fusion-positive TC patients in LIBRETTO-001 (n=19) and were used to inform the efficacy of selpercatinib in this population in the economic model. Given the small number of patients enrolled in this subgroup of the trial, a MAIC was not considered feasible. As such, a naïve indirect comparison was performed, with parametric curves fitted independently for selpercatinib and BSC.

The placebo arm of the SELECT study for lenvatinib was considered a suitable proxy for BSC in the UK in TA535.[21] In TA535[21] ERG noted differences between the SELECT and DECISION trials and noted PFS was worse in the SELECT trial for placebo for much of trial period. However, clinical expert opinion suggests that lenvatinib is the dominant choice in practice and the overall trial population is more comparable to the target population of interest as at least 1 prior TKI was permitted in the study. As such, the placebo arm of the SELECT ITT population was considered to represent the most suitable proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC as data were available for PFS and OS. The pre-treated subgroup from SELECT, which could be considered more representative of the target population, was not considered since data were not available for OS and were in few patients (n=27). Whilst the SELECT trial only included patients with DTC, since patients with other subtypes of TC have no suitable treatment options other than BSC, the placebo arm of the of SELECT ITT population was also considered a suitable proxy for comparator efficacy for the other subtypes of TC within the *RET* fusion-positive TC population (e.g. anaplastic or undifferentiated TC).

Published Kaplan-Meier data for 131 patients who received placebo from the SELECT ITT population (as shown in Figure 23A; Section B.2.8.2) were used in the economic model to estimate PFS for BSC for the *RET* fusion-positive TC population. OS for BSC in the model was based on RPSFT-adjusted OS data for patients receiving placebo in the ITT population, as shown in Figure 24 in Section B.2.8.2.

In TA535, results from the analysis group's (AG) analyses showed that, within the SELECT trial, the PH assumption did not hold for the majority of survival outcomes.[21] For consistency, unstratified models were not explored.

Progression-free survival

A range of stratified parametric functions were fitted to the PFS curve for the pre-treated TC population from LIBRETTO-001 (as shown in Figure 19; Section B.2.5.2) and the PFS curve for the SELECT ITT population receiving placebo (n=131) (as shown in Figure 23A; Section B.2.8.2). . Table 54 summarises the AIC and BIC values for the best-fitting survival models, and the long-term extrapolations of PFS are presented in

Figure 35 and Figure 36 for selpercatinib and BSC, respectively.

Table 54: Summary of goodness-of-fit data for selpercatinib and BSC progression-free survival in pre-treated *RET* fusion-positive TC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

As for MTC, statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit, clinical plausibility and external validation of the resulting clinical outcomes with the outcomes observed in the LIBRETTO-001 and SELECT trials.

Based on feedback from clinical experts, the Stratified Weibull model was used to extrapolate PFS in the base case analysis, as shown in Figure 37. The stratified Weibull provided the best visual fit to the KM-data and most reasonable extrapolations while the stratified lognormal, loglogistic and Gompertz all overestimated PFS, particularly for the BSC arm. A range of alternative stratified and spline-knot functions are explored in scenario analyses.

Figure 35: Extrapolations of progression-free survival – Selpercatinib, pre-treated *RET* fusion-positive TC

Abbreviations: TC: thyroid cancer; *RET*: rearranged during transfection.

Figure 36: Extrapolations of progression-free survival – BSC, pre-treated *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; TC: thyroid cancer; *RET*: rearranged during transfection.

Figure 37: Stratified Weibull PFS curves for *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; KM: Kaplan–Meier.

Overall survival

OS data from the LIBRETTO-001 trial are particularly immature.[56] A range of parametric functions were fitted to OS data available for pre-treated *RET* fusion-positive TC patients in LIBRETTO-001 and the RPSFT-adjusted OS curve for placebo from SELECT (as shown in Figure 24; Section B.2.8.2). Table 53 summarises the AIC and BIC values for each survival models, and the long-term extrapolations of OS are presented in Figure 38 and Figure 39 for selpercatinib and BSC, respectively.

Table 55: Summary of goodness-of-fit data for selpercatinib and BSC overall survival in pre-treated *RET* fusion-positive TC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

As for PFS, statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit, clinical plausibility and external validation of the resulting clinical outcomes with the outcomes observed in the LIBRETTO-001 and SELECT trials.

Visual assessment of stratified functions across treatment arms produced implausible extrapolations for the selpercatinib arm compared to BSC, often crossing or converging early along the time horizon. In TA535, the ERG argued that long-term OS for BSC was consistent with an exponential function, and fitted exponential functions starting at 6 months to predict the long-term risk of death. Therefore, a similar approach has been explored for the OS function, with piecewise exponential functions fitted to data for 0 to 6 months and for 6 months onwards. Based on feedback from clinical experts and for consistency with TA535, the piecewise exponential model was used to extrapolate OS in the base case analysis, as shown in Figure 40. Stratified functions are explored in scenario analyses.

Figure 38: Extrapolations of overall survival – Selpercatinib, pre-treated *RET* fusion-positive TC

Abbreviations: TC: thyroid cancer; *RET*: rearranged during transfection.

Figure 39: Extrapolations of overall survival – BSC, pre-treated *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; TC: thyroid cancer; *RET*: rearranged during transfection.

Figure 40: Piecewise exponential OS curves for RET fusion-positive TC

Abbreviations: BSC: best supportive care; KM: Kaplan–Meier.

B.3.3.3 Time to treatment discontinuation

As described in Section B.2.3.1, patients with documented PD in the LIBRETTO-001 trial could continue selpercatinib beyond progression if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the Sponsor. However, the base case assumes that TTD is equivalent to PFS as stated in the draft SmPC and due to the lack of comparative data to apply to the cabozantinib arm in the model. However, in line with the methodology described in B.3.3.2 and in accordance with the NICE DSU TSD14, a range of standard parametric distributions were explored for extrapolation of time to treatment discontinuation (TTD) data from the LIBRETTO-001 trial in order to estimate duration of treatment for selpercatinib and are presented in Appendix J.[80] The TTD analysis did not produce plausible time-on-treatment estimates compared to selected base case PFS survival functions.

B.3.3.4 Adverse events

Grade ≥3 adverse events with at least 2% difference in frequency between interventions were included in the model (see Table 56 and Table 57 for *RET*-mutant MTC and *RET* fusion-positive TC populations, respectively). Probabilities of individual adverse events for selpercatinib were based on the MTC safety analysis set of the LIBRETTO-001 trial (n=[redacted]). Probabilities of individual adverse events for cabozantinib and BSC in *RET*-mutant MTC were taken from the EXAM trial[62] and from SELECT[68] for BSC in *RET* fusion-positive TC.

The costs associated with the management of AEs are presented in Section B.3.5.3. The disutilities associated with AEs are presented in Section B.3.4.4.

Table 56: Incidence of Grade 3 or 4 adverse events included in the model for the *RET*-mutant MTC population

Adverse event	Selpercatinib	Cabozantinib	BSC
Diarrhoea	[redacted]	21.50%	1.83%
Hand foot syndrome	[redacted]	12.62%	0.00%
Hypertension	[redacted]	8.88%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%
Decreased weight	[redacted]	9.81%	0.00%
Abdominal pain	[redacted]	3.27%	0.92%
Haemorrhage	[redacted]	3.27%	0.92%
Dysphagia	[redacted]	4.21%	0.92%
Fatigue	[redacted]	9.81%	2.75%
Decreased appetite	[redacted]	7.01%	0.92%
Rash	[redacted]	0.93%	0.00%
Asthenia	[redacted]	6.54%	1.83%
Mucosal inflammation	[redacted]	3.27%	0.00%
Vomiting	[redacted]	2.34%	0.92%
Dyspnoea	[redacted]	2.34%	0.00%
Headache	[redacted]	0.47%	10.09%
Back pain	[redacted]	4.21%	0.92%

Syncope	[redacted]	0.00%	0.00%
Alanine aminotransferase increased	[redacted]	5.14%	1.83%
Aspartate aminotransferase increased	[redacted]	1.87%	0.00%
Hyponatraemia	[redacted]	0.93%	0.00%
Lymphopenia	[redacted]	7.48%	10.09%
Pneumonia	[redacted]	0.00%	0.00%
Hypocalcaemia	[redacted]	10.75%	0.00%
Dehydration	[redacted]	0.00%	0.00%
Weight increased	[redacted]	0.00%	0.00%

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer.

Table 57: Incidence of Grade 3 or 4 adverse events included in the model for the *RET*-mutant MTC population

Adverse event	Selpercatinib	BSC
Diarrhoea	[redacted]	0.00%
Hand foot syndrome	[redacted]	0.00%
Hypertension	[redacted]	3.82%
ECG QT prolonged	[redacted]	0.00%
Decreased weight	[redacted]	0.76%
Fatigue	[redacted]	1.53%
Decreased appetite	[redacted]	0.76%
Rash	[redacted]	0.00%
Asthenia	[redacted]	2.29%
Dyspnoea	[redacted]	3.05%
Headache	[redacted]	0.76%
Back pain	[redacted]	0.00%
Alanine aminotransferase increased	[redacted]	0.00%
Aspartate aminotransferase increased	[redacted]	0.00%
Hyponatraemia	[redacted]	0.00%
Lymphopenia	[redacted]	0.00%
Pneumonia	[redacted]	0.00%
Hypocalcaemia	[redacted]	0.00%
Dehydration	[redacted]	0.00%
Nausea	[redacted]	0.76%
Stomatitis	[redacted]	0.00%
Proteinuria	[redacted]	0.00%

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

EORTC QLQ-C30 (patients 18 years and older) was collected in the LIBRETTO-001 study for patients with *RET*-mutant MTC, presented in Section B.2.5.1. The questionnaires were to be answered by the subject to the best of his/her ability, prior to receiving drug on the first day of treatment, at the start of each 4-weekly treatment cycle (within 7 days of each subsequent radiologic assessment, preferably prior to learning the results of the radiologic disease assessment), and at the end of treatment visit. Therefore, few data were collected for patients in the progressed health state.

No EQ-5D data were collected from patients in the LIBRETTO-001 trial.

B.3.4.2 Mapping

No mapping was conducted in this analysis, as there was no literature available to map the EORTC QLQ-C30 in MTC to utility values.

B.3.4.3 Health-related quality-of-life studies

As direct elicitation of utilities and mapping of disease-specific measures of health status collected in LIBRETTO-001 was not possible, an SLR was conducted to identify any relevant HRQoL and utility data. Searches were performed on the 12th of August 2019 and details of the SLR search strategy and study selection can be found in Appendix H. No estimates specific to patients with *RET*-mutant MTC or *RET* fusion-positive TC were identified. In the base case utility values are assumed to be the same as those used in TA535 and TA516, sourced from a vignette study conducted by Fordham et al (2015).

B.3.4.4 Adverse reactions

Disutility values are applied to those experiencing adverse events to estimate the reduction in quality of life due to the event given the duration of impact of the event. All adverse reactions are assumed to occur in the first cycle of the model. In line with the model develop by the assessment group in TA516, the same utility decrement (−0.11) was applied for all AEs based on Beusterien *et al.* (2009), and AEs were assumed to have a duration of one month (30.44 days).[82]

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As described in Section B.3.4.1 and B.3.4.2, EORTC QLQ-C30 data were collected in the LIBRETTO-001 study for patients with *RET*-mutant MTC, but these data could not be used to generate utility values given the lack of available mapping algorithms. Given no utility estimates specific to patients with *RET*-mutant MTC or *RET* fusion-positive TC were identified in the SLR, health-state utility estimates identified in the TLR for past NICE TAs for patients with TC and MTC were considered for use in the model.

Health-state utility estimates reported by Fordham et al. (2015),[76] which were accepted by the NICE Appraisal Committee in NICE TA516,[22] and NICE TA535,[21] were used in base case

analysis of the model and are presented in Table 58. As there are no data available in the literature for the estimation of utility values for MTC patients, whether untreated or pre-treated, and pre-treated TC patients, the default utility values are assumed to be the same for the MTC and TC populations. Clinical expert opinion verified that the estimates are reasonable for patients with *RET*-altered tumours, and that HRQoL in this population may be expected to be similar to that of the wider patient population with the same tumour type.[26] These estimates relate to differentiated thyroid cancer and were estimated by valuation of health-state descriptions (vignettes).

Table 58: Health-state utility estimates in DTC by Fordham et al. (2015)[76]

Parameter	Mean (SD)	Adjusted Mean Increment (95% CI)[a]
Progression-free	0.80 (0.19)	0.87 (0.84–0.91)
Progressed	0.50 (0.28)	−0.35 (−0.41 to −0.29)
Dead	0	NA

[a] Incremental impact of health states on utilities compared with a base state of stable/no response with no adverse events, adjusted for educational qualification level and EQ-5D-3L (usual activities and anxiety/depression) ratings using UK norms. Fordham et al. (2015)[76] also reported a reduced parameter model which is not reported here.
Abbreviations: BSC: best supportive care; CI: confidence interval; DTC: differentiated thyroid cancer; NA: not applicable; SD: standard deviation.
Note: Utility estimates also were reported for response and selected adverse events.

Alternative estimates used in previous thyroid cancer drug submissions to the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) in the UK were explored in sensitivity analysis. An overview of utility values used in these submissions are presented in Table 59.

Table 59: Health Utility Values Applied in Other UK Thyroid Cancer Submissions

Body	Drug	Indication	Health Utility Values	Scenario analysis
SMC	Lenvatinib	Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/ Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	Derived from Fordham *et al.* (2015)[76] • Stable disease: 0.80 • Response: 0.86 • Progressive disease: 0.50 • Utility decrements of −0.042 for lenvatinib and −0.117 for sorafenib applied for AEs (diarrhoea, fatigue, hand and foot syndrome, alopecia)	No – utility values are not applicable since the model is structured by response
SMC	Sorafenib	Patients progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	Utilities derived from EQ-5D data from DECISION study: • Sorafenib, progression-free: 0.72 • Best supportive care, progression-free: 0.80	Yes

			• Post-progression (both groups): 0.64	
SMC	Cabozantinib	Adult patients with progressive, unresectable locally advanced or metastatic MTC	Published trial data in thyroid cancer (not specified) in which SF-36 outcomes had been converted to utilities by mapping to EQ-5D and converting to SF-6D values for the non-progressed and progressed states. • Progression-free: 0.796 • Post-progression: 0.624	Yes
AWMSG	Vandetanib	Patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC	FACT-G scores collected in the ZETA study mapped to time trade-off values. • Pre- and post-progression utility values not reported. • Disutilities for AEs based on Beusterien *et al.* (2009)[82] (values of −0.11 and −0.13 assumed)	No – utility values are not reported
AWMSG	Cabozantinib	Adult patients with progressive, unresectable, locally advanced or metastatic MTC	For the base case analysis, utility values were taken from 2 published studies in thyroid cancer, albeit in patients with less severe disease than the progressive MTC population (sources and values not specified) Utility decrements for AEs were derived from the published literature (also not specified)	No – utility values are not reported

Abbreviations: AE: adverse event; AWMSG: All Wales Medicines Strategy Group; FACT-G: Functional Assessment of Cancer Therapy–General; MTC: medullary thyroid cancer; SF-36: SF-36 Health Survey; SF-6D: SF-6D Health Survey; SMC: Scottish Medicines Consortium.

Age-adjustment

With increasing age, health utility is expected to decline. Given the base case time horizon of the model, which spans a patient's lifetime, the model base case includes an annual adjustment factor for age via a multiplicative approach derived from Ara and Brazier *et al.* (2010).[83]

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify any relevant cost and healthcare resource use data associated with the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy, and adults with advanced *RET* fusion-positive thyroid

cancer who require systemic therapy and who have progressed following prior systemic treatment. Searches were performed on the 12th of August 2019 and details of the SLR search strategy and study selection can be found in Appendix I. Costs were also supplemented by clinical opinion. Unit costs were taken from recognised sources for the UK. Relevant resource use and costs were extracted from TA516 for the RET-mutant MTC populations and from TA535 for the pre-treated RET-fusion TC population, identified from the TLR for past NICE TAs for patients with TC and MTC, and supplemented by clinical opinion.

Costs included in the model

The analysis was conducted from the NHS and PSS perspective. Appropriate sources of unit costs, such as NHS National Cost Collection 2018/19 and British National Formulary (BNF) online, were used for cost inputs in the model.

Specifically, the following cost components were considered in the model:

- Dug acquisition costs for interventions and comparators
- Associated drug administration costs
- Monitoring costs for intervention and comparators
- Cost of BSC
- Costs associated with the management of AEs
- Cost of end-of-life palliative care.

No subsequent treatment costs are included since BSC is the only follow-on treatment available across all patients populations.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition

Table 60 present the drug acquisition costs for selpercatinib and cabozantinib based on their current list prices and licensed doses. Table 61 presents the drug acquisition costs for selpercatinib and cabozantinib for patients who experience dose reductions.

In the first treatment cycle (model cycles 0–3), no dose reductions are applied, and thus treatment cycle costs as shown in Table 60 are applied. In subsequent treatment cycles, to account for selpercatinib dose reductions, a proportion of patients were assumed to receive a dose level of 120 mg orally, twice daily, such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted]%). Since the pack cost for selpercatinib 80 mg and 40 mg formulations is the same, dose reductions do not impact treatment cycle costs. In the absence of dose intensity data for cabozantinib, the dose intensity observed in the LIBRETTO-001 trial was also applied to cabozantinib, where a proportion of patients were assumed to receive a dose level of 120 mg orally, once daily. The proportion of patients experiencing dose reductions and the resulting weighted treatment cycle costs in treatment cycles 2 and onwards are shown in Table 62. The final dose reduction levels are yet undetermined for selpercatinib. Some patients in the LIBRETTO-001 trial, and in practice as determined by the final SmPC, may have had doses reduced beyond 120 mg, which would impact treatment cycle costs, and thus costs may be overestimated for selpercatinib in the model.

As described in Section B.3.3.3, the duration of treatment for selpercatinib and cabozantinib was assumed to be equivalent to PFS; time spent on treatment was assumed until disease progression at which point patients would discontinue treatment. Time on BSC is continuous throughout the PF and PD health states until death.

No drug wastage is assumed in the base case. For oral drugs, a drug wastage scenario is explored and assumes 4-week prescriptions.

Table 60: Drug acquisition costs for selpercatinib and cabozantinib (patients without dose reductions)

Regimen	Regimen description	Capsule strength (mg)	Capsules per pack	Pack cost (£)	Capsule cost (£)	Capsules per dose	Doses per week	Capsules per treatment cycle[a]	Costs per treatment cycle[a]
Selpercatinib	160 mg, orally, twice daily	80	60	£[redacted]	£[redacted]	2	14	112	£[redacted]
Cabozantinib	140 mg, orally, once daily	80	112	£4,800.00	£42.86	1	7	28	£4,800.00
		20	112	£4,800.00	£42.86	3		84	

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.

Table 61: Drug acquisition costs for selpercatinib and cabozantinib (patients with dose reductions)

Regimen	Regimen description (reduced dose)	Capsule strength (mg)	Capsules per pack	Pack cost (£)	Capsule cost (£)	Capsules per dose	Doses per week	Capsules per treatment cycle[a]	Costs per treatment cycle[a]
Selpercatinib	120 mg, orally, twice daily	80	60	£[redacted]	£[redacted]	1	14	56	£[redacted]
		40	60	£[redacted]	£[redacted]	1		56	
Cabozantinib	120 mg, orally, once daily	80	112	£4,800.00	£42.86	1	7	28	£3,600.00
		20	112	£4,800.00	£42.86	2		56	

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.

Table 62: Weighted drug acquisition costs for selpercatinib and cabozantinib in treatment cycles 2+ (including dose reductions)

Regimen	Dose	Costs per treatment cycle	Proportion of patients	Total cost per treatment cycle
Selpercatinib	160 mg	£[redacted]	[redacted]	[redacted]
	120 mg	£[redacted]	[redacted]	
Cabozantinib	140 mg	£4,800.00	[redacted]	[redacted]
	120 mg	£3,600.00	[redacted]	

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.

Drug administration and monitoring

Administration costs were based on National Health Service (NHS) National Cost Collection (2018/19).[77] For selpercatinib and cabozantinib, 12 minutes of pharmacy time (£9.20) was assumed every 30 days. During treatment, patients were assumed to have one oncologist visit every 3 weeks.

Best supportive care

BSC will be assumed to be monitoring, resource use and costs, and palliative care, consistent with the Assessment Group model in TA516 (as shown in Table 63). Clinical advice received by the Assessment Group suggested that the resource use associated with BSC is likely to be the same for both the progression-free and progressed health states as these patients have, by definition, progressed disease. BSC is assumed to be consistent across *RET*-mutant MTC and pre-treated *RET* fusion-positive TC populations.

Table 63: Annual BSC resource use in *RET*-mutation MTC and *RET*-fusion positive TC

Resource	Unit cost	Items per year
Consultant-led outpatient visits	£133.05	6 (2–12)
CT scan	£124.42	2 (0–4)
MRI scan	£145.75	1 (0–2)
Community palliative care support	£184.77	12 (0–20)
Palliative radiotherapy	£116.34	2 (fixed)
Bisphosphonates (for bone metastases)	£150.00	0.6 (fixed)[a]
Palliative surgery	£3,935.01	0.03 (fixed)

One clinical expert provided resource use estimates (central estimates, minimums and maximums); these were then verified and augmented with additional components by a second clinical expert. As the elicited information relates to ranges and some of the distributions are highly skewed, uncertainty surrounding these parameters was represented using triangular distributions. The experts' central estimates were taken to be the mode of the distribution; means were calculated as (lower limit+mode+upper limit)/3. The number of ECGs, CT scans, and blood tests were not associated with uncertain ranges and were thus held as fixed values within the probabilistic analysis.
[a] Assumed to reflect monthly IV regimen for 5% of patients, also costed to include outpatient visit.
Abbreviations: CT: computerised tomography; ECG: electrocardiogram; MTC: medullary thyroid cancer.
Source: NHS National Cost Collection 2018/19,[77] NICE TA516[22]

B.3.5.2 Health-state unit costs and resource use

The types of resource and frequency of use in the progression free (PF) and progressed disease (PD) health states in the MTC and TC analyses were based on the TA516 Assessment Group model, which in turn were based on clinical expert opinion (as shown in Table 64). Resource use for MTC and TC populations is assumed to be the same as default.

Table 64: Unit costs and resource use per year in *RET*-mutation MTC and *RET*-fusion positive TC

Resource	Unit cost	PF	PD
Consultant-led outpatient visits (range)	£133.05	12 (4–16)	6 (4–12)
Nurse-led outpatient visits (range)	£100.04	4 (0–6)	6 (0–6)

Blood tests	£3.71	12	6
CT scan	£124.43	4	4

Abbreviations: CT: computerised tomography; ECG: electrocardiogram; MTC: medullary thyroid cancer; PF: progression-free; PD: progressed disease.
Source: NICE TA516[22]

The costs associated with palliative care and palliative chemotherapy is applied at the point of death to all patients (Table 65). These costs are based on the data used in the Assessment Group and Sanofi model in TA516[22] which were, in turn, derived from the NHS National Cost Collection and the Personal Social Services Research Unit.

Table 65: Cost of end-of-life palliative care in TC

Resource	Cost	Assumptions
Palliative care	£5,775.52	Assumes equal weighting between child and adult inpatient and outpatient
Palliative chemotherapy	£827	NHS National Cost Collection, other, procure chemotherapy drugs for regimens in band 1-10, SB01Z-SB10Z

Source: NHS National Cost Collection 2018/19,[77] NICE TA516[22]

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs for adverse events were taken from NHS National Cost Collection (where available) or other sources and are consistent with the most recent relevant NICE appraisal where possible (TA516[22] for MTC, and TA535[21] for TC).

Table 66: Adverse event unit costs

Adverse event	Mean Cost	Source
Diarrhoea	£1,218.01	NHS National Cost Collection 2018/19; TA516 (FD10M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, with CC Score 9+; Elective inpatient)
Hand foot syndrome	£1,027.93	NHS National Cost Collection 2018/19; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Elective Inpatient)
Hypertension	£1,134.52	NHS National Cost Collection 2018/19; TA516 (EB04Z Hypertension; Elective Inpatient)
ECG QT prolonged	£1,027.53	NHS National Cost Collection 2018/19; TA516 (EB07E Arrhythmia or Conduction Disorders, with CC Score 0–3; Elective Inpatient)
Decreased weight	£1,613.91	NHS National Cost Collection 2018/19; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient)
Abdominal pain	£740.83	NHS National Cost Collection 2018/19; TA516 (FD05B Abdominal Pain without Interventions; Elective Inpatient)
Haemorrhage	£500.00	Assumption
Dysphagia	£915.75	NHS National Cost Collection 2018/19; TA516 (CB02F Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0; Elective Inpatient)

Fatigue	£0.00	Assumption
Decreased appetite	£1,613.91	NHS National Cost Collection 2018/19; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient)
Rash	£1,027.93	NHS National Cost Collection 2018/19; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Elective Inpatient)
Asthenia	£0.00	Assumption
Mucosal inflammation	£1,223.18	NHS National Cost Collection 2018/19; TA516 (FD01J Gastrointestinal Infections without Interventions, with CC Score 0-1; Elective Inpatient)
Vomiting	£1,613.91	NHS National Cost Collection 2018/19; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient)
Dyspnoea	£1,063.91	NHS National Cost Collection 2018/19; TA516 (DZ19N Other Respiratory Disorders without Interventions, with CC Score 0-4; Elective Inpatient)
Headache	£0.00	Assumption
Back pain	£1,393.30	NHS National Cost Collection 2018/19; TA516 (HC32K Low Back Pain without Interventions, with CC Score 0-2; Elective Inpatient)
Syncope	£864.83	NHS National Cost Collection 2018/19; TA516 (Syncope or Collapse, with CC Score 0-3; Elective Inpatient)
Alanine aminotransferase increased	£0.00	Assumption
Aspartate aminotransferase increased	£0.00	Assumption
Hyponatraemia	£785.84	NHS National Cost Collection 2018/19; Assumption (SA09L Other Red Blood Cell Disorders with CC Score 0-1; Elective Inpatient)
Lymphopenia	£2,621.33	NHS National Cost Collection 2018/19; Assumption (SA17H Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2; Elective Inpatient)
Pneumonia	£1,488.23	NHS National Cost Collection 2018/19; TA516 (DZ11V Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3; Elective Inpatient)
Hypocalcaemia	£785.84	NHS National Cost Collection 2018/19; Assumption (SA09L Other Red Blood Cell Disorders with CC Score 0-1; Elective Inpatient)
Dehydration	£500.00	Assumption
Weight increased	£500.00	Assumption

Abbreviations: ECG: electrocardiogram; NHS: National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

The cost of *RET* testing was not included in the model, since *RET* next generation sequencing (NGS) and fluorescent in situ hybridisation (FISH) testing are included in the 2019/2020 National

Genomic Test Directory for Cancer. The transition to NGS testing, completed at Genomic Hubs, will facilitate routine *RET* testing alongside other oncogenic drivers, and thus it is not anticipated that approval of selpercatinib would result in any additional costs to the healthcare system.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 67.

Table 67: Summary of variables applied in the economic model

Variable	*RET*-mutant MTC	Pre-treated *RET* fusion-positive TC	Reference to section in submission
Model settings			
Discount rate (costs)	3.50%		Section B.3.2.2
Discount rate (benefits)	3.50%		
Time horizon (years)	Lifetime (25 years)		
Patient characteristics			
Starting age, years (SD)	[redacted]	[redacted]	Section B.3.3.1
Percent female	[redacted]	52.6%	
Clinical inputs			
PFS (selpercatinib)	Log-logistic	Stratified Weibull	Section B.3.3.2
PFS (comparators)			
OS (selpercatinib)	Weibull	Piecewise exponential	
OS (comparators)			
TTD (selpercatinib and cabozantinib)	Assumed until disease progression, PFS	Assumed until disease progression, PFS	Section B.3.3.3
Adverse events, incidence	*Various*	*Various*	Section B.3.3.4
Utility inputs			
Utility for PF	0.80		Section B.3.4.5
Utility for PD	0.50		
AE disutilities	-0.11 to all AEs		
Cost inputs			
Selpercatinib acquisition cost (60 caps)	First cycle: £[redacted] Subsequent cycles: £[redacted]		Section B.3.5.1
Administration cost per treatment cycle (selpercatinib)	£9.20		
Drug acquisition cost per treatment cycle (cabozantinib)	First cycle: £4,800.00 Subsequent cycles: £[redacted]		
Administration cost per treatment cycle (cabozantinib)	£9.20		
Mean RDI (selpercatinib and cabozantinib)	[redacted]		

Drug wastage	No – whole tablets assumed		
Drug acquisition cost of BSC	N/A		
PF average weekly cost	£93.88		Section B.3.5.2
PD average weekly cost	£59.38		
One-time end-of-life cost	£6,545.00		
Adverse events, unit costs	*Various*	*Various*	Section B.3.5.3

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; N/A: not applicable; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression free survival; RDI: relative dose intensity; RET: rearranged during transfection; SD: standard deviation: TC: thyroid cancer; TTD: time to discontinuation.

B.3.6.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 68, alongside a description of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results. The results of these scenario analyses are presented in Section B.3.8.3.

Table 68: Modelling assumptions

Parameter	Assumption	Justification	Addressed in scenario analysis
Extrapolations of OS and PFS for BSC in *RET*-fusion positive TC	In the absence of data for *RET*-fusion positive TC, the ITT population of SELECT trial was used to inform OS and PFS for placebo. It was thereby assumed that *RET* alteration is not prognostic.	No data were identified for patients receiving BSC with *RET* fusion-positive TC, and there is conflicting evidence whether specific mutations are prognostic. A clinical expert also confirmed that the prognostic significance of *RET*-fusion in TC is unknown.[26]	No alternative data sources were identified, but a range of standard parametric distributions were explored for extrapolation in scenario analyses (see Section B.3.8.3)
	SELECT included only DTC patients. As such, it was assumed that data for these patients could be considered generalisable to other TC subtypes types.	No data for patients with other TC subtypes were identified. However, given prognosis is generally worse for the other TC subtypes,[20] data from the placebo arm of the SELECT likely represents an overestimate of the efficacy of BSC in these patients.	No alternative data sources were identified, but a range of standard parametric distributions were explored for extrapolation in scenario analyses (see Section B.3.8.3).
OS Kaplan-Meier data used for cabozantinib and BSC extrapolation in *RET* mutant MTC	OS HR for cabozantinib was applied to the OS survivor functions to the *RET* M918T subgroup for placebo (BSC)	No OS Kaplan-Meier data were available for the *RET* mutant subgroup from EXAM. OS for cabozantinib in the *RET* M918T population is not generalisable to the *RET* mutant population overall because cabozantinib is more effective in the *RET* M918T population than in	No alternative data sources were identified, but a range of standard parametric distributions were explored for extrapolation in scenario analyses (see Section B.3.8.3)

		the overall *RET* mutant population. Outcomes for the placebo arm in the RET M918T population are more likely to be generalisable to the *RET* mutant population overall as confirmed by the clinical expert	
Time to treatment discontinuation	Analyses assume no continuation of the treatment after disease progression (treatment discontinuation is dictated by the PFS curve).	This assumption is in line with the draft SmPC, and was utilised due to the lack of comparative data to apply to the cabozantinib arm in the model.	A range of standard parametric distributions were explored for extrapolation of TTD data from LIBRETTO-001 and are presented in Appendix J. Scenario analyses have not been conducted where these data were used to inform TTD in the model due to implausible estimations for time on treatment compared to the selected base case survival functions
Utility values	The default utility values are assumed to be the same for the MTC and TC populations.	No data were identified in the literature for the estimation of utility values for MTC patients or for pre-treated TC patients. As such, health-state utility estimates reported by Fordham et al. (2015),[76] which were accepted by the NICE Appraisal Committee in NICE TA516,[22] and NICE TA535,[21] were used in base case analysis of the model	Utility values reported for the PD and PF states from the SMC submission for sorafenib and cabozantinib were explored in scenario analyses (see Section B.3.8.3)
	It was assumed that utility weights for patients with *RET*-altered tumours are equivalent to patients with *RET* wild-type tumours.	No data were identified in the literature for the estimation of utility values in *RET*-altered tumours. Clinical expert opinion verified that HRQoL in patients with *RET*-altered tumours may be expected to be similar to that of the wider patient population with the same tumour type	
Intervention costs and drug wastage	In the 4th treatment cycles and beyond, to account for selpercatinib dose reductions, a proportion of patients were assumed to	The pack cost for selpercatinib 80 mg and 40 mg formulations is the same, therefore dose reductions do not impact treatment cycle costs. In the absence of dose	Whilst no scenarios have been explored relating to dose intensity specifically, a scenario exploring inclusion of drug wastage has been

	receive a dose level of 120 mg orally, such that the mean dose intensity matched that observed in the LIBRETTO-001 trial. This dose intensity was also applied to cabozantinib.	intensity data for cabozantinib, the dose intensity observed in the LIBRETTO-001 trial was also applied to cabozantinib.	conducted (see Section B.3.8.3).

Abbreviations: HRQoL: health-related quality-of-life; MKI: multikinase inhibitor; MTC: medullary thyroid cancer; NICE DSU TSD14: National Institute of Health and Care Excellence, the Decision Support Unit Technical Support Document 14; PFS: progression free survival; RET: rearranged during transfection; SmPC: summary of product characteristics; TC: thyroid cancer; TTD: time to treatment discontinuation.

B.3.7 *Base-case results*

B.3.7.1 Base-case cost-effectiveness analysis results

A summary of the base case analysis for *RET*-mutant MTC and *RET* fusion-positive TC is presented below. The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

As discussed in B.2.12.1, selpercatinib meets the NICE end of life criteria for adult patients with *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment and for adults and people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy who have previously received or who are ineligible for cabozantinib, based on the median survival of less than 2 years for BSC and the considerable improvement in survival conferred by selpercatinib. Therefore, the higher WTP threshold of £50,000 per QALY gained applies to these populations.

RET-mutant MTC

As discussed in Section B.1.3.2, for patients with *RET*-mutant MTC the only treatment that is currently recommended in the UK is cabozantinib.[22] However, due to its poor adverse event profile, a subset of patients are ineligible for first-line cabozantinib, with BSC representing their only treatment option. For patients who receive cabozantinib but who do not respond or who are unable to tolerate it, there are no further safe and effective treatment options available, and patients are treated palliatively with BSC. Patient populations receiving cabozantinib and BSC are therefore considered to be mutually-exclusive.

As such, pairwise comparisons for selpercatinib versus cabozantinib and BSC have been conducted for the base case. A summary of base-case pairwise comparisons for selpercatinib versus cabozantinib and BSC in *RET*-mutant MTC are presented in Table 69. For reference, results of a fully incremental analysis are presented in Table 70.

The base-case pairwise cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with £[redacted] for patients treated with cabozantinib (an incremental cost of [redacted]), and [redacted] for patients treated with BSC (an incremental cost of [redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with cabozantinib (an incremental QALY gain of [redacted]) and [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] and [redacted] per QALY gained versus cabozantinib and BSC, respectively.

[redacted]. It should also be noted that cabozantinib has an agreed commercial arrangement with the discount not visible to the Company, therefore cost effectiveness analyses are based upon list prices for all active interventions.

RET fusion-positive TC

The summary of base-case cost-effectiveness results for the *RET* fusion-positive TC population can be found in Table 71.

The base case incremental cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental cost of [redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

[redacted].

Table 69: Pairwise base-case results for selpercatinib versus cabozantinib in *RET*-mutant MTC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 70: Fully incremental base-case results for *RET*-mutant MTC

	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	[redacted]	[redacted]	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PFS: progression free survival; QALYs: quality-adjusted life years.

Table 71: Base-case results for pre-treated *RET* fusion-positive TC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed in order to assess the uncertainty associated with model input parameters. The input parameters and distributions associated with each parameter are presented in Appendix J.

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability, the standard error for each parameter was assumed to be 10% of the mean value.

RET-mutant MTC

Pairwise PSAs were conducted separately versus cabozantinib and versus BSC, as the patient populations eligible for each comparator are mutually exclusive, as noted above.

Versus cabozantinib

The probabilistic base case pairwise results versus cabozantinib are presented in Table 72. Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves versus cabozantinib are presented in Figure 41 and Figure 42. [redacted], selpercatinib was associated with [redacted] probability of being cost-effective versus cabozantinib, at a willingness to pay (WTP) threshold of £30,000/QALY gained over the range of values tested in the model.

Table 72: Probabilistic base case pairwise results versus cabozantinib – *RET*-mutant MTC

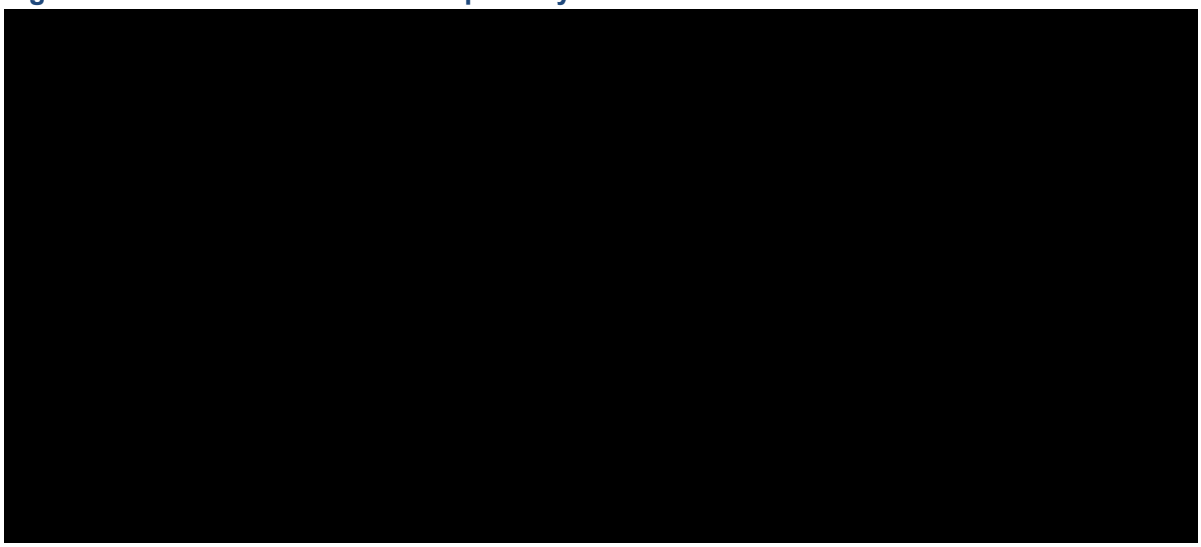
	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Figure 41: Cost-effectiveness plane scatterplot versus cabozantinib – *RET*-mutant MTC

Generated using 1,000 iterations of the PSA.

Figure 42: Cost-effectiveness acceptability curve versus cabozantinib – *RET*-mutant MTC



Generated using 1,000 iterations of the PSA.

Versus BSC

The probabilistic base case pairwise results versus BSC are presented in Table 73. Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves versus BSC are presented in Figure 43 and Figure 44, respectively. [redacted], selpercatinib was associated with [redacted] probability of being cost-effective versus BSC at a willingness to pay (WTP) threshold of £50,000/QALY.

Table 73: Probabilistic base case pairwise results versus BSC – *RET*-mutant MTC

	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	-	-	-

BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Figure 43: Cost-effectiveness plane scatterplot versus BSC – *RET*-mutant MTC

Generated using 1,000 iterations of the PSA.

Figure 44: Cost-effectiveness acceptability curve versus BSC – *RET*-mutant MTC

Generated using 1,000 iterations of the PSA.

RET fusion-positive TC

The probabilistic base case results are presented in and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are presented in Figure 45 and Figure 46, respectively. [redacted], selpercatinib was associated with [redacted]

probability of being cost-effective versus BSC at a willingness to pay (WTP) threshold of £30,000/QALY and £50,000/QALY threshold.

Table 74: Probabilistic base case results – *RET* fusion-positive TC

	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER vs BSC (£/QALY)
Selpercatinib	[redacted]	[redacted]	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Figure 45: Cost-effectiveness plane scatterplot versus BSC – *RET* fusion-positive TC

[redacted]

Generated using 1,000 iterations of the PSA.

Figure 46: Cost-effectiveness acceptability curve versus BSC – *RET* fusion-positive TC

Generated using 1,000 iterations of the PSA.

B.3.8.2 Deterministic sensitivity analysis

The input parameters and distributions associated with each input parameter in the DSA are presented in Appendix J.

RET-mutant MTC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus cabozantinib and selpercatinib versus BSC are presented as tornado plots in Figure 47 and Figure 48, respectively. For the comparison of selpercatinib versus cabozantinib, the OS treatment-effects for cabozantinib had the largest impact on the ICER, with the 'progressed' health state utility and the selpercatinib progression-free health state utility proving influential. For the comparison of selpercatinib versus BSC, the 'progressed' health state utility had the largest impact on the ICER with the selpercatinib progression-free health state utility, the health state cost of continuing care after progression, the progression-free health state cost and the BSC progression-free health state utility also proving influential.

Figure 47: Tornado plot (ICER) of selpercatinib versus cabozantinib – *RET*-mutant MTC

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 48: Tornado plot (ICER) of selpercatinib versus BSC – RET-mutant MTC

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; TCS: topical corticosteroids.

RET fusion-positive TC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus BSC are presented as a tornado plot in Figure 49. For the comparison of selpercatinib versus BSC, the selpercatinib progression-free health state utility had the largest impact on the ICER, with the 'progressed' health state utility, BSC progression-free health state utility and progression-free health state cost also proving influential.

Figure 49: Tornado plot (ICER) of selpercatinib versus BSC – RET fusion-positive TC

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio.

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. Recognising the complexity and inherent uncertainty in the survival analyses and the limitations of the data sources, a wide variety of extrapolation sets were explored for each indication. The pairwise results of the scenario analyses for *RET*-mutant MTC are presented in Table 75, and for *RET* fusion-positive TC in Table 76.

Table 75: Scenario analyses (pairwise) for the *RET*-mutant MTC population

Scenario	ICER vs cabozantinib (£/QALY)	% ICER change	ICER vs BSC (£/QALY)	% ICER change
Base case	[redacted]	-	[redacted]	-
Discount rate 1.5% (benefits)	[redacted]	-15.8%	[redacted]	-14.6%
Discount rate 6%	[redacted]	12.7%	[redacted]	11.7%
Undiscounted health outcomes and costs	[redacted]	-17.5%	[redacted]	-16.5%
Utilities, SMC sorafenib PF: 0.72, PD: 0.64	[redacted]	-11.6%	[redacted]	-7.8%
Utilities, SMC cabozantinib PF: 0.796, PD: 0.624	[redacted]	-13.0%	[redacted]	-10.5%
Disutility, SMC lenvatinib -0.042 (all treatments)	[redacted]	0.1%	[redacted]	-0.1%
Drug wastage included	[redacted]	-3.4%	[redacted]	-12.0%
Curve choice: PFS – Exponential	[redacted]	53.2%	[redacted]	43.0%
Curve choice: PFS – Weibull	[redacted]	-6.7%	[redacted]	-7.4%
Curve choice: PFS – lognormal	[redacted]	3.5%	[redacted]	3.4%
Curve choice: PFS – Gompertz	[redacted]	-25.3%	[redacted]	-22.7%
Curve choice: PFS – Gamma	[redacted]	-3.9%	[redacted]	-4.9%

Curve choice: PFS – spline knot 1	[redacted]	-9.0%	[redacted]	-9.3%
Curve choice: PFS – spline knot 2	[redacted]	-20.4%	[redacted]	-18.7%
Curve choice: PFS – spline knot 3	[redacted]	-30.5%	[redacted]	-28.2%
Curve choice: PFS – stratified Weibull	[redacted]	31.3%	[redacted]	24.2%
Curve choice: PFS – stratified lognormal	[redacted]	99.8%	[redacted]	83.4%
Curve choice: PFS – stratified loglogistic	[redacted]	71.3%	[redacted]	58.3%
Curve choice: PFS – stratified Gompertz	[redacted]	3.6%	[redacted]	1.1%
Curve choice: PFS – stratified gamma	[redacted]	36.7%	[redacted]	28.7%
Curve choice: PFS – stratified spline knot 1	[redacted]	28.0%	[redacted]	21.6%
Curve choice: PFS – stratified spline knot 2	[redacted]	24.2%	[redacted]	18.2%
Curve choice: PFS – stratified spline knot 3	[redacted]	224.5%	[redacted]	191.5%
Curve choice: PFS – HR vs placebo applied to cabozantinib, exponential	[redacted]	-5.4%	[redacted]	0.0%
Curve choice: OS – Exponential	[redacted]	-6.4%	[redacted]	-6.0%
Curve choice: OS – Gompertz	[redacted]	-12.0%	[redacted]	-11.3%
Curve choice: OS – spine knot 1	[redacted]	-11.5%	[redacted]	-10.7%
Curve choice: OS – spline knot 2	[redacted]	-17.3%	[redacted]	-16.7%
Curve choice: OS – spline knot 3	[redacted]	-7.3%	[redacted]	-12.6%
Curve choice: OS – stratified Weibull	[redacted]	62.9%	[redacted]	44.8%
Curve choice: OS – stratified Gompertz	[redacted]	225.8%	[redacted]	105.9%
Curve choice: OS – stratified spline knot 1	[redacted]	-37.6%	[redacted]	-35.0%
Curve choice: OS – stratified spline knot 2	[redacted]	-38.5%	[redacted]	-37.4%
Curve choice: OS – stratified spline knot 3	[redacted]	203.3%	[redacted]	84.0%

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; PD: progressed disease; PF: progression free; SMC: Scottish Medicine Consortium.

Table 76: Scenario analyses for the RET fusion-positive TC pre-treated population

Scenario	Pairwise ICER (£/QALY)[a]	% ICER change
Base case	[redacted]	-
Discount rate 1.5% (benefits)	[redacted]	-8.6%
Discount rate 6%	[redacted]	7.3%
Undiscounted health outcomes and costs	[redacted]	-10.9%

Utilities, SMC sorafenib PF: 0.72 PD: 0.64	[redacted]	0.6%
Utilities, SMC cabozantinib PF: 0.796 PD: 0.624	[redacted]	-5.5%
Disutility, SMC lenvatinib -0.042 (all treatments)	[redacted]	-0.3%
Drug wastage included	[redacted]	-12.1%
Curve choice: PFS – stratified lognormal	[redacted]	10.4%
Curve choice: PFS – stratified loglogistic	[redacted]	11.8%
Curve choice: PFS – stratified Gompertz	[redacted]	-1.3%
Curve choice: PFS – stratified gamma	[redacted]	1.0%
Curve choice: OS – stratified Weibull	[redacted]	103.6%
Curve choice: OS – stratified Gompertz	[redacted]	155.8%
Curve choice: OS – stratified lognormal	[redacted]	337.9%
Curve choice: OS – stratified loglogistic	[redacted]	185.6%
Curve choice: OS – stratified gamma	[redacted]	81.6%

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; PD: progressed disease; PF: progression free; SMC: Scottish Medicine Consortium.

B.3.8.4 Summary of sensitivity analyses results

[redacted]. Results of the scenario analyses exhibit substantial variation when different extrapolations for the PFS and OS for *RET*-mutant MTC population, and specifically OS in the *RET* fusion-positive TC population are used. This can be attributed to the uncertainty in the clinical data underpinning these endpoints, especially OS. As demonstrated by the DSA, in *RET*-mutant MTC, the most influential parameters driving the model for the comparison of selpercatinib with cabozantinib was the OS treatment-effects for cabozantinib; for the comparison of selpercatinib versus BSC, the 'progressed' health state utility and the selpercatinib progression-free health state utility were the most influential parameters. For the comparison of selpercatinib versus BSC in *RET* fusion-positive TC, the selpercatinib progression-free health state utility and the 'progressed' health state utility were the most influential parameters.

B.3.9 *Subgroup analysis*

No further subgroup analyses were carried out beyond the analysis of 'advanced RET fusion-positive TC adults with who require systemic therapy and whose disease has progressed following prior ***systemic*** treatment' and 'adults and people aged 12 years and over with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy' for the following reasons:

- Insufficient data were available to conduct subgroup analyses for selpercatinib according to thyroid cancer type. Patients in the *RET* fusion-positive TC arm were predominantly papillary, therefore analysis is not possible for the TC population
- Insufficient data for comparator therapies were available to conduct subgroup analyses according to *RET*-alteration

- In the *RET*-mutant MTC population, data are presented in the submission separately for patients who had received prior cabozantinib or vandetanib or who were treatment-naïve to cabozantinib or vandetanib in the LIBRETTO-001 trial. However, no data were available for comparators that were stratified by line of therapy, and thus the base case economic analysis focuses on the pooled "any-line" population as more data were available for the analysis, making it more robust.

B.3.10 *Validation*

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case,[69] and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%. The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions. The model structure is closely aligned with the model used in the previous NICE appraisals in thyroid cancer (TA516[22] and TA535[21]).

Face validity

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in TC.

Internal validity

Quality-control procedures for verification of input data and coding were performed by an independent reviewer not involved in the model development and in accordance with a prespecified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data were updated where required.

Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code. In addition, the model was validated by an independent health economist.

Cross Validity

Comparison of results with other models analysing the same problem was to be performed where suitable models were available. Because no economic evaluations have been performed in *RET*-altered TC, cross validation was not possible.

External Validity

Model predictions were compared with outcomes in studies used to build the model (i.e., dependent, external validity) and with outcomes in studies not used to build the model (i.e., independent, external validity) where data were permitting.

Predicted model outcomes compared to trial outcomes are presented in Appendix J. Due to the immaturity of median PFS (mPFS) and median OS (mOS) data from LIBRETTO-001 it was difficult to interpret external validity for the selpercatinib arm. mPFS and mOS was not reached for the 'any-line' MTC population. However, data were available for the *RET*-mutant subgroup from EXAM to compare to the modelled mPFS results for cabozantinib and placebo (BSC) and

showed good consistency to the trial data. Similarly, predicted mPFS was consistent with the placebo (BSC) ITT population from SELECT for the pre-treated *RET* fusion-positive TC population. However, these data were in a non-*RET* specific population, therefore firm interpretations of external validity for this patient group cannot be drawn.

Trial data were only available for *RET* M918T-positive subgroup from EXAM and mOS showed either an underestimation or overestimation for mOS compared to trial data for cabozantinib and placebo (BSC), respectively. However, it should be noted that the *RET* M918T subgroup cannot be directly compared to the *RET*-mutant target population, therefore, no firm conclusions can be drawn about the external validity of the modelled OS results for the cabozantinib arm. Clinical expert feedback confirms that the *RET* M918T data for placebo were generalisable to the overall *RET*-mutant population. It was not possible to assess validity of predicted mOS versus trial data for either selpercatinib or BSC due to immature data.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of cost-effectiveness evidence

The cost-effectiveness of selpercatinib as a treatment for adults and people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy was evaluated versus cabozantinib and BSC, the relevant comparators for this population, and versus BSC as a treatment for adult patients with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment. In the deterministic base-case analyses, selpercatinib demonstrated a substantial incremental QALY gains versus both cabozantinib in *RET*-mutant MTC and versus BSC in in both populations, demonstrating that it offers a step change for patients; [redacted] all results are at list price for all comparators.

The pairwise base-case results in the *RET*-mutant MTC population show that selpercatinib is associated with total QALYs of [redacted] compared with [redacted] for patients treated with cabozantinib (an incremental QALY gain of [redacted]) and [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] and [redacted] per QALY gained versus cabozantinib and BSC, respectively. The base-case results in the *RET* fusion-positive TC population show that selpercatinib is associated with total QALYs of [redacted] compared with [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC. This demonstrates that selpercatinib versus all comparators accumulated substantially more QALYs, but higher costs.

The results of the PSA align with the deterministic base case results, while the DSA results identified a small number of key influential parameters (cabozantinib efficacy and health state utility values) with the model being largely robust to uncertainty in the majority of parameters. Scenario analysis results exhibited substantial variation when different extrapolations for the PFS and OS for *RET*-mutant MTC population, and specifically OS in the *RET* fusion-positive population were used, due to the underlying immaturity of the clinical data these extrapolations were based on.

Overall, the results indicate selpercatinib to be not yet be cost-effective for the treatment for adults and people aged 12 years and over with advanced *RET*-mutant MTC who require

systemic therapy was evaluated versus cabozantinib and BSC, the relevant comparators for this population, and versus BSC as a treatment for adult patients with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment in the NHS. [redacted]

Strengths

The clinical evidence presented within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including selpercatinib, in *RET*-altered thyroid cancers. While the data from the LIBRETTO-001 trial was immature and was not from a head-to-head trial versus the relevant comparators, the results of the MAIC indicated that selpercatinib was associated with a statistically significant improvement in PFS and OS compared with cabozantinib and placebo for patients with *RET*-mutant MTC. Similarly, based on a naïve comparison versus the pre-treated subgroup of the SELECT trial, selpercatinib offers a considerable improvement in PFS compared with BSC in the previously-treated *RET* fusion-positive TC population. This translates to an increase in QALYs gained versus comparators in all relevant populations. The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%.

Limitations

The key limitations associated with the analysis are due to the absence of head-to-head trial data between selpercatinib and comparators, as such, relative efficacy is based on unanchored population-adjusted and naïve indirect comparisons, which may be subject to selection bias and confounding. The use of indirect comparison techniques inherently results in a greater level of parameter uncertainty in the relative effectiveness estimates than head-to-head trial data. In addition, data for comparator therapies in the relevant population of interest are not available for all outcomes. Furthermore, sample sizes are small across the LIBRETTO-001 and comparator trials, especially for *RET*-fusion positive TC patient population, and OS data are immature. This leads to uncertainty in the long-term estimates of treatment efficacy in the model. Limitations were therefore addressed by use of conservative assumptions as well as extensive scenario analysis. Further data cuts from the LIBRETTO-001 trial, evidence from the Phase III trial investigating the efficacy and safety of selpercatinib versus standard treatment (cabozantinib or vandetanib) in patients with untreated RET-Mutant MTC (LIBRETTO-531; NCT04211337) and collection of data via the systemic anticancer therapy (SACT) cohort may help resolve these uncertainties. As such, selpercatinib is positioned as a candidate for approval on the CDF in this submission. Lastly, LIBRETTO-001 may not be fully generalisable to patients in UK clinical practice. Patients in the LIBRETTO-001 trial in the PAS and IAS are relatively heavily pre-treated, specifically with MKIs (including cabozantinib, vandetanib, sorafenib and lenvatinib) in comparison to patients in UK clinical practice, where cabozantinib is the only NICE approved MKI for the treatment of progressive, advanced or metastatic MTC. Therefore, the effect of this difference is expected to result in conservative estimations with respect to selpercatinib.

Conclusion

There is an unmet clinical need within clinical practice for an effective and tolerable treatment option for patients in *RET*-mutant MTC following cabozantinib and in *RET*-fusion positive TC

following either lenvatinib or sorafenib, whose only alternative is BSC. Furthermore, there is an unmet need for patients with *RET*-mutant MTC who are unable to tolerate the side-effect profile of cabozantinib. It is expected that clinicians will use selpercatinib as an alternative to BSC in both *RET*-mutant MTC following cabozantinib and in *RET*-fusion positive TC following either lenvatinib or sorafenib, and is favourable in that it has demonstrated clinical efficacy and a substantial increase in QALYs versus BSC in both these populations. It is also expected to be used as an alternative to cabozantinib in patients with *RET*-mutant MTC, as it has demonstrated to be a more favourable treatment due to the lower rate of adverse events and discontinuation rate seen in LIBRETTO-001 compared to EXAM. While selpercatinib has not yet been able to demonstrate superior cost-effectiveness versus comparators at list price, [redacted].

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Appendices

Selpercatinib for advanced thyroid cancer with RET alterations [ID3744]

Clarification questions

Updated base case scenario analyses

November 2020

Appendix

Scenario analysis results of any-line *RET*-mutant MTC adjusted for prior TKI use

A number of scenario analyses were explored in which model assumptions or parameters were altered. Recognising the complexity and inherent uncertainty in the survival analyses and the limitations of the data sources, a wide variety of extrapolation sets were explored for each indication. The pairwise results of the scenario analyses for the any-line *RET*-mutant MTC adjusted for prior TKI use population are presented in Table 1.

Table 1: Scenario analyses (pairwise) for the any-line *RET*-mutant MTC population adjusted for prior TKI use

Scenario	ICER vs BSC (£/QALY)	% ICER change
Base case	[redacted]	-
Discount rate 1.5% (benefits)	[redacted]	-16.73%
Discount rate 6%	[redacted]	14.36%
Undiscounted health outcomes and costs	[redacted]	-19.58%
Utilities, SMC sorafenib PF: 0.72, PD: 0.64	[redacted]	-11.21%
Utilities, SMC cabozantinib PF: 0.796, PD: 0.624	[redacted]	-12.72%
Disutility, SMC lenvatinib -0.042 (all treatments)	[redacted]	-0.04%
Drug wastage not included	[redacted]	-11.87%
Curve choice: PFS – Exponential	[redacted]	63.81%
Curve choice: PFS – Weibull	[redacted]	-5.17%
Curve choice: PFS – lognormal	[redacted]	3.16%
Curve choice: PFS – Gompertz	[redacted]	-26.22%
Curve choice: PFS – Gamma	[redacted]	-2.99%
Curve choice: PFS – spline knot 1	[redacted]	-8.34%
Curve choice: PFS – spline knot 2	[redacted]	-22.89%
Curve choice: PFS – spline knot 3	[redacted]	-32.26%
Curve choice: PFS – stratified Weibull	[redacted]	35.09%
Curve choice: PFS – stratified lognormal	[redacted]	104.62%
Curve choice: PFS – stratified loglogistic	[redacted]	73.80%
Curve choice: PFS – stratified Gompertz	[redacted]	-7.49%
Curve choice: PFS – stratified gamma	[redacted]	42.80%
Curve choice: PFS – stratified spline knot 1	[redacted]	26.98%
Curve choice: PFS – stratified spline knot 2	[redacted]	-4.02%
Curve choice: PFS – stratified spline knot 3	[redacted]	19.36%
Curve choice: OS – Exponential	[redacted]	-4.58%
Curve choice: OS – Gompertz	[redacted]	-5.80%
Curve choice: OS – spine knot 1	[redacted]	-5.09%
Curve choice: OS – spline knot 2	[redacted]	-10.00%

Curve choice: OS – spline knot 3	[redacted]	17.95%
Curve choice: OS – stratified Weibull	[redacted]	114.34%
Curve choice: OS – stratified Gompertz	[redacted]	770.62%
Curve choice: OS – stratified spline knot 1	[redacted]	145.15%
Curve choice: OS – stratified spline knot 2	[redacted]	923.57%
Curve choice: OS – stratified spline knot 3	[redacted]	-

NICE National Institute for Health and Care Excellence

Professional organisation submission

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	**RCP registrar**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The NCRI Thyroid Cancer Subgroup is a multidisciplinary group of clinicians and patient representatives from across the UK with an interest in thyroid cancer research. The group is supported by the NCRI secretariat which receives funding from a number of major UK cancer charities.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment for radioiodine refractory differentiated thyroid cancer (DTC) and advanced medullary thyroid cancer (MTC) is to delay progression, improve symptoms, reduce the risk of disease related morbidity and to extend overall survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Objectively - radiological response according to RECIST criteria. Subjectively - a response in symptoms
8. In your view, is there an unmet need for patients and	There are very few established treatments available (sorafenib or lenvatinib for radioiodine refractory differentiated thyroid cancer, and cabozantinib for medullary thyroid cancer), and these treatments are associated with significant toxicity. A selective RET inhibitor such as selpercatinib would provide an

healthcare professionals in this condition?	alternative treatment option which may be better tolerated and more effective for patients with a RET alteration.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients with advanced thyroid cancer (radioiodine refractory differentiated thyroid cancer or medullary thyroid cancer) are often monitored initially, with the aim of commencing therapy at the point at which they are imminently symptomatic, actually symptomatic, or have radiological or biochemical evidence of increasingly rapid progressive disease. If symptoms or progression of the disease is localised to particular anatomical sites, targeted treatment such as local radiotherapy, surgery, or embolization may be effective, and may delay the need for systemic therapy. If symptoms or progression are more diffuse, systemic therapy is commenced. Lenvatinib or sorafenib are licensed for use in radioiodine refractory differentiated thyroid cancer, and cabozantinib for medullary thyroid cancer. Larotrectinib and entrectinib have recently been approved by NICE for treating patients with NRTK fusion-positive solid tumours (including thyroid cancer).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• British Thyroid Association Guidelines for the management of thyroid cancer. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Clin Endocrinol (Oxf). 2014 Jul;81 Suppl 1:1-122. • 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Haugen BR, Alexander EK, Bible KC, et al. *Thyroid*. 2016;26(1):1-133. doi:10.1089/thy.2015.0020

	• Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma.Wells SA Jr, Asa SL, Dralle H, et al. *Thyroid*. 2015;25(6):567-610. doi:10.1089/thy.2014.0335 • Schlumberger M, Bastholt L, Dralle H, et al. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer [published correction appears in Eur Thyroid J. 2012;1(2):54]. *Eur Thyroid J*. 2012;1(1):5-14. doi:10.1159/000336977
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Management of this group of patients seems to be consistent amongst clinicians who treat this condition in the UK. There will be some variation, as the timing of starting systemic therapy is individualised and it is important to decide this on a case by case basis. In general though, the concepts that underpin the management of these patients are well accepted.
• What impact would the technology have on the current pathway of care?	This technology would add an additional line of treatment, for those patients whose tumours have a RET alteration.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.

• How does healthcare resource use differ between the technology and current care?	Resource use in terms of clinic visits and medical imaging for monitoring would be comparable with current treatments such as lenvatinib, sorafenib and cabozantinib. However, due to the reported lower toxicity it is likely that supportive care costs for managing side effects will be lower.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This drug should be used in secondary or tertiary care, by clinicians who are experienced in the management of this group of patients, and particularly in the use of systemic anti-cancer therapy (SACT).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an oral, outpatient based treatment, so the infrastructure required is already in place in the form of outpatient clinics. It would be important for patients to have easy access to the clinical team for advice and support. A thyroid clinical nurse specialist is crucial, and there should also be a reliable way for patients to obtain advice out of hours. Facilities would need to be available to perform molecular testing for RET fusions (DTC) and RET mutations (MTC) in order to identify which patients may benefit from selpercatinib. This is already available in England via the Genomics England Test Directory, and in Wales via the All Wales Medical Genetic Service, so would not be an additional cost.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There have been no head to head comparisons of selpercatinib versus current standards of care (lenvatinib, sorafenib, cabozantinib). However, the LIBRETTO-001 trial (selpercatinib) reported response rates of between 69-79%, compared with 64% (lenvatinib; SELECT), 12.2% (sorafenib: objective response rate DECISION), 28% (cabozantinib; EXAM). Duration of response appears to be longer with selpercatinib, 20.1-27.4 months compared with 18.3 months (lenvatinib), 10.8 months (sorafenib) and 11.2 months (cabozantinib). The toxicity profile of selpercatinib appears more favourable than other treatments, with 28% of patients suffering a G3 adverse event, and 2% having a G4 adverse event. This compares with 75.9% >/=G3 (lenvatinib), 69% G3 and 33% G4 (cabozantinib). In the LIBRETTO-001 study only 2% patients had to discontinue treatment due to adverse events, compared with 14.2% (lenvatinib), 18.8%

	(sorafenib) and 16% (cabozantinib). It therefore appears that selpercatinib could provide clinically meaningful benefit, with less toxicity, than currently available treatments.
• Do you expect the technology to increase length of life more than current care?	This information is not currently available. The LIBRETTO-001 study was not designed to report on overall survival. The SELECT, DECISION and EXAM studies did not show an overall survival benefit, although a subsequent subgroup analysis of the SELECT trial has demonstrated an overall survival benefit in patients over the age of 65yrs.
• Do you expect the technology to increase health-related quality of life more than current care?	As selpercatinib appears to have a more favourable side effect profile than current treatments, health related quality of life may be increased.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Selpercatinib is a specific RET inhibitor, therefore it would only be recommended for use in patients with RET alterations.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	Practicalities of using selpercatinib would be very similar to treating patients with the currently available drugs. These patients do require frequent monitoring, particularly in the initial stages of treatment. However, if selpercatinb was introduced, it should not lead to an overall increase in the number of patients receiving systemic therapy, as any patients recommended for selpercatinib would be the same patients

care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	who would have been treated with existing agents. In addition, if selpercatinib is better tolerated, this could ease the burden on healthcare facilities, and the treatment would be more acceptable to patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with currently available treatments, selpercatinib would be commenced at the point of symptomatic and/or progressive disease, and stopped when there is evidence of disease progression or intolerability of the drug. There would be no need for any additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	We are not aware of any aspects that are not included in the QaLY system.

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Selpercatinib would provide an additional and/or alternative line of treatment for patients who have otherwise limited treatment options. Unlike the other available treatments, selpercatinib does not have VEGF activity therefore could be a better option for patients at risk of bleeding or other vascular complications.
• Is the technology a 'step-change' in the management of the condition?	Yes, in view of the fact that is appears to be effective, and significantly less toxic than currently available treatments.
• Does the use of the technology address any particular unmet need of the patient population?	There are very few established treatments available (sorafenib or lenvatinib for radioiodine refractory differentiated thyroid cancer, and cabozantinib for medullary thyroid cancer), and these treatments are associated with significant toxicity. A selective RET inhibitor such as selpercatinib would provide an alternative treatment option which may be better tolerated and more effective for patients with a RET alteration. Ideally selpercatinib should be considered for use in the first and second line settings as the current treatments are only recommended as first line treatments.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Some side effects are inevitable. As with existing treatments, patients would need to be carefully monitored for side effects, and any toxicity pro-actively managed in order to maintain quality of life, and optimise treatment.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Selpercatinib is not currently approved for use in the UK, so is not 'current UK clinical practise'. An international clinical trial comparing selpercatinib with current standard of care (cabozantinib in the UK) in the first line treatment setting for advanced medullary thyroid cancer with RET mutations is about to open in a number of UK centre and this will clearly add to the evidence base.
• If not, how could the results be extrapolated to the UK setting?	The characteristics of the patients enrolled in the LIBRETTO-001 trial are similar to the patient population in the UK, so it would be reasonable to extrapolate the results to the UK setting.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The treatment intent is palliative, so it is crucial to balance the benefits of treatment with the risk of side effects and reduced quality of life. Outcome measures such as response rate, duration of response, and toxicity are therefore critical. These measures were reported in the LIBRETTO-001 trial.
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	There is very limited 'real world' experience of using this drug in the UK today. Most patients have been treated within the context of clinical trials.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No issues identified.

21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- There are limited treatment options available for the management of patients with radioiodine refractory differentiated thyroid cancer (DTC) or advanced medullary thyroid cancer (MTC)
- Selpercatinib appears to be an effective treatment for management of patients with advanced DTC and MTC with RET alterations/mutations
- Selpercatinib appears to have a favourable toxicity profile compared with existing treatments
- It would be ideal to consider the use of selpercatinib both in first and second line settings
- It will be crucial to ensure clinicians have access to molecular testing for RET fusions and RET mutations, in order to identify patients who may be suitable for treatment with selpercatinib

Thank you for your time.

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Professional organisation submission

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Society for Endocrinology**
3. Job title or position	**Professor of Endocrinology**

4. Are you (please tick all that apply):	X☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? X ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Society for Endocrinology is the national membership organisation supporting scientists, clinicians and nurses who work in endocrinology throughout their careers.** **They also engage policy-makers, journalists, patients and the public with hormone science to encourage informed health decisions, and to demonstrate the value of endocrinology to the wider world. The Society is a not-for-profit organisation and a registered charity. The SfE activities are made possible by funding from our wholly owned trading subsidiary, Bioscientifica, which publishes their journals, manages their events and provides membership services.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treating radioiodine refractory differentiated thyroid cancer and advanced medullary thyroid cancer is to delay disease progression, to improve symptoms and quality of life and to reduce thyroid cancer related morbidity and mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	1. A radiological response as determined by RECIST criteria 2. Clinically: improvement of symptoms or quality of life 3. Longer overall survival

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The NICE approved treatment options for radioiodine refractory DTC are limited to Sorafenib and Lenvatinib, for NTRK positive tumours to Larotrectinib and Entrectinib and for medullary thyroid cancer to Cabozatinib. All these treatments have significant toxic adverse effects. There are no approved alternative treatment options for patients who do not tolerate these treatments. A selective RET inhibitor such as Selpercatinib would provide an alternative treatment option which may be better tolerated and more effective for patients with a RET alteration
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The initial treatment of patients with differentiated thyroid cancer is with surgery, radioiodine ablation and TSH suppression. Initial treatment of medullary cancer is with surgery. Sometimes external beam radiotherapy is needed. Advanced radioiodine refractory differentiated and medullary thyroid are often monitored initially. Additional therapies are started at the point at when patients become symptomatic or have radiological or biochemical evidence of increasingly rapid progressive disease. If symptoms or progression of the disease is localised to particular anatomical sites, targeted treatment such as local radiotherapy, surgery, or embolization may be effective, and may delay the need for systemic therapy. If symptoms or progression are more diffuse, systemic therapy is commenced. Lenvatinib or sorafenib are licensed for use in radioiodine refractory differentiated thyroid cancer, and cabozantinib for medullary thyroid cancer.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• British Thyroid Association Guidelines for the management of thyroid cancer. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Clin Endocrinol (Oxf). 2014 Jul;81 Suppl 1:1-122. • 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Haugen BR, Alexander EK, Bible KC, et al. *Thyroid*. 2016;26(1):1-133. doi:10.1089/thy.2015.0020

	• Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma.Wells SA Jr, Asa SL, Dralle H, et al. *Thyroid*. 2015;25(6):567-610. doi:10.1089/thy.2014.0335 • Schlumberger M, Bastholt L, Dralle H, et al. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer [published correction appears in Eur Thyroid J. 2012;1(2):54]. *Eur Thyroid J*. 2012;1(1):5-14. doi:10.1159/000336977
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In the UK management is consistent amongst clinicians treating patients with early and advanced thyroid cancer. Treatment decisions are by and large governed by MDT decisions and national and international guidelines are followed. There may be some variation as to when systemic therapies are started although mostly the existing guidelines are followed.
• What impact would the technology have on the current pathway of care?	This is a new therapy offering an additional option for patients with RET positive tumours, potentially with fewer adverse effects than the other therapies available to us.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	Healthcare resource use in terms of clinic visits and medical imaging for monitoring would be comparable with current treatments such as Cabozantinib, Sorafenib and Lenvatinib. It is possible that there may be less use of healthcare resources if the toxicity of the new treatment is lower.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary or tertiary care to be used by clinicians who are experienced in the use of systemic anti-cancer targeted therapies
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The treatment will be administered in oral form in an outpatient setting. The infrastructure if clinics with specialist nurse support is already available in most centres. It is likely that further investment by way of additional thyroid cancer clinical nurse specialists may be required. Patients should have access to out of hours advice. Facilities would need to be available to perform molecular testing for RET fusions (DTC) and RET mutations (MTC) in order to identify which patients may benefit from selpercatinib. This is already available in England via the Genomics England Test Directory, so would not be an additional cost, although additional role out to more centres may be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Selpercatinib has not been compared with the currently available targeted agents including lenvatinib, sorafenib and cabozantinib. However, the LIBRETTO-001 trial (selpercatinib) reported response rates of between 69-79%, compared with 64% (lenvatinib; SELECT), 12.2% (sorafenib: objective response rate DECISION), 28% (cabozantinib; EXAM). Duration of response appears to be longer with selpercatinib, 20.1-27.4 months compared with 18.3 months (lenvatinib), 10.8 months (sorafenib) and 11.2 months (cabozantinib). The toxicity profile of selpercatinib appears more favourable than other treatments, with 28% of patients suffering a G3 adverse event, and 2% having a G4 adverse event. This compares with 75.9% >/=G3 (lenvatinib), 69% G3 and 33% G4 (cabozantinib). In the LIBRETTO-001 study only 2% patients had to discontinue treatment due to adverse events, compared with 14.2% (lenvatinib), 18.8% (sorafenib) and 16% (cabozantinib). It therefore appears that selpercatinib could provide clinically meaningful benefit, with less toxicity, than currently available treatments.

• Do you expect the technology to increase length of life more than current care?	It is possible although we don't have any current data. The LIBRETTO-001 study was not designed to report on overall survival. The SELECT, DECISION and EXAM studies did not show an overall survival benefit, although a subsequent subgroup analysis of the SELECT trial has demonstrated an overall survival benefit in patients over the age of 65yrs.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes since the currently available data indicate that Selpercatinib indicate that this is an efficacious drug with fewer side effects than the other available treatments, health related quality of life may be improved.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Selpercatinib is a RET inhibitor and therefore is only incated in patients with tumours harbouring RET alterations.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Practicalities of using selpercatinib would be very similar to treating patients with the currently available drugs. In the early stages of treatment and throughout the use of these medications frequent monitoring is needed. The total number of patients requiring systemic therapies however should not increase since any patients recommended for selpercatinib would be the same patients who would have been treated with

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	existing agents. In addition, if selpercatinib is better tolerated, this could ease the burden on healthcare facilities, and the treatment would be more acceptable to patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Similar to other targeted treatments, selpercatinib would be commenced at the point of symptomatic and/or progressive disease, and stopped when there is evidence of disease progression or intolerability of the drug. There would be no need for any additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Selpercatinib would provide an effecteive and better tolerated treatment option in patients who otherwise have limited options available. Since unlike the other tyrosine kinase inhibitors, Selpercatinib does not have VEGF activity this may be a better option for patients at risk of bleeding or other vascular complications.
• Is the technology a 'step-change' in the management of the condition?	Yes since this is an effective and less toxic treatment compared with the currently available options.
• Does the use of the technology address any particular unmet need of the patient population?	There are very few established and approved treatments available for advanced thyroid cancer (sorafenib or lenvatinib for radioiodine refractory differentiated thyroid cancer, and cabozantinib for medullary thyroid cancer), and these treatments are associated with significant toxicity. There are no approved alternative treatment options for patients who do not tolerate these treatments. A selective RET inhibitor such as selpercatinib would provide an alternative treatment option which may be better tolerated and more effective for patients with a RET alteration. Ideally selpercatinib should be considered for use in the first and second line settings as the current treatments are only recommended as first line treatments.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Some side effects are inevitable. As with existing treatments, patients would need to be carefully monitored for side effects, and any toxicity pro-actively managed in order to maintain QoL, and optimise treatment. As always the balance between the tolerability of side-effects and the potential benefits of the treatment should be prioritised.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Selpercatinib is not currently approved for use in the UK, so is not 'current UK clinical practise'. An international clinical trial comparing Selpercatinib with current standard of care (Cabozantinib in the UK) in the first line treatment setting for advanced medullary thyroid cancer with RET mutations is about to open in a number of UK centre these results will be very informative.
• If not, how could the results be extrapolated to the UK setting?	The characteristics of the patients enrolled in the LIBRETTO-001 trial are similar to the patient population in the UK, so it would be reasonable to extrapolate the results to the UK setting.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The treatment intent is palliative, so it is crucial to balance the benefits of treatment with the risk of side effects and reduced quality of life. Outcome measures such as response rate, duration of response, and toxicity are therefore critical. These measures were reported in the LIBRETTO-001 trial.
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	This drug has only been used in a clinical trial setting and no real-world data are available
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Current data indicate that Selpercatinib is an effective treatment for management of patients with advanced DTC and MTC with RET alterations/mutations
- Selpercatinib appears to have a favourable toxicity profile compared with existing treatments
- The use of Selpercatinib should be considered both in first and second line settings in patients with advanced thyroid cancers with RET mutations/alteration
- It will be crucial to ensure clinicians have access to molecular testing for RET fusions and RET mutations, in order to identify patients who may be suitable for treatment with Selpercatinib
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Thyroid Cancer Forum-UK**
3. Job title or position	**Consultant Clinical Oncologist,** [redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	I set up TCF-UK in 2005. It is a free, independent organisation for consultants involved in the management of thyroid cancer in the UK. There are approximately 250 members. The main roles are to circulate journal abstracts, articles, guidelines, announcements on clinical trials and drug availability. There is a confidential forum for discussion of complex cases and management scenarios. There is also a separate branch for CNSs and AHPs. The only funding to date has come from occasional meeting registration fees paid by consultant members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	TCF-UK has received no funding from this source. I personally, have attended one expert panel for this company for which I was paid. I have met with staff and am in email contact with staff from the competing company. I have no allegiance to either company.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment would be used for patients with symptomatic, progressive inoperable locoregional recurrent disease or metastatic disease. The aim would be symptom control, improved quality of life and to slow disease progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	An improvement in quality of life such that WHO performance status increased, activities of daily living increased, independence maintained, pain and other symptoms (e.g. dyspnoea, liver pain, haemoptysis) reduced. The above may be accompanied by serum calcitonin and CEA (for MTC) and serum thyroglobulin (for DTC) decreases and radiological evidence of stable disease or partial response.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Definitely. We currently have cabozantinib for progressing medullary thyroid cancer patients and one approved and funded systemic therapy (lenvatinib) for radioiodine refractory differentiated thyroid cancer and one drug that is only suitable for a small proportion of DTC patients who are NTRK fusion positive (entrectinib). For the majority of patients who do not have the necessary NTRK alteration, who progress on lenvatinib or have to discontinue due to toxicity there are no further active oncological interventions available. These are very different scenarios to patients with many of the commoner cancers where multiple lines of therapy are available.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Advanced medullary thyroid cancer is currently treated with cabozantinib. A very small number of patients with metastatic disease may benefit from peptide receptor radiotherapy but this isn't routinely funded across the UK. Radioactive iodine (RAI) is the first line of treatment for metastatic differentiated thyroid cancer. This is rarely curative and the majority of patients will become RAI refractory. For progressive, symptomatic disease the next systemic options are lenvatinib if no contraindications or entrectinib if there is a NTRK fusion present. If these systemic therapies are contraindicated, not tolerated or inactive the only other options are best supportive care or consideration of clinical trials if available.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	In the UK we tend to utilise the British Thyroid Association Guidelines but these were last published in 2014 before NTRK and RET targeted therapies were available. The BTA guidance is being updated but has to recommend in accordance with NICE approved therapies. We also utilise the American and European Thyroid Associations' guidelines but these too predate the advent of new drugs.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The thyroid oncology community in the UK is small and we have an excellent communication network and approachable leaders. The pathway is well defined and we ensure that if any new drugs are available that the information is disseminated UK wide and likewise if clinical trials are opened in key UK centres we encourage out of area referrals for patients to be able to access new avenues of therapy.
• What impact would the technology have on the current pathway of care?	It would offer patients a new avenue of therapy. Clinical trial data suggest the drug is very active in the thyroid cancer setting and if available could have a significant benefit for subsets of patients who currently have limited options. If selpercatinib, cabozantinib, lenvatinib and entrectinib were available we could utilise molecular testing to better personalise patient care and utilise resources more efficiently.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Now that we have access to molecular testing across the UK, we should be able to test tumour tissue from medullary thyroid cancer and radioiodine refractory patients and select systemic therapy based on the results. Opting for targeted therapy in the first instance if the relevant molecular defect is present. Targeted therapy would be expected to be effective in the selected population and toxicity profile of targeted therapy is likely to be less than with a broader spectrum drug such as cabozantinib and lenvatinib. A better toxicity profile could translate in to less hospital visits and the need for less supportive medicines.
• How does healthcare resource use differ	Selpercatinib would be appropriate for a subset of patients with a RET mutation so molecular testing would be required to select appropriate patients.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Medullary thyroid cancer patients with symptomatic and or progressive inoperable locoregional or metatstaic disease with a RET mutation. Radioiodine refractory differentiated thyroid cancer patients who have a RET fusion.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Molecular testing has been set up UK wide so accessing RET mutation tests should be straightforward. Regarding training, the pharmaceutical company has already been in discussions with clinicians regarding educational resources that would cover testing, drug contraindications, monitoring and toxicity management so there would be no significant additional funding required from the NHS. TCF-UK regularly circulates education resources so this is an easy platform to promote knowledge.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Potentially
• Do you expect the technology to increase health-related quality of	Yes

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Effective for RET mutation positive MTC patients and RET fusion positive DTC patients only.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	I would anticipate similar ease of use once the usual initial learning curve has passed. There is the potential for less supportive measures being required if the toxicity profile is less than current standard of care by virtue of its more targeted mechanism of action.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	An initial RET molecular test would be needed (funding already available). Same approach as current systemic therapies for stopping treatment (patient choice, toxicity, disease progression).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Using the drug for selected patients with RET mutations or RET fusions should avoid non responders and wasting of resources. A more targeted drug will hopefully reduce toxicity and hence reduce toxicity related reductions in quality of life.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The expectation is that the toxicity profile will be less than current standards of care and therefore would anticipate less need for dose reductions, drug holidays and drug discontinuation.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Trial data included ORR, duration of response, PFS and safety which are all key outcome measures
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. There are likely to be patients who will have received the drug through an expanded access programme whose data will not be in the trial literature.

20. How do data on real-world experience compare with the trial data?	I have not seen this data.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Unmet need
- Molecular testing and selective use reduces futile treatment
- Potential for reduced toxicity
- Equity with other cancers in terms of more than one line of systemic therapy

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for treating advanced thyroid cancer with RET alterations

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Pim Wetzelaer, Health Economics Researcher, Erasmus School of Health Policy & Management (ESHPM), EUR, the Netherlands
Hannah Penton, Health Economist, ESHPM, EUR
Annette Chalker, Systematic Reviewer, KSR Ltd
Edyta Ryczek, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Mohammed Islam, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Steven Duffy, Information Specialist, KSR Ltd
Maiwenn Al, Health Economics Researcher , ESHPM, EUR
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 15/12/2020

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number STA 13/32/48.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Riemsma R, Wetzelaer P, Penton H, Chalker A, Ryczek E, Armstrong N, Ryder S, Islam M, Worthy G, Duffy S, Al M, Kleijnen J. Selpercatinib for treating advanced thyroid cancer with RET alterations: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2020.

Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Pim Wetzelaer acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hannah Penton, Steve Ryder, Mohammed Islam and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Edyta Ryczek acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse events
AESI	Adverse event of special interest
AG	Assessment group
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid cancer
AWMSG	All Wales Medicines Strategy Group
BI	Budget impact
BIC	Bayesian information criteria
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BOR	Best objective response
BSC	Best supportive care
CAP	College of American Pathologists
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CE	Cost effectiveness
CEA	Carcinoembryonic antigen
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
cfDNA	cell free DNA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical laboratory improvement amendments
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CUA	Cost utility analysis
CYP3A4	Cytochrome P450 3A4
DLT	Dose limiting toxicity
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DTC	Differentiated thyroid cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Extendedly dominated
EMA	European Medicines Agency
EORTC QLQ-C30	European Platform of Cancer Research Quality of Life Questions C30
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EU	European Union
EUR	Erasmus University Rotterdam
FACT-G	Functional assessment of cancer therapy–general
FAD	Final appraisal document

FDA	Food and Drug Administration
FISH	Fluorescein in-situ hybridisation
FTC	Follicular thyroid cancer
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IAS	Integrated analysis set
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardisation/Independent Ethics Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LPS	Lansky Performance Score
LTFU	Long term follow-up
LYG	Life years gained
MAIC	Matching-adjusted indirect comparisons
MEN2	Multiple endocrine neoplasia type 2
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MKI	Multikinase inhibitor
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NE	Not evaluable
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OSAS	Overall safety analysis set
PAS	Patient access scheme
PAS	Primary analysis set
PASLU	Patient Access Scheme Liaison Unit
PCR	Polymerase chain reaction
PD	Progressed disease
PD1	Programmed death receptor 1
PDTC	Poorly differentiated thyroid cancer
PF	Progression free
PFS	Progression free survival
PH	Proportional hazards
PK	Pharmacokinetics
PPI	Proton pump inhibitors
PPPY	Per patient per year
PR	Partial response

PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Papillary thyroid cancer
QALY	Quality-adjusted life years
QD	Once daily
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAI	Radioactive iodine
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RET	Rearranged during transfection
RP2D	Recommended Phase II dose
RPSFT	Rank preserving structural failure time
RR	Relative risk; Risk ratio
RR-DTC	Radioactive iodine refractory differentiated thyroid cancer
SACT	Systemic anticancer therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SAS1/2/3	Supplemental analysis set 1/2/3
ScHARR	School of Health and Related Research
SD	Stable disease
SE	Standard error
SFU	Safety follow-up
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of product characteristics
SRC	Safety Review Committee
STA	Single technology appraisal
STiDAT	Systemic Treatment-Induced Diarrhoea Assessment Tool
TA	Technology assessment
TC	Thyroid cancer
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitors
TLR	Targeted literature review
ToT	Time on treatment
TSD	Technical support document
TSH	Thyroid-stimulating hormone
TTD	Time to discontinuation
TTO	Time trade-off
TTOT	Time-to-off treatment
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
WTP	Willingness to pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 discussed the decision problem, Section 1.3 issues related to the clinical effectiveness, and Section 1.4 issues related to the cost effectiveness. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID3744	Summary of issue	Report sections
1.	Appropriateness of cabozantinib as a comparator	**Executive summary**: Table 1.2 **Main report**: Section 3.3, 4.3, 4.4 and 4.5
2.	Immaturity of effectiveness data	Section 4.2.5
3.	Reliability of the matching-adjusted indirect comparison (MAIC) for the rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC) population	Sections 4.3 and 4.4
4.	Reliability of the naïve indirect comparison for the RET fusion-positive thyroid cancer (TC) population	Sections 4.3 and 4.4
5.	Extrapolations of survival data	5.2.6.1
6.	Source of health state utility values	5.2.8
7.	In- or exclusion of genetic testing costs	5.2.9.6
8.	Time on treatment	5.2.9.1

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival and overall survival
- Disutilities due to treatment-related adverse events

Overall, the technology is modelled to affect costs by:

- Its additional drug acquisition costs (i.e. a higher unit price than current treatment), pharmacy dispensing costs, monitoring costs, and costs for the treatment of adverse events.
- The need for genetic testing to assess eligibility for treatment

The modelling assumptions that have the greatest effect on the ICER are:

- Use of extrapolations for progression-free and overall survival based on alternative parametric functions
- The inclusion of genetic testing costs
- Use of alternative utility values
- Assuming that treatment with selpercatinib may continue beyond progression

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, the company claims that best supportive care (BSC) is the only relevant comparator for both populations given the latest wording of the anticipated conditional marketing authorisation for selpercatinib (Response to clarification, Question A8) (Table 1.2).

Table 1.2: Key issue 1: Appropriateness of cabozantinib as a comparator

Report section	**Sections 3.3, 4.3, 4.4 and 4.5**
Description of issue and why the ERG has identified it as important	Choice of comparators. The company claims that BSC is the only relevant comparator for both populations given the latest wording of the anticipated conditional marketing authorisation for selpercatinib (Response to clarification, Question A8). This may be the case for the RET fusion-positive TC population because Technology Appraisal nr. 535 (TA535) explicitly states that lenvatinib and sorafenib are only recommended for patients who did not have a tyrosine kinase inhibitor (TKI) before. However, this may not be the case for the RET-mutant MTC patient population, as it would be possible that patients treated with one TKI in this population can be treated with cabozantinib subsequently.
What alternative approach has the ERG suggested?	Cabozantinib is a relevant comparator for the RET mutation-positive MTC population as specified in the final scope.
What is the expected effect on the cost effectiveness estimates?	The company has not provided an economic analysis for selpercatinib versus cabozantinib in the updated license population. Therefore, the expected effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	The company needs to provide an economic analysis for selpercatinib versus cabozantinib in the updated license population.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified three major concerns with the evidence presented on the clinical effectiveness, namely the short follow-up of the LIBRETTO-001 study (Table 1.3), the reliability of the MAIC for the RET-mutant MTC population. (Table 1.4) and the reliability of the naïve indirect comparison for the RET fusion-positive TC population (Table 1.5).

Table 1.3: Key issue 2: Immaturity of effectiveness data

Report section	Sections 4.2.5
Description of issue and why the ERG has identified it as important	Immaturity of effectiveness data. Several outcomes of the LIBRETTO-001 study are unreliable due to data immaturity, such as overall survival (OS), progression-free survival (PFS) and duration of response (DOR).
What alternative approach has the ERG suggested?	Given the available evidence, the ERG is unable to suggest an alternative approach. The company stated that currently there is no set date for an additional interim analysis, thus, no new data will be available before technical engagement planned for February 2021 (response to clarification, Question A15).
What is the expected effect on the cost effectiveness estimates?	The expected change to the point estimate of the ICER is unclear. However, the uncertainty surrounding the ICER estimates is increased by this issue.
What additional evidence or analyses might help to resolve this key issue?	Longer term follow-up would resolve this key issue.

Table 1.4: Key issue 3: Reliability of the MAIC for the RET-mutant MTC population

Report section	Sections 4.3 and 4.4
Description of issue and why the ERG has identified it as important	Reliability of the MAIC for the RET-mutant MTC population. An unanchored MAIC was used to generate relative efficacy estimates vs. cabozantinib and placebo (used a proxy for BSC) for the RET-mutant MTC population. As pointed out in the CS both the MAIC for the RET-mutant MTC population and the indirect treatment comparison (ITC) for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators. Specific problems: 1. The EXAM study did not report separate results for treatment-naïve and pre-treated patients; therefore, the any-line pooled population from the LIBRETT0-001 trial was used in the MAIC to provide a larger patient-level data set and closer matching to the characteristics of the RET-mutant subgroup of the EXAM trial. 2. Results are also based on subgroups with small numbers of patients, which affects their reliability. 3. The baseline characteristics of the RET-mutant subgroups were not available for the placebo arm of the EXAM study, therefore the baseline characteristics of the cabozantinib group were assumed to be similar to those of the placebo arm and were use in the MAIC. 4. The MAIC only included those prognostic factors and effect modifiers which were reported by both studies; other important factors may be missing and MAIC results are likely to be biased due to unobserved confounding. 5. OS data were not available for the RET-mutant MTC population and had to be estimated using the results for the RET M918-positive population.

	6. The CS did not contain any discussion on the likely amount of residual systematic error in the MAIC but did also present results from a naïve indirect treatment comparison (unweighted results) which were similar to the MAIC results. However, as both analyses used selpercatinib data from a single-arm study, the results may be unreliable.
What alternative approach has the ERG suggested?	Given the available evidence, the ERG is unable to suggest an alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the point estimate of the ICER is unclear. However, the uncertainty surrounding the ICER estimates is increased by this issue.
What additional evidence or analyses might help to resolve this key issue?	A randomised controlled trial (RCT) comparing selpercatinib with the relevant comparators in the relevant populations would resolve this key issue.

Table 1.5: Key issue 4: Reliability of the naïve indirect comparison for the RET fusion-positive TC population

Report section	**Sections 4.3 and 4.4**
Description of issue and why the ERG has identified it as important	Reliability of the naïve indirect comparison for the RET fusion-positive TC population. A naïve (unanchored) indirect comparison was used to compare selpercatinib with BSC (using the placebo arms of two RCTs) for the RET fusion-positive TC population. As pointed out in the CS both the MAIC for the RET-mutant MTC population and the ITC for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators. Specific problems: 1. The comparator arms only included patients with differentiated thyroid cancer (DTC). It was unknown to what extent these data are representative for patients with other types of TC. The company indicated that the prognosis for other types of TC is generally known to be worse. 2. A higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the SELECT and DECISION trials. Other important differences between the populations are: 100% of patients are RET fusion-positive in LIBRETTO-001 but this was unknown in the SELECT trial; and differences in prior systemic therapy as selection was mostly first-line patients (100% of LIBRETTO-001 and 20.6% of SELECT had received at least one prior therapy). 3. Subgroup results by line of therapy were not reported for OS for the comparator arm. OS was also affected by patient crossover in the comparator trials as placebo patients could crossover to the intervention. 4. Given that this analysis was based on small patient numbers and a comparison of single arms without any attempts to balance the patient groups, the PFS results are also likely to be uncertain.

What alternative approach has the ERG suggested?	Given the available evidence, the ERG is unable to suggest an alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the point estimate of the ICER is unclear. However, the uncertainty surrounding the ICER estimates are increased by this issue.
What additional evidence or analyses might help to resolve this key issue?	An RCT comparing selpercatinib with the relevant comparators in the relevant populations would resolve this key issue.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

The ERG identified four key issues related to the cost effectiveness evidence and the company's preferred assumptions. These are the choice of parametric function (stratified Weibull versus Weibull) for OS in *RET*-mutant MTC population (Table 1.6), the lack of adherence to the NICE reference case of the health state utility values (Table 1.7), the inclusion of genetic testing costs (Table 1.8) and assumed time on treatment (Table 1.9).

A full summary of the cost effectiveness evidence review conclusions can be found in Section 7.4 of this report. The company's cost effectiveness results are presented in Section 6, the ERG's summary and detailed critique in Section 5, and the ERG's amendments to the company's model and results are presented in Section 7.

The key issues in the cost effectiveness evidence are discussed in Tables 1.6 to 1.9.

Table 1.6: Key issue 5: Extrapolation of survival data

Report section	**Section 5.2.6.1**
Description of issue and why the ERG has identified it as important	There are many uncertainties in the extrapolation of the survival data required for use in the model. The extrapolations were based on a MAIC comparison, based on trial data from populations which in some cases do not match the marketing authorisation for selpercatinib. These issues, as summarised in section 1.4, introduce substantial and unresolvable uncertainty into the analyses. Additionally, the trial data for selpercatinib was fairly immature, particularly for OS. This led to a wide range of substantially different extrapolations which led to vastly different ICERs. A lack of long-term validity estimates in the exact population expected to receive selpercatinib in clinical practice made it very difficult to be sure which extrapolations were most plausible in each case.
What alternative approach has the ERG suggested?	Mature survival data from a head to head trial matching the population who will receive selpercatinib in clinical practice would be required to resolve this uncertainty.
What is the expected effect on the cost effectiveness estimates?	The results of the ERG scenarios in section 7.2.2 of this report show the range of potentially plausible ICERs obtained from changing either PFS or OS in each population. These results show that the range of potentially plausible ICERs ranges from £[redacted] to £[redacted] for the *RET*-mutant MTC population and £[redacted] to £[redacted] for the *RET*-fusion positive TC population. These ranges are based on the assumption that the underlying data is representative of the population who will receive selpercatinib in clinical practice, and the unbiased

	estimation of relative treatment efficacy with the MAIC and naïve ITC.
What additional evidence or analyses might help to resolve this key issue?	Mature survival data from a head to head trial matching the population who will receive selpercatinib in clinical practice would be required to resolve this uncertainty. In the meantime, systematic and minuted expert elicitation of the clinical plausibility of extrapolated curves would be helpful.

Table 1.7: Key issue 6: Health state utility values

Report section	**Section 5.2.8**
Description of issue and why the ERG has identified it as important	There is uncertainty surrounding how reflective the health state utility values (HSUVs) obtained from the literature would be for this population and how appropriately they meet the NICE reference case as they were not measured using the European Quality of Life-5 Dimensions (EQ-5D) and did not measure health-related quality of life (HRQoL) directly in patients as the chosen utilities were estimated using a vignette study. Choice of HSUVs used has a substantial impact on the ICER, particularly in the *RET* fusion-positive TC population as demonstrated in ERG scenarios.
What alternative approach has the ERG suggested?	The ERG would have preferred that the EQ-5D were collected in the trial, but as a second option that the QLQ-C30 LIBRETTO-001 trial data were mapped to EQ-5D utility values.
What is the expected effect on the cost effectiveness estimates?	The impact on the ICER is uncertain as the full QLQ-C30 data were not available to the ERG to enable them to map HSUVs. The mapped baseline QLQ-C30 scores aligned well with the progression-free utility from Fordham used in the base-case, but the progressed utility value from Fordham could not be validated as this LIBRETTO data was not available. More uncertainty surrounds the progressed value as different literature sources available reported different values and scenarios showed that increasing the progressed utility value from 0.5 to 0.64 decreased the ICER by approximately £[redacted] in the *RET*-mutant MTC population and £[redacted] in the *RET* fusion-positive TC population
What additional evidence or analyses might help to resolve this key issue?	EQ-5D data in the exact population of interest or at least appropriately mapped LIBRETTO-001 QLQ-C30 data (using an algorithm which provides plausible results), either for direct use in the model or to validate the chosen base-case values.

Table 1.8: Key issue 7: Genetic testing costs

Report section	**Sections 5.2.9.6, 7.1.3 and 7.2.2**
Description of issue and why the ERG has identified it as important	Uncertainty regarding whether genetic testing costs should be in- or excluded, and assumptions regarding which cost estimate was appropriate to use Whether additional costs can be expected due to genetic testing costs depends on assumptions regarding the number of patients that receive such testing as part of standard practice. The company assumed that all patients would receive testing as part of standard practice and therefore excluded genetic testing costs. The final

	scope by NICE indicates that these costs should be included, and a scenario should be performed that excludes them. In addition, there is uncertainty regarding the costs of genetic testing. Two sources were identified for cost estimates, which are very different: Hamblin et al, 2017, provided an estimate of £367 and Schwarze et al, 2020, provided an estimate of £6,479.
What alternative approach has the ERG suggested?	The ERG assumed the number of patients who currently receive genetic testing routinely to be almost zero and preferred their base-case to be in line with the final scope by NICE. The ERG used the lower cost estimate for their base case to be conservative and performed scenario analyses excluding genetic testing costs as well as using the higher cost estimate.
What is the expected effect on the cost effectiveness estimates?	*RET*-mutant MTC ERG base-case using the lower estimate: £[redacted] per QALY Scenario with costs excluded: £[redacted] per QALY Scenario using the higher estimate: £[redacted] per QALY *RET* fusion-positive TC ERG base-case using the lower estimate: £[redacted] per QALY Scenario with costs excluded: £[redacted] per QALY Scenario using the higher estimate: £[redacted] per QALY
What additional evidence or analyses might help to resolve this key issue?	Advice from experts in genetic testing could be sought on the numbers of patients that can be expected to receive testing as part of standard practice, and which cost estimate is appropriate to use.

Table 1.9: Key issue 8: Time on treatment

Report section	Section 5.2.9.1
Description of issue and why the ERG has identified it as important	Treatment with selpercatinib should continue until progression yet may also continue beyond progression as indicated by data from LIBRETTO-001 and clinical expert opinion. The company assumed that time on treatment (ToT) was equal to progression-free survival (PFS).
What alternative approach has the ERG suggested?	The ERG preferred the assumption that ToT was in line with data from LIBRETTO-001 and clinical expert opinion for their base-case, to better reflect total drug acquisition costs.
What is the expected effect on the cost effectiveness estimates?	*RET*-mutant MTC ERG base-case: £[redacted] per QALY Scenario ToT equal to PFS: £[redacted] per QALY *RET* fusion-positive TC ERG base-case: £[redacted] per QALY Scenario ToT equal to PFS: £[redacted] per QALY
What additional evidence or analyses might help to resolve this key issue?	Advice from clinical experts could be sought on whether treatment in clinical practice is continued beyond progression.

1.6 Other key issues: summary of the ERG's view

No other key issues were identified.

1.7 Summary of the ERG's view

The ERG preferred assumptions are described in detail in section 7.1.2 of this report and summarised in Table 1.10, with the impact of each assumption on results also shown. The assumption change which had the largest impact on results was using the stratified Weibull for OS in *RET*-mutant MTC, and in the *RET* fusion-positive TC population this were the inclusion of treatment continuation beyond progression and the costs of genetic testing.

The full deterministic cost effectiveness results of the ERG preferred base-case are presented in Table 1.11. The probabilistic sensitivity analysis (PSA) results were similar to the deterministic results, and for both populations there was a [redacted] chance of being considered cost effective at thresholds of £30,000 and £50,000 per QALY gained.

The scenarios conducted by the ERG are displayed in section 7.2.2. The ERG scenarios with the largest impact on the results were those exploring various OS curves. Looking at plausible alternatives, we find ICERs ranging from approximately [redacted] for the *RET*-mutant MTC population and from approximately [redacted] for the *RET* fusion-positive TC population. When for the costs of genetic testing the higher cost per test is used, the ICER in the *RET* fusion-positive TC population goes up to approximately [redacted].

Table 1.10: Summary of ERG's preferred assumptions and ICER

	***RET*-mutant MTC**			***RET* fusion-positive TC**		
	Incr. cost	**Incr. QALYs**	**ICER (£/QALY)**	**Incr. cost**	**Incr. QALYs**	**ICER (£/QALY)**
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company post-clarification base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Errors corrected by ERG (all changes below are relative from this model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull for OS in *RET*-mutant MTC	[redacted]	[redacted]	[redacted]	N.A.	N.A.	N.A.
Genetic testing costs included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Only PD health state costs for BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs based on 'non-elective short stay' setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Starting age 55.0 for the *RET*-mutant MTC population	[redacted]	[redacted]	[redacted]	N.A.	N.A.	N.A.
Treatment continuation beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; MTC = medullary thyroid cancer; N.A. = not applicable; OS = overall survival; PD = progressed disease; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer.

Table 1.11: Summary of ERG's base-case results

Scenario	Incremental cost	Incremental QALYs	ICER
***RET*-mutant MTC**			
Company base-case, post clarification, including ERG corrections	[redacted]	[redacted]	[redacted]
Deterministic ERG base case	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**			
Company base-case, post clarification, including ERG corrections	[redacted]	[redacted]	[redacted]
Deterministic ERG base case	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, MTC = medullary thyroid cancer; QALY = quality-adjusted life year; *RET* = rearranged during transfection; SoC = standard of care; TC = thyroid cancer.

2. BACKGROUND

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by Eli Lilly in support of selpercatinib, trade name Retsevmo®, for the treatment of *RET*-fusion positive thyroid cancer (TC) and *RET*-mutant MTC. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the Company Submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

The underlying health problem in this appraisal is TC which is characterised by abnormal growth and proliferation of the cells in a small gland at the base on the neck (the thyroid gland). The gland is part of the endocrine system and regulate a range of vital bodily functions through secretion of hormones.[2] TC is usually found incidentally in asymptomatic patients or in those with a lump, a persistent hoarse voice, a sore throat and/or difficulty swallowing.[3]

The thyroid gland is made primary of the two types of cells from which five major histological subtypes of TC arise: follicular cells, giving rise to papillary, follicular, Hürthle cell and anaplastic TCs, and non-follicular C cells, leading to medullary thyroid cancer (MTC).

Various genetic variations have been associated with TC, with the focus of CS on *RET* fusions, alterations, or point mutations that can occur in specific histological subtypes such as MTC and papillary thyroid cancer (PTC) and result in oncogenic activation.[4] *RET*-fusion positive PTC patients account for approximately 25% of all cases of this cancer and *RET* alterations are usually acquired during a person's lifetime.[5] Nearly all patients with hereditary MTC (approximately 25% of cases of this cancer) will inherit *RET* mutation, while about 50% of sporadic MTC cases carry a *RET* mutation.[5]

Classification and prognosis of TCs

Papillary or follicular TCs, classified as differentiated thyroid cancer (DTC), account for approximately 90% of all TCs.[3] The most common subtype, PTCs, accounts for 80-85% of thyroid malignancies in Europe and is associated with a five-year survival in men of around 90% and 95% in women. Follicular TCs, the second most common subtype that accounts for approximately 5-10% of all TCs, has a five-year survival of 90% in men and women.[3] While Hürthle cell cancers are usually grouped with follicular TCs, they are histologically distinct and grow more rapidly. Hürthle cell TC are rare (approximately 4% of TCs) and affect more women than men.[6, 7]

Anaplastic, or undifferentiated, TCs account for 1-3% of all TC cases with a five-year survival of 10% in both men and women.[3]

MTC accounts for approximately 3% in adults and 10% in paediatric TCs[8] with a five-year survival of 75% in men and 90% in women[3]. Sporadic and hereditary MTC, two distinct forms of MTC, are associated with different disease risk levels and various types of *RET* mutations contributing to oncogenicity.[9].

Distant metastases occur in 4-15% of patients with higher changes of metastases in the more aggressive TC forms. The lungs are the most commonly affected organ in metastatic disease.[10] The five-year survival rate is 78% for metastatic PTC, 63% for metastatic Follicular thyroid cancer (FTC), 39% for metastatic MTC and only 4% for metastatic anaplastic thyroid cancer.[1]

RET alterations

The *RET* is an oncogene. Oncogenic *RET* fusion proteins, termed *RET*/PTC, are a feature of approximately 20-40% of PTCs with estimates varying globally. The most common, CCDC6-*RET* (also named *RET*/PTC1), accounts for approximately 60% of *RET*-associated PTC; NCOA4-*RET* (also named *RET*/PTC3) represents approximately 30% and PRKAR1A-*RET* (*RET*/PTC2) represents 10%. Other members of *RET*/PTC family are extremely rare.[9, 11] Conflicting evidence exists on association between *RET*/PTC family members and tumour aggressiveness with any further impact on patient's prognosis.[12, 13]

RET fusions are uncommon in thyroid cancer subtypes other than PTC. FTC is generally negative for *RET* fusions. Other TCs can derive from pre-existing carcinomas and therefore inherit *RET* fusions.[14]

As mentioned above, MTC can be sporadic or hereditary with the latter contributing to inherited cancer syndromes called multiple endocrine neoplasia type 2. Almost 100% of hereditary MTC is associated with mutations of the *RET* gene.[5] The syndromes are associated with different mutations such as M918T (the highest risk with earliest onset and most aggressive phenotype), C634R or A883F among others.[4, 9]

Epidemiology

The CS reports that in the UK, TC is the 20th most common cancer accounting for 1% of all new cancer cases with approximately 3,700 new cases every year between 2015-2017[15]. The incidence has increased over the last three decades by 164% and is projected to increase even further in subsequent years.[15] Incidence rates for thyroid cancer in the UK are highest in people aged 65 to 69, and higher in males than females (1 in 332 UK males and 1 in 170 UK females will be diagnosed with thyroid cancer in their lifetime).[15]

Impact of TC

The CS highlights gaps in the literature in terms of humanistic burden of *RET*-altered TC. The company states that patients with TC have poorer HRQoL than the general population.[1] TC as a disease is a costly, resource-intensive condition with healthcare and patient costs increasing with advanced disease. The disease can affect many aspects of patient's personal life such as employment.[1]

ERG comment: Overall, the company provided an adequate overview of the disease However, some epidemiological information, such as prevalence of TC, was inadequately referenced.

2.3 Critique of company's overview of current service provision

The CS[1] states that multikinase inhibitors (MKIs) are so far the only treatments that have been appraised by NICE for the treatment of progressive, locally advanced, or metastatic thyroid cancer; these include:

- TA535: lenvatinib and sorafenib for treating DTC after radioactive iodine[16]
- TA550: vandetanib for treating MTC[17]
- TA516: cabozantinib for treating MTC[18]

Diagnostic pathway

The CS states that TC is usually diagnosed during medical evaluation of other reasons in asymptomatic patients. The most common symptoms in symptomatic patients are thyroid nodules and neck masses. Other include difficulty swallowing or breathing, pain or tenderness around the neck or ears, change in voice quality, throat clearing and cough.[19] For MTC, additional symptoms to those already described, such as flushing, loose stools or diarrhoea, can occur.[20]

Thyroid nodules are routinely evaluated with ultrasonography; diagnosis can be made by fine needle aspiration or core biopsy in addition to other tests such as imaging studies or blood tests (e.g. thyroid-stimulating hormone (TSH)).[19-21] Additionally for MTC, evaluation of blood and tumour calcitonin and carcinoembryonic antigen levels can be checked as their levels are often higher in patients with MTC than in other thyroid malignancies.[20]

In addition to the thyroid cancer diagnostic pathway, the CS states that confirmation of the *RET*-testing will be required in order to determine eligibility for selpercatinib in TC including MTC. The company highlights that single gene fluorescence in-situ hybridisation (FISH) testing used previously increased the time taken to make a molecular diagnosis and mentions the transition to next generation sequencing (NGS), completed in Genomic Hubs, which has the potential to identify genetic mutations, rearrangements and fusions (including *RET*-fusions).[22]

Treatment pathway

Treatment pathways for differentiated and undifferentiated TC vary with DTC having better long-term prognosis conditional to effective treatment. The CS stated that DTC has an overall survival rate of 84% in the UK.[15] Patients with DTC first undergo partial or full thyroidectomy followed by I^{131} (radioactive iodine) ablation. In cases of local, regional or metastatic disease in approximately 5-20% of patients not amenable to surgery, radioactive iodine therapy will be used instead.[20] However, approximately 5-15% of people with DTC will develop iodine refractory DTC for which lenvatinib and sorafenib are the only recommended treatments for DTC patients who are classified as progressive, advanced or metastatic who were not responsive to radioactive iodine, if they are tyrosine kinase inhibitor naïve (TKI; TA535).[16] For patients who are not responsive to, do not tolerate or with contraindications to treatment with MKIs there is no further treatment options other than best supportive care (BSC).

For undifferentiated TC, surgery may only be of benefit if full resection can be achieved ('debulking' surgery should be avoided). In patients undergoing resection with no evident distant disease, external beam radiotherapy and chemotherapy may be used. Palliative chemoradiation can be considered for some cases, but BSC has a principal role in the management of undifferentiated TC patients.[20]

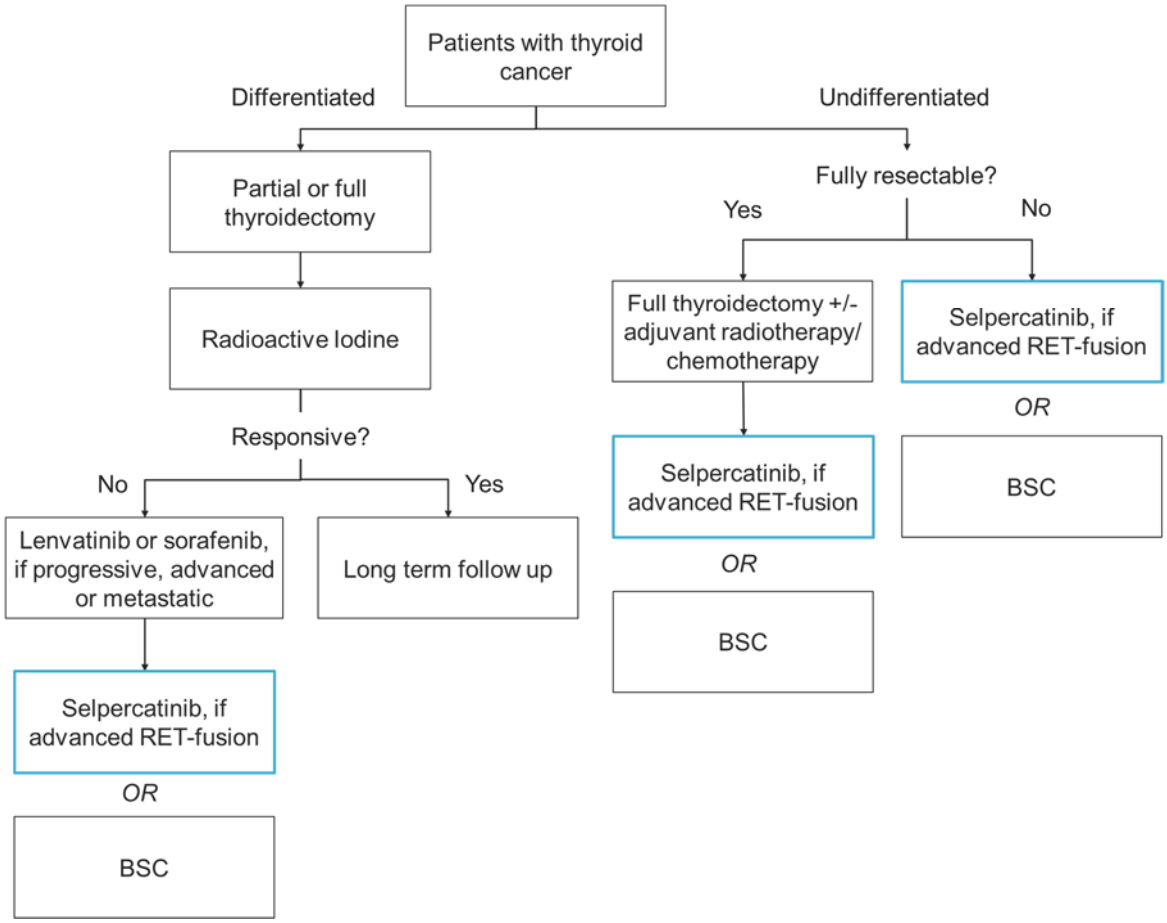
Patients with MTC typically undergo a partial or full thyroidectomy with an optional selective neck dissection. For inoperable MTC patients, radiotherapy can be used to control local symptoms.[20] Cabozantinib,[18] but not vandetanib,[17] is recommended in the UK for adult patients with progressive, unresectable locally advanced or metastatic MTC (TA516).[18] No treatments other than BSC are available for patients not responsive to or who are unable to tolerate the side effects of cabozantinib.[1]

The CS presents the selpercatinib positioning within the patient pathways:

- adults with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment (Figure 2.1).
- people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (Figure 2.2).[1]

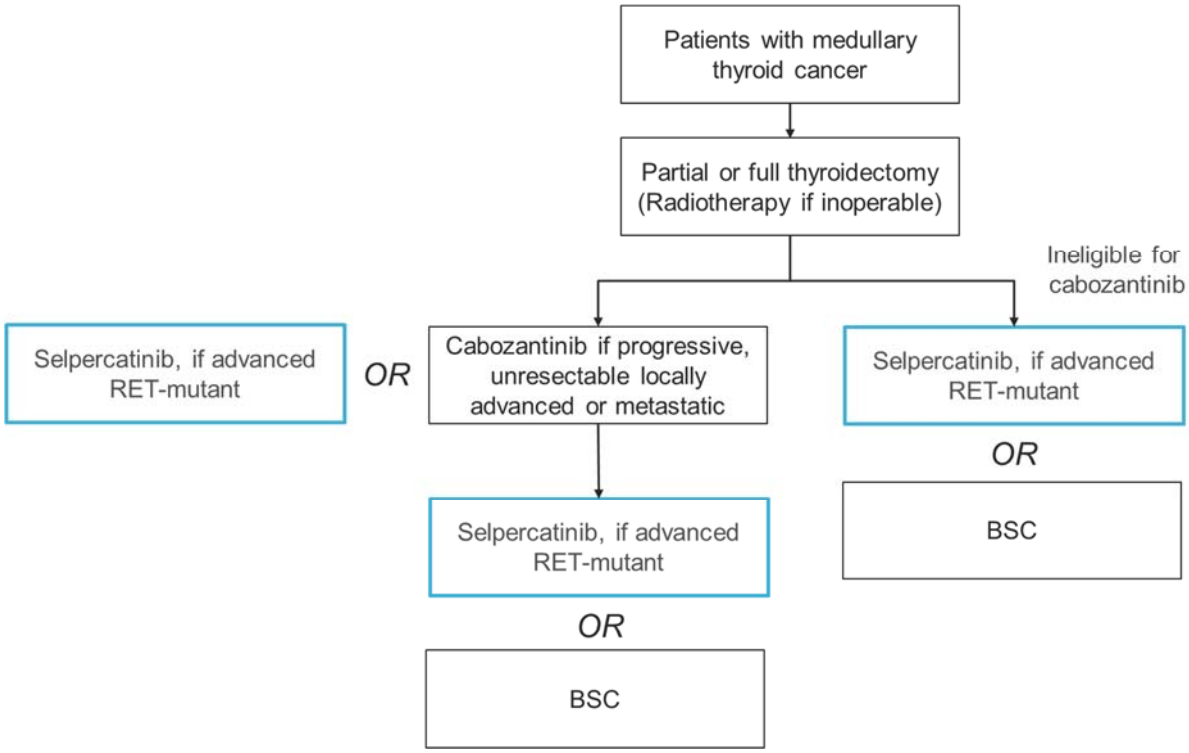
The company highlights the unmet needs in TC treatment pathways and states that, upon approval, selpercatinib would become the first selective *RET* kinase inhibitor available to patients in the UK.[1] The CS states that the use of selpercatinib can offset side effects associated with MKIs, due to its highly specific and potent targeting of *RET* alterations, in patients who progress following MKIs in *RET*-altered thyroid cancers, as a safe and effective alternative to cabozantinib for patients with *RET*-altered MTC, and as an effective treatment option for patients who are ineligible for cabozantinib due to its significant toxicity profile.[1]

Figure 2.1: Treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET* fusion-positive thyroid cancer



Source: Figure 3 of the CS[1]
Abbreviations: BSC – best supportive care; *RET* - rearranged during transfection

Figure 2.2: Treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET*-mutant medullary thyroid cancer



Source: Figure 4 of the CS[1]
Abbreviations: BSC – best supportive care; *RET* - rearranged during transfection

ERG comment: The population for *RET*-mutant MTC is narrower than in NICE's final scope[23] and includes patients from 12 years of age. No other changes to the patient population have been noted by ERG. The company provided a comprehensive summary of current practice within the UK with reference to existing guidelines and drugs currently recommended by NICE.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	*RET*-fusion positive TC: People with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment *RET*-mutant positive MTC: People with advanced *RET* mutation-positive medullary thyroid cancer (MTC) who require systemic therapy	*RET*-fusion positive TC: Adults with advanced *RET* fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment *RET*-mutant MTC: Adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer who require systemic therapy	*RET*-fusion positive thyroid cancer: The population considered in the decision problem specifies that patients must have received prior systemic therapy. This is narrower than the full anticipated marketing authorisation for selpercatinib in TC and is in line with the subgroup in the LIBRETTO-001 trial that received prior systemic therapy. *RET*-mutant MTC: This patient population is in line with the full anticipated marketing authorisation for selpercatinib in MTC and the eligibility criteria for the LIBRETTO-001 trial, where patients with MTC either received prior systemic therapy with 1 or more lines of prior cabozantinib or vandetanib or were naïve to cabozantinib or vandetanib.	The narrower population considered in the company submission is in line with updated wording for the anticipated EU conditional marketing authorisation.
Intervention	Selpercatinib	Selpercatinib	N/A – in line with NICE final scope	The intervention is in line with NICE scope
Comparator(s)	For advanced RET fusion-positive thyroid cancer which has progressed following prior treatment:	RET-fusion positive TC: • Best supportive care (BSC) or palliative care	RET-fusion positive TC: The population for the submission focusses on patients who have received prior systemic therapy, in line with the	The comparators are not in line with NICE scope. See Section 3.3 below.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Lenvatinib or sorafenib for differentiated thyroid cancer which did not respond to radioactive iodine (adults only) • Best supportive care or palliative care For advanced RET mutation-positive MTC: • Cabozantinib (adults only) • Best supportive care or palliative care	RET-mutant MTC: • Cabozantinib • Best supportive care or palliative care	previously treated subgroup of the LIBRETTO-001 trial. In clinical practice, this leaves the only remaining treatment as BSC (MKI following radioactive iodine and MKI retreatment not being permitted by TA535), thus representing the relevant comparator for RET-fusion positive differentiated TC patients. For other subtypes of TC (i.e. anaplastic or undifferentiated TC) there are no suitable systemic alternatives. Therefore, BSC is also considered a suitable comparator for these patients. RET-mutant MTC: N/A – in line with the NICE final scope. Cabozantinib is associated with significant toxicity, and thus a proportion of patients may not be eligible for first-line systemic therapy, with BSC representing the only remaining treatment option. Thus, BSC is considered a relevant comparator for patients who have progressed beyond or who are ineligible for first-line systemic therapy.	
Outcomes	• Overall survival • Progression-free survival • Response rate	Primary endpoints • Best overall response and objective response rate	N/A – in line with the NICE final scope	The outcomes reported are in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Adverse effects of treatment • Health-related quality of life	Major secondary endpoints • Duration of response • Time to response and time to best response • Clinical benefit rate • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of	NR	NR	The economic analysis was in line with the reference case, and costs were considered from an NHS and Personal Social Services perspective. The company did not include the costs of genetic testing, assuming that the transition to NGS testing will facilitate routine *RET* alongside other oncogenic drivers so that approval of selpercatinib would not result in additional costs. The ERG anticipated that the number of patients who at the time of this appraisal receive routine genetic testing was almost zero, and therefore included the costs of genetic testing in their base-case analysis. The ERG also included a scenario

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	any managed access arrangement for the intervention will be taken into account. The use of selpercatinib is conditional on the presence of RET mutation or fusion. The economic modelling should include the costs associated with diagnostic testing for RET mutation/fusion in people with advanced MTC/advanced thyroid cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.			in which genetic testing costs are excluded.
Subgroups to be considered	If the evidence allows, subgroups based on the following will be considered: • Type of thyroid cancer within advanced *RET* fusion-positive TC (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma) • Specific type of *RET* alteration (within *RET*	• No subgroups have been considered for the economic analysis by type of thyroid cancer • No subgroups have been considered for the economic analysis by specific type of *RET* alteration • For *RET* fusion-positive TC, no subgroups have been considered for the economic analysis by line of treatment	• Insufficient data were available to conduct subgroup analyses for selpercatinib according to thyroid cancer type. Patients in the thyroid cancer arm were predominantly papillary, therefore analysis is not possible for the TC population. • Insufficient data for comparator therapies were available to conduct subgroup analyses according to *RET*-alteration.	Analogous to the CS, the ERG has not included any subgroup analyses by type of TC, by specific type of RET alteration, or by line of treatment.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	fusion-positive TC or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib • Line of treatment (position in pathway)		• In the *RET* fusion-positive TC population, the population for the submission focusses on patients who have received prior systemic therapy, in line with the previously treated subgroup of the LIBRETTO-001 trial, thus subgroup analysis by line of therapy is not relevant to the decision problem. • In the *RET*-mutant MTC population, data are presented in the submission separately for patients who had received prior cabozantinib or vandetanib or who were treatment-naïve to cabozantinib or vandetanib in the LIBRETTO-001 trial. However, no data were available for comparators that were stratified by line of therapy, and thus the base case economic analysis focuses on the pooled "any-line" population as more data was available for the analysis making it more robust.	
Special considerations including issues related to equity or equality	NR	NR	NR	

Source: CS, Table 1, pages 13-16.
MKI = multikinase inhibitor; MTC = medullary thyroid cancer; NICE = National Institute for Health and Care Excellence; RET = rearranged during transfection; TC: thyroid cancer.

3.1 Population

The population defined in the scope is: 'People with advanced RET fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment' and 'People with advanced RET mutation-positive medullary thyroid cancer (MTC) who require systemic therapy'.[23] The population in the CS is limited to 'Adults with advanced RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior systemic treatment' and 'Adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer who require systemic therapy'.[1]

The first population is limited to adults only and to patients who have progressed following prior **systemic** treatment. This is in narrower than the original full anticipated marketing authorisation for selpercatinib in TC but is in line with the updated wording for the anticipated EU conditional marketing authorisation. The second population is in line with the full anticipated marketing authorisation for selpercatinib in MTC.

For the first population, the company have provided data for the subgroup in the LIBRETTO-001 trial that received prior systemic therapy. The second population is in line with the eligibility criteria for the LIBRETTO-001 trial, where patients with MTC either received prior systemic therapy with one or more lines of prior cabozantinib or vandetanib, or were naïve to cabozantinib or vandetanib (CS, Table 1, page 13).[1]

A conditional marketing authorisation application for selpercatinib for the treatment of RET-fusion positive TC and RET-mutant MTC was submitted to the European Medicines Agency (EMA) on 20th December 2019 and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 10th December 2020.

The EU marketing authorisation wording for the selpercatinib indications of interest for this submission are:

- "Selpercatinib as monotherapy is indicated for the treatment of adults with advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with lenvatinib and/or sorafenib"
- "Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib"

The recommended dose of selpercatinib is 160 mg orally, twice daily. Treatment should be continued until disease progression or unacceptable toxicity.

3.2 Intervention

The intervention (selpercatinib) is in line with the scope.

Selpercatinib is an orally available, selective small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.

According to the company, the following additional tests and investigations are necessary:[1]

- An accurate and validated assay for the presence of a RET gene fusion (non-small cell lung cancer (NSCLC) and thyroid cancer) or mutation (MTC) in tumour specimens is necessary for the selection of patients for treatment with selpercatinib.

- Either RET fusion-positive or RET-mutant status should be established prior to initiation of selpercatinib therapy. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.
- While RET-mutant or RET fusion-positive status must be established prior to initiation of selpercatinib therapy, RET, next generation sequencing (NGS) and fluorescent in situ hybridisation (FISH) testing is included in the 2019/2020 National Genomic Test Directory for Cancer. In England, the transition to NGS testing, completed at Genomic Hubs, means it will be possible to test for RET rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres.

ERG comment: The company did not include the costs of genetic testing, assuming that the transition to NGS testing will facilitate routine RET alongside other oncogenic drivers so that approval of selpercatinib would not result in additional costs. The ERG anticipated that the number of patients who at the time of this appraisal receive routine genetic testing was almost zero, and therefore included the costs of genetic testing in their base case analysis. The ERG also included a scenario in which genetic testing costs are excluded.

3.3 Comparators

The description of the comparators in the NICE scope is as follows:[23]

- For advanced RET fusion-positive thyroid cancer which has progressed following prior treatment:
  - lenvatinib or sorafenib for differentiated thyroid cancer which did not respond to radioactive iodine (adults only)
  - best supportive care or palliative care
- For advanced RET mutation-positive MTC:
  - cabozantinib (adults only)
  - best supportive care or palliative care

Regarding advanced RET fusion-positive thyroid cancer, the company states that 'the population for the submission focusses on patients who have received prior systemic therapy. In clinical practice, this leaves the only remaining treatment as BSC (MKI following radioactive iodine and MKI retreatment not being permitted by TA535), thus representing the relevant comparator for RET-fusion positive differentiated TC patients'.[1]

ERG comment: In the response to clarification[24] the company stated further that the wording of the anticipated conditional marketing authorisation for selpercatinib in RET fusion-positive thyroid cancer has been updated to the following: "[redacted]". This new wording specifies [redacted] and is in line with the original positioning as outlined above. According to the company, comparisons of selpercatinib with lenvatinib and sorafenib are therefore not relevant for this patient population, since further MKI retreatment is not permitted by TA535 following progression.[16]

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival
- Progression-free survival
- Response rate
- Adverse effects of treatment
- Health-related quality of life

These were all assessed in the LIBRETTO-001 trial. In addition, duration of response, time to response and time to best response and clinical benefit rate were included as outcome measures. However, most of these outcomes were only reported for selpercatinib, as the LIBRETTO-001 trial was a one-arm study and did not include any comparator treatments. Only OS and PFS were reported for the comparative results.

3.5 Other relevant factors

According to the company, selpercatinib is innovative because it offers a novel treatment approach and is the first treatment of its kind to demonstrate efficacy in RET altered TC patients through highly selective targeting of the RET receptor (CS, Section B.2.11).[1]

[redacted] (CS Table 2, page 19).[1]

According to the company, selpercatinib should be considered as an end of life treatment for adult patients with RET fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment and for adults and people aged 12 years and over with advanced RET-mutant MTC who require systemic therapy who have previously received or who are ineligible for cabozantinib, given (a) these patients have a short life expectancy, normally less than two years and (b) there is sufficient evidence to indicate that the selpercatinib offers an extension to life of at least an additional three months, compared with current NHS treatment (CS, Section B.2.12.1).[1] The ERG is not convinced there is robust evidence to say that selpercatinib meets the end-of-life criteria (see Section 8 in this report).

According to the company, no equality issues related to the use of selpercatinib in this indication have been identified or are foreseen (CS, Section B.1.4).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of the CS provided details of the systematic literature search used to identify clinical efficacy and safety evidence. Database searches were conducted on 25 September 2019, 14-15 October 2019 and 2 December 2019. A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for clinical efficacy and safety

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Elsevier	Not reported	25 September 2019
	PubMed	Not reported	Not reported	25 September 2019
	Cochrane Library	Not reported	Not reported	25 September 2019
Conference proceedings	ESMO	https://www.esmo.org/	2019	2 December 2019
	IASLC	https://www.iaslc.org/	2019	2 December 2019
Clinical trial registries	ClinicalTrials.gov	https://clinicaltrials.gov	-	14 October 2019
	WHO ICTRP	http://www.who.int/ictrp/en/	-	15 October 2019
Bibliographic lists of relevant systematic reviews and meta-analyses were searched.				
ESMO = European Society for Medical Oncology; IASLC = International Association for the Study of Lung Cancer; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform				

ERG comments:

- The selection of databases searched was satisfactory. The database name and date searched were provided. The host platform and database issue number were not provided for the Cochrane Library, and the database date range was not provided for any of the databases searched.
- Conference proceedings were searched (2019). Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS, but full details of the conference proceedings searches were provided in response to the ERG clarification letter.
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS. Full details of the trials register searches were provided in response to the ERG clarification letter.
- The database search strategies were not clearly reported; a population facet for NSCLC, search terms for second-line therapy, and eight comparators were included in the search strategies, but these lines were greyed out and not used in the final set of results. The search strategies would have been clearer if these redundant lines had been removed.
- The final line in all three database search strategies (total excluding PTC/DTC) were redundant.

- Study design filters were included for RCTs and single arm trials. It is not clear if the study design filters were based on validated search filters, such as those published on the ISSG Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/. It is recommended practice to provide citation details of any study design filters used.[25]
- The ERG noted that an RCT filter was included in the Cochrane Library search. As this consists of prefiltered databases of clinical trials and systematic reviews the ERG believes it was not necessary to include this facet, as this may have resulted in unnecessarily restricting the results retrieved.
- There were no search terms for safety included in the search strategies. CRD guidance[26] recommends that if searches have been limited by inclusion of a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. Ideally, this would entail searching for adverse effects alongside the efficacy searches without any study design filters, and would include generic and specific adverse effect and safety search terms.[27]
- Truncation was used inconsistently throughout, and proximity operators were only occasionally used. Better use of these powerful search tools would have enhanced the search strategies, making them more sensitive and may have identified more potentially useful studies.
- There was a search line limiting 'articles' and 'conference abstracts' by date (articles, September 2015 to September 2019; 'conference abstracts', September 2017 to September 2019). This would have been a major cause for concern to the ERG as date limits are not reported anywhere in the search methods and could have resulted in relevant studies being missed. However, the unusual set combination for the final results, where the date limits were combined with a redundant line for NSCLC and with Boolean OR, meant that this date limit was irrelevant.
- The searches were conducted in September, October and December 2019. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since 2019.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria were specified over two phases. During level 1 screening, titles and abstracts of studies were identified. Level 2 screening involved the review of full text studies. The eligibility criteria used are presented in Table 4.2.

Table 4.2: Eligibility criteria used for SLR of clinical trial evidence

Criteria	Inclusion Criteria	Exclusion Criteria
Level 1		
Population	• Adult and paediatric patients • RET tumours	• Other types of cancer
Interventions	• LOXO-292 MTC • Cabozantinib • Vandetanib • Best supportive care PTC • Sorafenib • Lenvatinib • Best supportive care	• Studies that do not have an intervention of interest in at least one arm.

Criteria	Inclusion Criteria	Exclusion Criteria
Comparators	• Any active systemic therapy, placebo, best supportive care, or no treatment	• Studies that do not have a comparator of interest in at least 1 arm (unless single-arm RET) • Nonpharmacological treatment
Study Design	• Randomised, controlled, prospective clinical trials • Systematic reviews (including meta-analyses) • Single-arm trials or RCTs in RET-altered tumours (any tumour site, any intervention, any line of therapy)	• Preclinical trials • Prognostic studies • Retrospective studies • Prospective observational studies • Case reports • Commentaries and letters (publication types) • Consensus reports • Non-systematic reviews
Language	• All languages	• None
Date	• None	• None
Level 2		
Population	• Adult and paediatric patients • RET tumours	• Other types of cancer
Interventions	• LOXO-292 MTC • Cabozantinib • Vandetanib • Best supportive care PTC • Sorafenib • Lenvatinib • Best supportive care	• Studies that do not have an intervention of interest in at least one arm.
Comparators	• Any active systemic therapy, placebo, best supportive care, or no treatment	• Studies that do not have a comparator of interest in at least 1 arm (unless single-arm RET) • Nonpharmacological treatment
Study Design	• Randomised, controlled, prospective clinical trials • Systematic reviews (including meta-analyses) • Single-arm trials or RCTs in RET-altered tumours (any tumour site, any intervention, any line of therapy)	• Systematic reviews and meta-analyses
Outcomes	• To be included in the review, a study must report at least 1 of the outcomes of interest • Efficacy outcomes: -Progression-free survival -Overall survival -Overall response rate • Safety outcomes: -Overall AEs -Serious AEs -Grade 3 or 4 AEs -Discontinuation due to AEs	• Studies that do not report at least 1 outcome of interest

Criteria	Inclusion Criteria	Exclusion Criteria
	-Mortality -TRAES -Specific AEs: ➢ Nausea ➢ Rash ➢ Neutropenia ➢ Thrombocytopenia ➢ Bleeding rate ➢ Hypertension ➢ Fatigue • Febrile neutropenia	
Language	• All languages	• None
Date	• None	• None
Source: CS, Tables 4 and 5 of the Appendix AE= adverse event; MTC= medullary thyroid cancer; NSCLC= non-small cell lung cancer; PTC= papillary thyroid cancer; RCT= randomised controlled trials; RET= rearrangements and/or mutations during transfection; TRAES= treatment related adverse events		

ERG comment: The inclusion criteria seem appropriate given the scope of this appraisal.

4.1.3 Critique of data extraction

There was no mention of the data extraction process in the CS or the supporting documents.

ERG comment: The data extraction process was unclear due to no mention of the number of authors involved nor confirmation of how the process was completed.

4.1.4 Quality assessment

The LIBRETTO-001 trial was subjected to a risk of bias assessment based on NICE requirements and was considered to be at low risk of bias, with some points being inconclusive due to the trial being ongoing.[1]

ERG comment: The ERG has no further comment regarding quality assessment.

4.1.5 Evidence synthesis

The company notes a network meta-analysis was not possible due to the LIBRETTO-001 trial being a single arm trial. They performed an unanchored matching-adjusted indirect comparison (MAIC) for the RET-mutant MTC population and an indirect comparison for the RET fusion-positive population, further details are provided in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company has used one trial, LIBRETTO-001, to provide evidence for the present submission. The LIBRETTO-001 trial is an ongoing, multicentre, single arm, open-label study with the intent of studying the pharmacokinetics, safety, and maximum tolerated dose of selpercatinib and to permit a preliminary efficacy and safety assessment in patients with RET-altered solid tumours.[1] The company recognises that the eligible population for the LIBRETTO-001 trial was broader than the population of relevance

for the submission.[1] However, the company notes that a subset of the study patients are in line with the population of relevance, which include adults, whose treatment includes monotherapy, with advanced RET fusion-positive thyroid cancer (PTC) who require systemic therapy and whose disease has progressed following prior systemic treatment and people aged 12 years and over with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. Information about the LIBRETTO-001 trial is presented in Table 4.3.

Table 4.3: Clinical effectiveness evidence in the company submission

Study	**LIBRETTO-001 (NCT03157128)**
Design (N)	Multicentre, open-label, Phase I/II study in patients with advanced solid tumours, with RET activations (N=[redacted]).
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including RET fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation) who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator, were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and an ECOG ≥2 or LPS≥40%. As of the 16 December 2019 data cut-off, enrolled patients included: • 226 patients with RET-mutant MTC • 27 patients with RET fusion-positive thyroid cancer
Intervention	Selpercatinib, once or twice daily, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study.
Comparator	N/A
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • DOR • PFS • OS HRQoL: • EORTC QLQ-C30 Safety outcomes: • AEs • Changes from baseline in clinical safety laboratory and vital signs
All other reported outcomes	• Best overall response • Clinical benefit rate • Best change in tumour size from baseline • CNS ORR • CNS DOR • Time to any and best response • Determination of the safety and tolerability of selpercatinib • Characterisation of the pharmacokinetic properties
Duration of study and follow-up	The study is ongoing. The first patient was treated on 9 May 2017. At the latest data cut-off of 16 December 2019, the median follow-up was [redacted]. Individual patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity, or other reasons for treatment discontinuation. Four weeks after the last dose of the study drug, all treated patients underwent a SFU

Study	LIBRETTO-001 (NCT03157128)
	assessment. All patients were also to undergo LTFU assessments every 3 months.
Countries	Australia, Canada, Denmark, France, Germany, Hong Kong, Japan, Israel, Italy, Singapore, Spain, South Korea, Switzerland, Taiwan, United Kingdom, and the United States.

Source: Adapted from Table 3 and Table 5 of the CS[1]
Abbreviations: AE: adverse event; BID: twice daily; BOR: best overall response; CBR: clinical benefit rate; CNS: central nervous system; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; LPS: Lansky Performance Score; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RET: rearranged during transfection; TC: thyroid cancer.
Note: BOR as an abbreviation was used for both best objective rate and best overall rate in the company submission; ORR as an abbreviation was used for both overall response rate and objective response rate. In this report we used the same.

4.2.2 Methodology of included studies

4.2.2.1 LIBRETTO-001

LIBRETTO-001 is a multicentre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET-alterations. Patients were included in the study provided that they were at least 18 years of age, however, if sites approved, patients as young as 12 could participate. Patients also had to have a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy. The CS noted that as of the 16 December 2019 data cut-off, the enrolled participants included 226 patients with RET-mutant MTC and 27 patients with RET fusion-positive thyroid cancer.

Phase I of the LIBRETTO-001 study was the dose escalation phase during which patients were not selected based on RET alteration. The Phase I objective was to determine the maximum tolerated dose (MTD) and the recommended dose for Phase II. A 3+3 dose escalation design was used, in which the three to six patients were enrolled in each dose level cohort. The starting dose of selpercatinib was a once daily 20 mg capsule for 1 Cycle consisting of 28 days. Patients received doses ranging from 20 mg once daily to 240 mg twice daily, depending on the dose level assignment. Escalations were completed in increments of 100% above the previous dose for the first three escalations. After the third dose increase, smaller dose increments were used, with increments ranging from 33-67%, with additional dose escalations if needed.

During Phase II, the dose expansion phase, five cohorts of patients harbouring RET alterations were defined and selpercatinib safety and efficacy was assessed. The five cohorts are described in Table 4.4.

Table 4.4: LIBRETTO-001 patient cohorts

Patient cohort	Description
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib

Cohort 4	*RET*-mutant MTC without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity
Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample
Source: Table 4 of the CS [1] Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RET: rearranged during transfection.	

The primary endpoint of Phase II was to identify the ORR, as appropriate to the tumour type.

Four weeks after receiving the last dose, patients had a safety follow-up (SFU) assessment. Patients also completed follow-up assessments every three months. Patients could continue selpercatinib if they were determined to be receiving a clinical benefit.

ERG comment: The company noted a full clinical study report (CSR) for the LIBRETTO-001 study was unavailable. Instead the company provided a Summary of Clinical Efficacy and a Summary of Clinical Safety.

4.2.3 Baseline characteristics

The baseline and disease characteristics of the of patients with RET-mutant MTC in the LIBRETTO-001 study are presented in Table 4.5.

Table 4.5: Baseline demographics and disease characteristics of patients with *RET*-mutant MTC in the LIBRETTO-001 trial

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88	SAS2 Non-measurable disease n=14	Total n=226
Age, years					
Median	57.0	[redacted]	58.0	[redacted]	[redacted]
Range	17–84	[redacted]	15–82	[redacted]	[redacted]
Overall age group, n (%)					
<18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18–44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45–64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)					

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) n=55	**IAS Prior cabozantinib /vandetanib n=124**	**SAS1 Cabozantinib/ vandetanib-naïve n=88**	**SAS2 Non-measurable disease n=14**	**Total n=226**
Male	36 (65.6)	[redacted]	58 (65.9)	[redacted]	[redacted]
Female	19 (34.5)	[redacted]	30 (34.1)	[redacted]	[redacted]
Race, n (%)					
White	49 (89.1)	[redacted]	75 (85.2)	[redacted]	[redacted]
Black	1 (1.8)	[redacted]	1 (1.1)	[redacted]	[redacted]
Asian	0	[redacted]	4 (4.5)	[redacted]	[redacted]
Other/Missing	5 (9.1)	[redacted]	8 (9.1)	[redacted]	[redacted]
Ethnicity, n (%)					
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body weight (kg)					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height (cm)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body mass index, kg/m^2					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG, n (%)					
0	11 (20.0)	[redacted]	43 (48.9)	[redacted]	[redacted]
1	41 (74.5)	[redacted]	42 (47.7)	[redacted]	[redacted]
2	3 (5.5)	[redacted]	3 (3.4)	[redacted]	[redacted]
Stage at initial diagnosis, n (%)					
I–III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) n=55	**IAS Prior cabozantinib /vandetanib n=124**	**SAS1 Cabozantinib/ vandetanib-naïve n=88**	**SAS2 Non-measurable disease n=14**	**Total n=226**
IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis, months					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of metastatic disease, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis of metastatic disease, months					
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of diarrhoea at baseline, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcitonin (pg/ml)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CEA (ng/ml)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour burden (at least one measurable lesion per Investigator), n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 11 of the CS[1]

Abbreviations: CEA: carcinoembryonic antigen; ECOG: Eastern Cooperative Oncology Group; IAS: Prior Platinum Chemotherapy; MTC: medullary thyroid cancer; PAS: Primary Analysis Set; RET: rearranged during transfection; SAS1: Treatment-naïve; SAS2: Prior Other Systemic Therapy; SAS3: Non-measurable Disease

The RET-mutant MTC IAS patients were identified as being comprised of a heavily pre-treated population with over a quarter receiving at least three prior systemic regimens. The number of prior

systemic therapies included [redacted]. The breakdown of prior cancer-related treatments for the RET-mutant MTC patients is depicted in Table 4.6.

Table 4.6: Prior cancer-related treatments for *RET*-mutant MTC patients in the LIBRETTO-001 trial

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) n=55	**IAS Prior cabozantinib /vandetanib n=124**	**SAS1 Cabozantinib/ vandetanib-naïve n=88**	**SAS2 Non-measurable disease n=14**	**Total n=226**
Received prior systemic therapy, n (%)					
Yes	55 (100.0)	[redacted]	[redacted]	[redacted]	[redacted]
No	0	[redacted]	[redacted]	[redacted]	[redacted]
Type of prior systemic therapy, n (%)					
MKI	55 (100.0)	[redacted]	7 (8.0)	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other MKIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radioactive Iodine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxane Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Systemic Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic regimens, n (%)					
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1–2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic regimens					
Median	2.0	[redacted]	0.0	[redacted]	[redacted]
Range	1–8	[redacted]	0–2	[redacted]	[redacted]
Best response to last systemic treatment, n (%)					
Partial response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	*RET*-mutant MTC				
	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88	SAS2 Non-measurable disease n=14	Total n=226
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer-related surgery, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Table 12 of the CS[1] Abbreviations: PAS: Primary Analysis Set; IAS: Prior Platinum Chemotherapy; SAS1: Treatment-naïve; SAS2: Prior Other Systemic Therapy; SAS3: Non-measurable Disease.					

The CS noted that of the 27 patients with RET fusion-positive TC, 19 patients received a prior systemic treatment. Eight RET fusion-positive TC patients were identified as systemic therapy naïve. The baseline demographics of the RET fusion-positive TC patients are depicted in Table 4.7.

Table 4.7: Baseline demographics of patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	Previously treated[a] n=19	Systemic therapy naïve[b] n=8	*RET* fusion-positive TC n=27
Age, years			
Median	54.0	[redacted]	[redacted]
Range	25–88	[redacted]	[redacted]
Overall age group, n (%)			
18–44 years	[redacted]	[redacted]	[redacted]
45–64 years	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	9 (47.4)	[redacted]	[redacted]
Female	10 (52.6)	[redacted]	[redacted]
Race, n (%)			
White	14 (73.7)	[redacted]	[redacted]
Black	1 (5.3)	[redacted]	[redacted]
Asian	2 (10.5)	[redacted]	[redacted]
Other/Missing	2 (10.5)	[redacted]	[redacted]

	Previously treated[a] n=19	Systemic therapy naïve[b] n=8	*RET* fusion-positive TC n=27
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Height (cm)			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Body weight (kg)			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Body mass index, kg/m2			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Baseline ECOG, n (%)			
0	5 (26.3)	[redacted]	[redacted]
1	12 (63.2)	[redacted]	[redacted]
2	2 (10.5)	[redacted]	[redacted]
Smoking history, n (%)			
Never smoked	[redacted]	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Source: Table 14 of the CS[1]

[a]≥1 systemic therapy in addition to RAI, [b]No prior systemic therapy other than RAI

Abbreviations: ECOG: Eastern Cooperative Oncology Group; RAI: radioactive iodine; RET: rearrange during transfection.

Of the *RET* fusion-positive TC patients [redacted] had received radioactive iodine (RAI) as a prior form of treatment and [redacted] had received at least three prior regimens. The summary of prior cancer-related treatments experienced by RET fusion-positive TC patients is provided in Table 4.8.

Table 4.8: Prior cancer-related treatments for *RET* fusion-positive TC patients in the LIBRETTO-001 trial

Characteristic	*RET* fusion-positive TC n=27
Received prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Type of prior systemic therapy, n (%)	
MKI	[redacted]
Cabozantinib	[redacted]
Vandetanib	[redacted]
Sorafenib	[redacted]
Lenvatinib	[redacted]
Other MKIs	[redacted]
Chemotherapy	[redacted]
Platinum chemotherapy	[redacted]
Radioactive iodine	[redacted]
Anti-PD1/PD-L1 therapy	[redacted]
Taxane chemotherapy	[redacted]
Other systemic therapy	[redacted]
Number of prior systemic regimens, n (%)	
0	[redacted]
1–2	[redacted]
≥3	[redacted]
Prior systemic regimens	
Median	[redacted]
Range	[redacted]
Best response to last systemic treatment, n (%)	
Partial response	[redacted]
Stable disease	[redacted]
Progressive disease	[redacted]
Not Evaluated	[redacted]
Unknown	[redacted]
Prior radiotherapy, n (%)	[redacted]
Prior cancer-related surgery, n (%)	[redacted]

Source: Table 16 of the CS[1]
Abbreviations: RAI: radioactive iodine; RET: rearrange during transfection.

As of the 16 December 2019 data cut-off, disposition of patients of *RET*-mutant MTC and *RET* fusion-positive TC in the LIBRETTO-001 trial is presented in Tables 4.9 and 4.10, respectively.

Table 4.9: Patient disposition of RET-mutant MTC patients in the LIBRETTO-001 trial

	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88	SAS2 Non-measurable disease n=14	Total n=226
Treatment ongoing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated post-progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status continuing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 17 of the CS[1]
Abbreviations: PAS: Primary Analysis Set; IAS: Integrated Analysis Set; SAS1: cabozantinib/vandetanib-naïve; SAS2: non-measurable disease.

Table 4.10: Patient disposition of *RET* fusion-positive TC patients in the LIBRETTO-001 trial

	RET fusion-positive TC n=27
Treatment Ongoing, n (%)	[redacted]
Discontinuation, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Non-compliance	[redacted]
Withdrawal of consent	[redacted]

	***RET* fusion-positive TC n=27**
Treated post-progression, n (%)	[redacted]
Study status continuing, n (%)	[redacted]
Study status discontinued, n (%)	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]
Source: Table 18 of the CS[1] Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.	

ERG comment: The ERG highlights the very low number of patients in the *RET* fusion-positive TC population (27 patients overall).

4.2.4 Statistical analyses

Details of the statistical methods of the LIBRETTO-001 trial are presented in Table 4.11. All results were descriptive and reported as estimates with 95% confidence interval (CI). There was no statistical hypothesis testing.

Table 4.11: Statistical methods of the LIBRETTO-001 trial

Trial name	LIBRETTO-001
Hypothesis objective	Phase I • The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib Phase II • The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	• Efficacy analyses per starting dose may not provide dose–response information, given that intra-patient dose escalation was allowed during Phase I. Therefore, efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyses • The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the investigator are presented in Appendix L • For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response • Best overall response was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e. the crude proportion of patients with best overall response of CR or PR) • Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions • The estimate of the ORR was accompanied by two-sided 95% exact binomial confidence intervals (CI)
Sample size, power calculation	**Phase I** • Three to six patients were to be enrolled in each dose cohort based on a 3+3 design. Each patient was to participate in only a single dose cohort for the purpose of DLT evaluation (however, after completion of the DLT evaluation period, intra-patient dose escalation was allowed, provided that the patient was tolerating their current dose, and the dose level to which the patient was escalated to had already been evaluated, had a DLT rate of <33%, and was declared safe by the SRC) • A starting sample size of at least three patients per dose cohort, expanding to six patients in the event of a marginal DLT rate (30%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e. observing

Trial name	LIBRETTO-001
	two or more patients with DLT). If a true DLT rate of 50% was assumed, then there would be an 89% chance that dose escalation would be halted in a given cohort • During Phase I, selected dose cohorts previously declared safe by the SRC could be expanded to a total of approximately 15 patients to further investigate the tolerability, PK and biological activity of selpercatinib • The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1–8), a total of approximately 120 patients would be enrolled in Phase I **Phase II** • For Cohort 1 (patients with *RET* fusion-positive solid tumours who progressed on or were intolerant to standard first-line therapy for their cancers), a true ORR of ≥50% was hypothesised when selpercatinib was administered to patients with such malignancies. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%. Ruling out a lower limit of 30% was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly defined patient populations who have failed prior therapies • For Cohort 2 (patients with *RET* fusion-positive solid tumours without prior standard first-line therapy), a true ORR of ≥55% was hypothesised when selpercatinib was administered to such patients. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35% • For Cohort 3 (patients with *RET*-mutant MTC who progressed on or were intolerant to vandetanib and/or cabozantinib), a true ORR of ≥ 35% was hypothesised when selpercatinib was administered to such patients. A sample size of 83 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% was considered clinically meaningful in patients who have failed prior MKI therapy (e.g., cabozantinib) and currently have limited treatment options for their advancing disease • For Cohort 4 (patients with *RET*-mutant MTC who are MKI-naïve), a true ORR of ≥ 50% was hypothesised when selpercatinib was administered to such patients. A sample size of 55 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%. • Notwithstanding the statistical considerations above, if approved by the SRC, enrolment beyond the above sample sizes in each of Cohorts 1 through 5, was allowed, in order to accommodate enrolment demand and allow for the characterisation of AEs that may occur with low frequency

Trial name	LIBRETTO-001
	• With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% was 77.9% and 95.2%, respectively. Up to ~150 patients in Cohort 1 would be allowed to accommodate enrolment of other *RET* fusion-positive solid tumours
Data management, patient withdrawals	Data censoring conditions for DOR, OS and PFS were as described below. If a patient met more than one of these conditions, then the scenario that occurred first was used for the analysis. **DOR and OS** DOR and OS were right censored for patients who met one or more of the following conditions: • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression o Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or experienced documented disease progression after missing two or more consecutively scheduled disease assessment visits o Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit • Alive and without documented disease progression on or before the data cut-off date o Censored at the date of the last evaluable disease assessment **PFS** PFS was right censored for patients who met one or more of the following conditions: • No postbaseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event) o Censored at the date of the first dose of selpercatinib • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression o Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits o Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit • Alive and without documented disease progression on or before the data cut-off date o Censored at the date of the last evaluable disease assessment
Source: Table 7 of the CS	

Trial name	**LIBRETTO-001**
AE = adverse event; CI = confidence interval; DLT = dose limiting toxicity; DOR = duration of response; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; RET = rearranged during transfection; PFS = progression-free survival; PK = pharmacokinetic; RP2D = recommended Phase II dose; SRC = Safety Review Committee.	

ERG comment: LIBRETTO-001 was a single-arm study and no statistical hypothesis testing was performed. The methods used to present the data appeared to be appropriate.

4.2.5 Results

The company noted that the presented results are based on the 16 December 2019 data cut-off, unless otherwise disclosed. Of the 531 patients comprised of the LIBRETTO-001 trial who had been treated with selpercatinib as of 17 June 2019, [redacted] patients were treated with RP2D of 160 mg twice daily. The efficacy data for new patients treated between 18 June 2019 and 16 December 2019 was not included in the CS.

4.2.5.1 RET-mutant medullary thyroid cancer

Objective response rate

The objective response rate (ORR) was defined as the proportion of patients with the best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. The CS presented the BOR and ORR for RET-mutant MTC patients in Table 4.12.

Table 4.12: Best overall response and objective response rate for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/vandetanib-naïve n=88
No. of eligible patients[a], n	[redacted]	[redacted]	[redacted]
Best overall response, n (%)			
Complete response	5 (9.1)	[redacted]	10 (11.4)
Partial response	33 (60.0)	[redacted]	54 (61.4)
Stable disease	14 (25.5)	[redacted]	20 (22.7)
Progressive disease	1 (1.8)	[redacted]	2 (2.3)
Not evaluable	2 (3.6)	[redacted]	2 (2.3)
Objective response rate (CR + PR)			
n (%)	38 (69.1)	[redacted]	64 (72.7)
95% CI	55.2, 80.9	[redacted]	(62.2, 81.7)

Source: Table 20 of the CS[1]
[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP), i.e., all patients treated on or before 17 December 2018.
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set IRC: Independent Review Committee; MTC: medullary thyroid cancer; No.: number; PAS: Primary Analysis Set; PR: partial response; RET: rearranged during transfection; SAP: statistical analysis plan; SAS1: Treatment-naïve.

The CS presented Waterfall plots of best change in tumour size per RECIST v1.1 in *RET*-mutant MTC for the PAS (Figure 4.1), IAS (Figure 4.2), and SAS1 (Figure 4.3).

Figure 4.1: Waterfall plot of best change in tumour size in RET-mutant MTC (PAS)

Source: Figure 7 of the CS[1]
Note: Seven patients are not shown due to 5 having non-target lesions only, and 2 patients discontinued treatment prior to first post-baseline assessment.
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Figure 4.2: Waterfall plot of best change in tumour size in RET-mutant MTC (IAS)

Source: Figure 8 of the CS[1]
Eleven patients are not shown due to 5 having non-target lesions only, and 6 patients do not have post-baseline target lesion measurement.
Abbreviations: CR = complete response; NE = not estimable; PD: = progressive disease; PR = partial response; SD = stable disease.

Figure 4.3: Waterfall plot of best change in tumour size in *RET*-mutant MTC (SAS1)

Source: Figure 9 of the CS[1]
Eight patients are not shown due to six patients having non-target lesions only (though assessed otherwise by the investigator and thus included in SAS1), and 2 do not have post-baseline target lesions measurement.
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Duration of response

Duration of response (DOR) was defined as the number of months from the start date of CR or PR (whichever was first) and subsequently confirmed, to the first date that recurrent or progressive disease was objectively documented. In case of patient death, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death was used to denote the response end date. The DOR of the PAS, IAS and SAS1 for RET-mutant MTC patients are summarised in Table 4.13.

Table 4.13: Duration of response for RET-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) n=55	**IAS Prior cabozantinib /vandetanib n=124**	**SAS1 Cabozantinib/vandetanib-naïve n=88**
Responders (n)	38	[redacted]	64
Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)			
Median	NE	[redacted]	21.95[a]
95% CI	19.1, NE	[redacted]	NE, NE
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of duration of response			

	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/vandetanib-naïve n=88
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)			
Median	14.06	[redacted]	7.79
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)[b]			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
Response status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no prior disease progression)	[redacted]	[redacted]	[redacted]
Censored	32 (84.2)	[redacted]	60 (93.8)
Probability (%) of remaining in response (Kaplan–Meier estimate)			
6 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

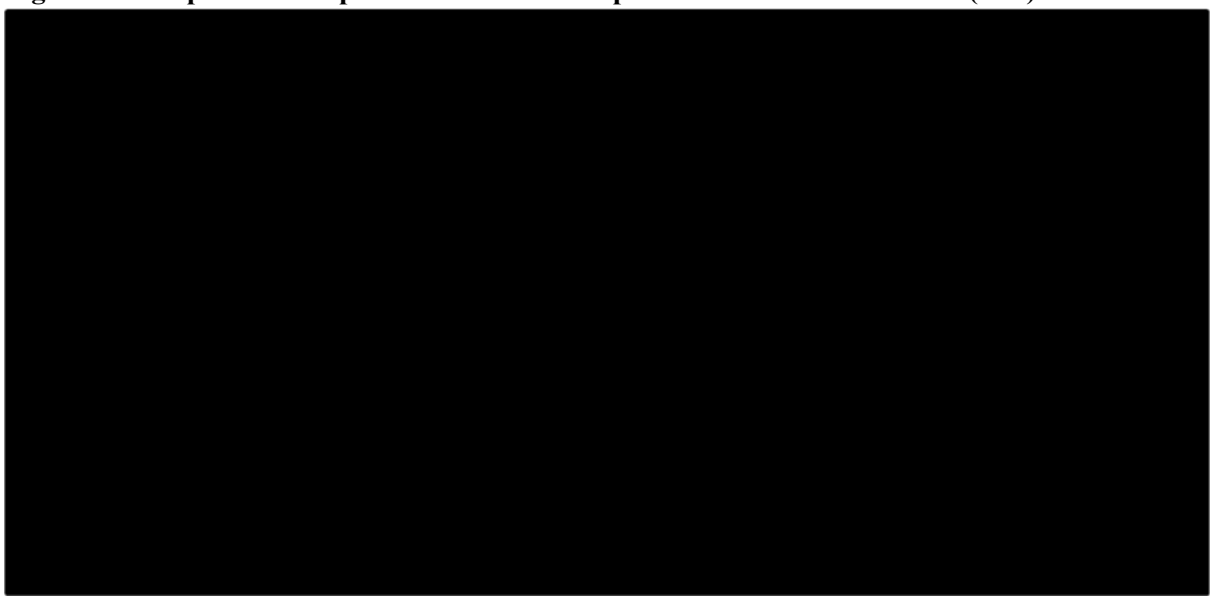
Source: Table 21 of the CS[1]
[a]Note that these median estimates are highly unreliable due to data immaturity, as evidenced by the inability to evaluate a confidence interval. [b]Includes censored patients who have not yet progressed
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IAS: prior platinum chemotherapy; NE: not estimable; PAS: Primary Analysis Set; PD: disease progression; SAS1: treatment-naïve.

Kaplan–Meier plots of DOR for PAS, IAS and SAS1 are presented in Figure 4.4, Figure 4.5 and Figure 4.6, respectively. The CS notes that median DOR was not reached by the 16 December 2019 (the CS mentions the date as 17 December 2020, but the company confirmed this was an error) data cut-off date in the PAS and IAS groups due to a low number of events and the large numbers of patients still on treatment and in response (see Tables 4.9 and 4.10 above). As for the SAS1 group, median DOR estimates are immature, as evidenced by the inability to evaluate a confidence interval.

Figure 4.4: Kaplan–Meier plot of duration of response in RET-mutant MTC (PAS)

Source: Figure 10 of the CS[1]
Abbreviations: DOR: duration of response; No.: number.

Figure 4.5: Kaplan–Meier plot of duration of response in RET-mutant MTC (IAS)



Source: Figure 11 of the CS[1]
Abbreviations: DOR: duration of response; No.: number.

Figure 4.6: Kaplan–Meier plot of duration of response in RET-mutant MTC (SAS1)

Source: Figure 12 of the CS[1]
Abbreviations: DOR: duration of response; No.: number.

Progression-free survival

Progression-free survival (PFS) was defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression (PD) or death (whatever the cause). Unless specified otherwise, the analytical methods described for DOR were used for PFS.

PFS is summarised in Table 4.14. Kaplan–Meier plots of PFS for the PAS, IAS and SAS1 are shown in Figure 4.7, Figure 4.8 and Figure 4.9, respectively.

Table 4.14: Progression free survival for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) n=55	**IAS Prior cabozantinib /vandetanib n=124**	**SAS1 Cabozantinib/ vandetanib-naïve n=88[a]**
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)			
Median[b]	NE	NE	23.56

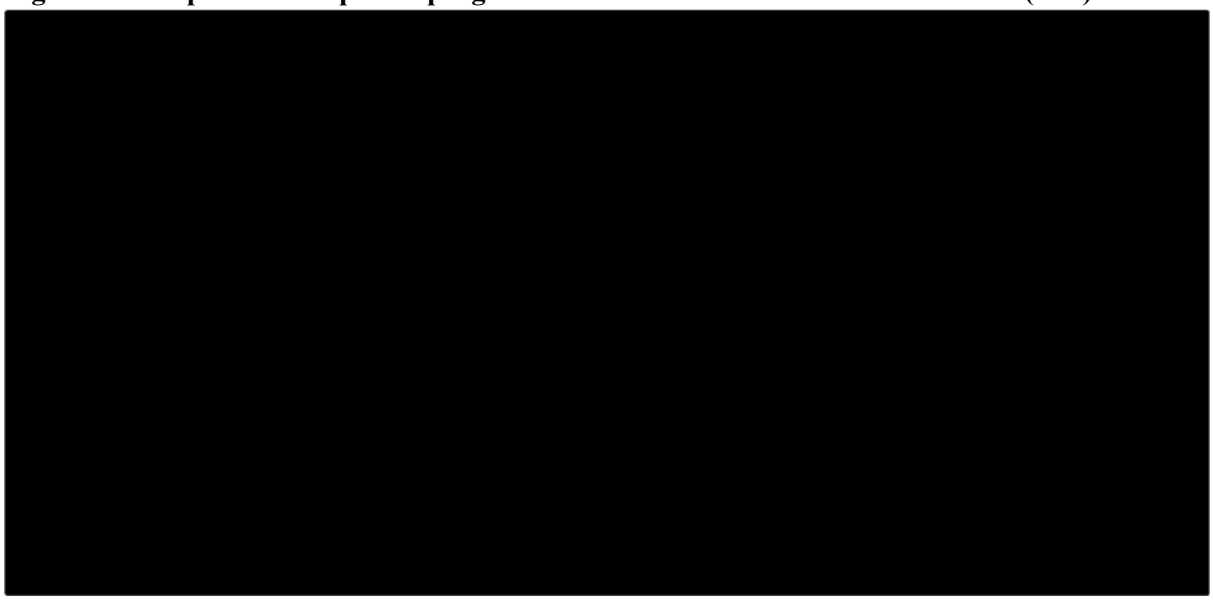
	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88[a]
95% CI	24.4, NE	[redacted]	NE, NE
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	82.3	[redacted]	92.4
95% CI	68.7, 90.4	[redacted]	82.1, 96.8
Duration of follow-up (months)			
Median	16.69	[redacted]	11.07
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of progression-free survival (n, %)[c]			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
Progression status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	42 (76.4)	[redacted]	80 (90.9)
Probability (%) of being progression-free (Kaplan–Meier estimate)			
6 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

Source: Table 22 of the CS[1]
[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP), i.e., all patients treated on or before 17 December 2018. [b]Note that these median estimates are highly unreliable due to data immaturity, as evidenced by the inability to evaluate a confidence interval. [c]Includes censored patients who have not yet progressed.
'*' denotes where some data have been censored.

Figure 4.7: Kaplan–Meier plot of progression-free survival in RET-mutant MTC (PAS)

Source: Figure 13 of the CS
Abbreviations: PFS: progression-free survival.

Figure 4.8: Kaplan–Meier plot of progression-free survival in RET-mutant MTC (IAS)



Source: Figure 14 of the CS
Abbreviations: PFS: progression-free survival.

Figure 4.9: Kaplan–Meier plot of progression-free survival in RET-mutant MTC (SAS1)

Source: Figure 15 of the CS
Abbreviations: PFS: progression-free survival.

Overall survival

Overall survival (OS) was defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who were alive or lost to follow-up as of the data cut-off date were right-censored. The censoring date was determined from the date the patient was last known to be alive.

OS is summarised in Table 4.15. Kaplan–Meier plots of OS for the PAS-population is shown in Figure 4.10.

Table 4.15: Overall survival for *RET*-mutant MTC in the LIBRETTO-001 trial

	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88
Duration of overall survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of OS			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]

	PAS (a subset of IAS) n=55	IAS Prior cabozantinib /vandetanib n=124	SAS1 Cabozantinib/ vandetanib-naïve n=88
Survival status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]

Source: Table 23 of the CS[1]
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IAS: Prior Platinum Chemotherapy; NE: not evaluable; PD: progressive disease; PAS: Primary Analysis Set; SAS1: Treatment-naïve.

Figure 4.10: Kaplan–Meier plot of overall survival in *RET*-mutant MTC (PAS)

[redacted]

Source: Figure 16 of the CS[1]
Abbreviations: OS: progression free survival.

EORTC-QLQ-C30

The CS presented the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (Version 3.0), a well-validated instrument that assesses health-related quality of life (HRQoL) in adult cancer patients. The instrument includes a total of 30 items which are composed of scales to evaluate various symptoms (physical (five items), emotional (four), role (two), cognitive (two), and social (two) functioning; global health status (two), nausea and vomiting (two), fatigue (three), pain (two) and six single items assessing financial impact and various physical symptoms). Higher mean scores (scale from 0 to 100) represent greater symptomatology.

The CS defines a clinically meaningful difference as 10-point difference from the baseline assessment value for each patient. Patients with "improvement" were defined as those who demonstrated a ≥10-point change from their baseline score; "worsening" – a decrease by ≥10-points from the baseline score. A definite change (improvement or worsening) was defined as an improvement or worsening, respectively, as defined above without any further change in score ≥10 points.

EORTC-QLQ-C30 data was available from [redacted] patients with *RET*-mutant MTC as of the 16 December 2019 data cut-off. The mean baseline score for global health status/QoL subscale was [redacted] (SD=[redacted]). Of the [redacted] patients, [redacted] patients experienced definite improvement in the global health status/QoL subscale with the median time to definite improvement of [redacted] months.

Of the [redacted] patients, the proportion of patients experiencing definite improvement in QLQ-C30 subscales was as follows: physical (n=[redacted]), emotional (n=[redacted]), role (n=[redacted]), cognitive (n=[redacted]), and social (n=[redacted]). The proportion of patients experiencing definite worsening in QLQ-C30 subscales was as follows: [redacted] (physical functioning), [redacted] (emotional functioning), [redacted] (role functioning), [redacted] (cognitive functioning), and [redacted] (social functioning). The proportion of patients with any clinically meaningful improvement or worsening is reported in Table 4.16 by cycle.

Table 4.16: Proportion of patients with *RET*-mutant MTC with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		***RET*-mutant MTC** [redacted]			
		Cycle 3	**Cycle 5**	**Cycle 7**	**Cycle 9**
Global Health Status/QoL	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Symptom subscales					
Nausea & vomiting	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

QLQ-C30 Subscale, n (%)		*RET*-mutant MTC [redacted]			
		Cycle 3	Cycle 5	Cycle 7	Cycle 9
Pain	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	n	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 25 of the CS[1]
The proportion of patients with no change, reported as "stable", are not included in this table.
Abbreviations: EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MTC: medullary thyroid cancer; QoL: quality of life; RET: rearranged during transfection.

Bowel diaries

A modified version of the Systemic Treatment-Induced Diarrhoea Assessment Tool (mSTIDAT) was given to RET-mutant MTC patients only and completed weekly during cycle 1, and on day 1 of each cycle thereafter.

As of the 16 December 2019 data cut-off, mSTIDAT data were available from [redacted] patients with RET-mutant MTC. A summary of average scores for mSTIDAT items measuring the impact of bowel habits and diarrhoea on daily living and quality of life among patients who reported diarrhoea at baseline is presented in Table 4.17.

Table 4.17: Modified STIDAT – impact of bowel habits and diarrhoea on daily living and quality of life in patients with RET-mutant MTC who reported diarrhoea at baseline (N=99)

Modified STIDAT Items (Scale range: 0-10)	Baseline		Cycle 3		Cycle 5		Cycle 7		Cycle 9	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Bowel habits affecting ability to perform work or daily activities of living	[redacted]									
Bowel habits affecting energy level	[redacted]									
Bowel habits affecting mood	[redacted]									
Diarrhoea affecting family life	[redacted]									
Diarrhoea affecting social life	[redacted]									
Diarrhoea affecting overall quality of life	[redacted]									
Source: Table 26 of the CS[1]										

4.2.5.2. *RET* fusion-positive thyroid cancer

Objective responsive rate

ORR for the RET fusion-positive TC patients is summarised in Table 4.18. Waterfall plot of best change in tumour size per RECIST v1.1 in *RET* fusion-positive MTC TC is presented in Figure 4.11.

Table 4.18: Best overall response and objective response rate for RET fusion-positive TC in the LIBRETTO-001 trial

	Previously treated[b] n=19	Systemic therapy naïve[c] n=8	*RET* fusion-positive TC n=27
No. of eligible patients[a], n	19	[redacted]	[redacted]
Best overall response, n (%)			
Complete response	1 (5.3)	[redacted]	[redacted]
Partial response	14 (73.7)	[redacted]	[redacted]
Stable disease	4 (21.1)	[redacted]	[redacted]
Progressive disease	0	[redacted]	[redacted]
Not evaluable	0	[redacted]	[redacted]
Objective response rate (CR + PR)			
n (%)	15 (78.9)	[redacted]	[redacted]
95% CI	(54.5, 93.9)	[redacted]	[redacted]

Source: Table 27 of the CS[1]
[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP), i.e., all patients

treated on or before 17th December 2018. [b]≥1 systemic therapy in addition to RAI. [c]No prior systemic therapy other than RAI. 4Investigator assessments of stable disease include unconfirmed partial responses.
Abbreviations: CI: confidence interval; CR: complete response; PR: partial response; RAI: radioactive iodine.

Figure 4.11: Waterfall plot of best change in tumour burden in RET fusion-positive TC patients with ≥6 months follow-up

Source: Figure 17 of the CS[1]
Abbreviations: CR: complete response; PR: partial response; SD: stable disease.

Duration of response

DOR for *RET* fusion-positive TC patients is summarised is Table 4.19. Kaplan–Meier plot of DOR in *RET* fusion-positive TC is presented in Figure 4.12.

Table 4.19: Duration of response rate for RET fusion-positive TC

	Previously treated[a] n=19	**Systemic therapy naïve[b] n=8**	***RET* fusion-positive TC n=27**
Responders	15	[redacted]	[redacted]
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)			
Median	18.43	[redacted]	[redacted]
95% CI	7.6, NE	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of duration of response			
6 months or more	[redacted]	[redacted]	[redacted]

	Previously treated[a] n=19	Systemic therapy naïve[b] n=8	*RET* fusion-positive TC n=27
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)			
Median	17.51	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
Response status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	9 (60.0)	[redacted]	[redacted]

Source: Table 28 of the CS[1]
[a]≥1 systemic therapy in addition to RAI. [b]No prior systemic therapy other than RAI.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not evaluable; PD: disease progression; RAI: radioactive iodine.

Figure 4.12: Kaplan–Meier plot of duration of response in RET fusion-positive TC

Source: Figure 18 of the CS[1]

Progression-free survival

The PFS of the *RET* fusion-positive TC patients is summarised in Table 4.20. Kaplan–Meier plot of PFS in *RET* fusion-positive TC is presented in Figure 4.13.

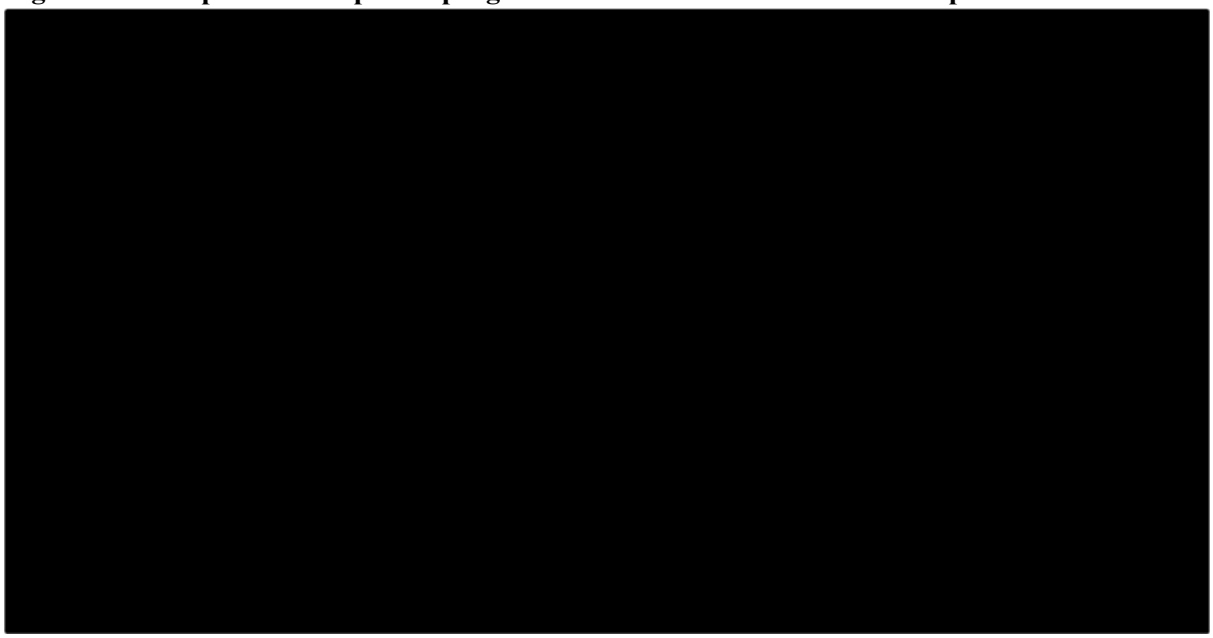
Table 4.20: Progression free survival for *RET* fusion-positive TC

	Previously treated[b] n=19	**Systemic therapy naïve[c] n=8**	***RET* fusion-positive TC n=27**
No. of eligible patients[a], n	[redacted]	[redacted]	[redacted]
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)			
Median	20.07	[redacted]	[redacted]
95% CI	9.4, NE	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	64.4	[redacted]	[redacted]
95% CI	37.0, 82.3	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Observed duration of progression-free survival (n, %)			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
Progression status (n %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no prior disease progression)	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]

Source: Table 29 of the CS

[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP), i.e., all patients treated on or before 17th December 2018.[b]≥1 systemic therapy in addition to RAI. [c]No prior systemic therapy other than RAI.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not estimable; PD: progressive disease; RAI: radioactive iodine.

Figure 4.13: Kaplan–Meier plot of progression-free survival in RET fusion-positive TC



Source: Figure 19 of the CS[1]

Overall survival

The OS of the *RET* fusion-positive TC patients is summarised in Table 4.21.

Table 4.21: Overall survival for RET fusion-positive TC

	Previously treated[a] n=19	**Systemic therapy naïve[b] n=8**	***RET* fusion-positive TC n=27**
Duration of overall survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate (%) of overall survival			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Survival status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]

Source: Table 30 of the CS[1]
[a]≥1 systemic therapy in addition to RAI. [b]No prior systemic therapy other than RAI.
'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not estimable; RAI: radioactive iodine.

EORTC-QLQ-C30

As of the 16 December 2019 data cut-off, no EORTC-QLQ-C30 data were available from patients with RET fusion-positive TC.

ERG comment: The ERG notes that the data are immature (e.g. inability to evaluate confidence intervals) which limits the analysis of the results and conclusions regarding the potential effect of selpercatinib.

The company was asked if any other interim analyses of the LIBRETTO-001 trial are planned. The company stated that currently there is no set date for an additional interim analyses, thus, no new data will be available before technical engagement planned for February 2021.[24]

4.2.6 Adverse events

The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 trial (Phase I) regardless of tumour type or treatment history (overall safety analysis set (OSAS), n=[redacted]) and specifically in those patients with *RET*-mutant MTC (MTC SAS, n=[redacted]). All adverse events (AEs) from the time the informed consent form was signed until the end of the safety follow up period (28 ±7 days post last dose) were recorded in patients who received one or more doses of selpercatinib as of the 16 December 2019 data cut-off date. Following the Phase I dose escalation portion of the study, the Phase II dose of selpercatinib recommended for treatment is 160 mg twice daily (BID).

The company was asked to provide adverse events specifically for the two populations described in the scope and for the population used in the MAIC instead of the data presented in the CS[1] (overall OSAS and *RET*-mutant MTC populations). Data for the exact patient populations requested in the Clarification letter was not available, and instead, the company provided safety data for:

- the pre-treated *RET*-mutant MTC (representing patients treated with prior cabozantinib/vandetanib),
- any-line *RET*-mutant MTC (naïve to cabozantinib and treated with prior cabozantinib/vandetanib)
- the RET-fusion TC (naïve to prior systemic treatment and treated with prior TKI).

According to the company, these data represent the available safety data collected from all relevant patients at the time of the 16 December data cut-off, hence the higher patient numbers to those used in the economic analysis

A summary of safety trends for the above populations is presented in Table 4.22. A list of common adverse events of all grades (15% or greater in any analysis set, including those analysis sets outside the scope of this appraisal) for the pre-treated RET-mutant MTC, any-line RET-mutant MTC and RET-fusion TC analysis sets are presented in Table 4.23, Table 4.24 and Table 4.25, respectively.

Three of AEs were investigates as being of special interest: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase, hypertension and drug hypersensitivity reaction. The number of patients with ALT/AST increase and hypertension are presented in Tables 4.23, 4.24 and 4.25. Drug

hypersensitivity reaction was not provided separately for the relevant populations in this appraisal, only for the full OSAS cohort (see Table 4.26).

Table 4.22: Summary of safety across pre-treated and any-line RET-mutant MTC analysis sets and the RET-fusion TC safety analysis set

	Incidence, n (%)		
	Pre-treated *RET*-mutant MTC n=[redacted]	**Any-line *RET*-mutant MTC n=[redacted]**	**RET-fusion TC n=[redacted]**
Any AE			
All	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]
Grade3 or4 AE			
All	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]
AE leading to treatment discontinuation			
All	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]
SAE			
All	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]
Fatal AE (none related to selpercatinib)	[redacted]	[redacted]	[redacted]

Source: Table 8 of the Clarification Letter[24]
Abbreviations: AE: adverse event; MTC: medullary thyroid cancer; RET rearranged during transfection; SAE: serious adverse event; SAS: safety analysis set.

Table 4.23: Common adverse events all grades (15% or greater in any safety analysis set) in the pre-treated RET-mutant MTC analysis set

Preferred term	**Maximum severity incidence, n (%)**				
	Pre-treated *RET*-mutant MTC n=[redacted]				
	Grade1	Grade2	Grade3	Grade4	Total
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase Increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Maximum severity incidence, n (%)				
	Pre-treated *RET*-mutant MTC n=[redacted]				
	Grade1	Grade2	Grade3	Grade4	Total
Constipation	[redacted]				
Cough					
Diarrhoea					
Dry mouth					
Dysphagia					
Dysphonia					
Dyspnoea					
Electrocardiogram QT prolonged					
Fatigue					
Headache					
Hyperphosphataemia					
Hypertension					
Hypocalcaemia					
Myalgia					
Nausea					
Oedema peripheral					
Oropharyngeal pain					
Pyrexia					
Rash					
Thrombocytopenia					

Source: Table 9 of the Clarification Letter[24]
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; MTC: medullary thyroid cancer; RET rearranged during transfection.

Table 4.24: Common adverse events all grades (15% or greater in any safety analysis set) in the any-line RET-mutant MTC analysis set

Preferred term	Maximum severity incidence, n (%)				
	Any-line *RET*-mutant MTC n=[redacted]				
	Grade1	Grade2	Grade3	Grade4	Total
Abdominal pain	[redacted]				
Alanine aminotransferase increased					
Arthralgia					

Preferred term	**Maximum severity incidence, n (%)**				
	Any-line *RET*-mutant MTC n=[redacted]				
	Grade1	Grade2	Grade3	Grade4	Total
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 10 of the Clarification Letter[24]
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; MTC: medullary thyroid cancer; RET rearranged during transfection.

Table 4.25: Common adverse events all grades (15% or greater in any safety analysis set) in the RET-fusion TC analysis set

Preferred term	Maximum severity incidence, n (%)				
	RET-fusion TC n=[redacted]				
	Grade1	Grade2	Grade3	Grade4	Total
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 11 of the Clarification Letter[24]
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; MTC: medullary thyroid cancer; RET rearranged during transfection.

Table 4.26: Hypersensitivity AESIs in the LIBRETTO-001 trial (OSAS)

Adverse event of special interest	LIBRETTO-001 OSAS n=[redacted]
Drug hypersensitivity, n (%)	[redacted]
Singe event	[redacted]
Multiple events	[redacted]
Range	[redacted]
Median time to first onset, weeks	[redacted]
Range	[redacted]
Grade 3 hypersensitivity events, n (%)	[redacted]
Grade 4 hypersensitivity events	[redacted]
AEs deemed 'serious' attributed to selpercatinib	[redacted]
Dose interruptions or reductions	[redacted]
Dose discontinuations	[redacted]

Source: Table 45 of the CS[1]
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of randomised controlled trials of selpercatinib vs. any specified comparator, and because LIBRETTO-001[28] is a single arm study, an unanchored MAIC was used to generate relative efficacy estimates vs. cabozantinib and placebo (used a proxy for BSC) for the *RET*-mutant MTC population. A naïve (unanchored) indirect comparison was used to compare selpercatinib with BSC (using the placebo arms of two RCTs) for the *RET* fusion-positive TC population. Details of the analysis methods are reported in section B.2.8 of the CS and Appendix D.[1]

The company stated that an SLR was conducted to identify evidence on the efficacy and safety of selpercatinib and its potential comparators, in people with *RET*-altered solid tumours, including *RET* fusion-positive TC and *RET*-mutant MTC. Details of the SLR were provided in appendix D of the CS.[29]

In addition to LIBRETTO-001,[28] the company stated that the SLR identified two relevant trials of comparator therapies (cabozantinib and vandetanib) at their recommended doses in patients with *RET*-mutant MTC (EXAM[30-32] and ZETA[33]). Vandetanib is not considered a relevant comparator in the UK and was not included in the scope for this appraisal,[23] hence, only LIBRETTO-001[28] and EXAM[30] were considered in the CS.

ERG comment: The company excluded the ZETA trial because vandetanib is not considered a relevant comparator in the UK. However, that is not a valid argument when single arms from trials have been selected. The placebo arm from the ZETA trial fulfils the inclusion criteria and should have been included. We will present some results from the ZETA in Section 4.5 of this report to show how this omission may have impacted results.

The EXAM study did not report separate results for treatment-naïve and pre-treated patients; the company stated that the any-line pooled population from the LIBRETT0-001 trial was therefore used in the MAIC to provide a larger patient-level data set and closer matching to the characteristics of the *RET*-mutant subgroup of the EXAM trial.[1] Table 4.27 provides a comparison of the study characteristics

of LIBRETTO-001 and EXAM, and Table 4.28 provides a comparison of baseline participant characteristics, between the two trials. The baseline characteristics of the *RET*-mutant subgroups were not available for the placebo arm of the EXAM study, therefore the baseline characteristics of the cabozantinib group were assumed to be similar to those of the placebo arm and were use in the MAIC.[1]

In section B.2.8.1 of the CS,[1] the company noted the following key differences in the study populations of the LIBRETTO-001 trial and cabozantinib group of the EXAM trial:

- The LIBRETTO-001 trial population is slightly older than the EXAM trial population
- The percentage of male patients in LIBRETTO-001 is slightly lower than in EXAM
- A higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the EXAM trial population
- The proportion of patients in the LIBRETTO-001 any-line MTC cohort with prior anticancer therapy was substantially higher than in the EXAM trial.
- The proportion of patients in the LIBRETTO-001 any-line MTC cohort with prior tyrosine kinase inhibitor therapy was substantially higher than in the EXAM trial
- The proportion of patients in the LIBRETTO-001 trial who never smoked was higher than in the EXAM trial

The company further stated that the populations appeared to be similar for other reported characteristics.[1]

ERG comment: The ERG notes that the proportion of participants with *RET* M918T mutation was lower in the LIBRETTO-001 any-line MTC cohort than in the EXAM cabozantinib group. Although baseline data were not reported for the placebo arm of the *RET*-mutant subgroup of EXAM, the baseline data for all patients were comparable to the cabozantinib patients suggesting that they would also be similar for placebo.

The CS reports that the SLR did not identify any RCTs of relevant comparators, in patients with *RET* fusion-positive TC. Two phase III, double-blind, trials were identified that included a placebo arm that the company considered could be considered a reasonable proxy for BSC, in patients with *RET* fusion-positive TC who have received prior TKIs (DECISION[34] and SELECT[35]). SELECT included adult patients with DTC (including a PTC sub-population) with evidence of radioactive iodine-refractory disease and DECISION included patients with locally advanced or metastatic radioactive iodine-refractory DTC progressing within the previous 14 months according to RECIST. Patients received lenvatinib 24 mg, orally QD, or sorafenib 400 mg, orally BID, in the SELECT and DECISION trials respectively, or a matching placebo.

Table 4.29 provides a comparison of baseline participant characteristics, between the pre-treated *RET* fusion-positive TC patients from the LIBRETTO-001 trial and the placebo arms of the SELECT and DECISION trials.

- In section B.2.8.2 of the CS,[1] the company noted the following key differences in the study populations of the LIBRETTO-001 trial and the SELECT and DECISION trials:
- All patients are *RET*-fusion positive in LIBRETTO-001, while *RET* fusion status is unknown in the SELECT trial
- SELECT only included patients with confirmed progressive DTC type whereas all subtypes of thyroid cancer were permitted in LIBRETTO-001
- All patients had received at least 1 prior therapy in LIBRETTO-001, compared with 20.6% in SELECT

ERG comment: The ERG notes that a higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the SELECT and DECISION trials.

Table 4.27: Comparison of study characteristics of trials identified for intervention and comparators in RET-mutant MTC

Trial	LIBRETTO-001 (NCT03157128)	EXAM (NCT00704730)
Study arms	Selpercatinib	Cabozantinib Placebo
Line of therapy	Any line (results not reported for any line; reported separately for first-line[a] and ≥second-line therapy)	Any line
Population	Patients with a variety of advanced solid tumours, including NSCLC, MTC, and PTC with activating RET alterations (gene fusions and/or mutations)	Patients with progressive MTC
Key subgroups of interest for which data are available	First-line[a] MTC ≥Second-line MTC	*RET*-mutation *RET* M918T-mutation
Key inclusion criteria	Inclusion criteria for Phase I 1. Locally advanced or metastatic solid tumour who: Have progressed on or are intolerant to standard therapy, or No standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from Standard therapy, or Decline standard therapy 2. Prior MKIs with anti-RET activity are allowed; prior selective RET inhibitor(s) are prohibited. 3. A *RET* gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of *RET* gene alteration in tumour and/or blood required. 4. Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type. 5. At least 18 years of age.	1. Histologically confirmed MTC that is unresectable, locally advanced, or metastatic, and disease that is measurable or non-measurable per mRECIST. 2. ≥18 years old. 3. ECOG PS ≤2 4. Documented PD on CT, MRI, bone scan, or X-ray (determined by the Investigator) per mRECIST at screening compared with a previous image done within 14 months of screening. 5. Recovered to NCI CTCAE v3.0 grade ≤1 from clinically significant AEs due to antineoplastic agents, investigational drugs, or other medications that were administered prior to randomisation. Additional criteria, e.g., for organ function, no other malignancy.

Trial	LIBRETTO-001 (NCT03157128)	EXAM (NCT00704730)
	For countries and sites where approved, patients as young as 12 years of age may be enrolled. 6. ECOG PS 0, 1, or 2 (age ≥16 years) or Lansky Performance Score ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. 7. Life expectancy of at least 3 months. 8. Archived tumour tissue sample available. Inclusion criteria for Phase II: Inclusion criteria were the same as for Phase I, with the following modifications: 1. Cohorts 1 and 3: failed or intolerant to standard of care.	
Key exclusion criteria	1. Phase II cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. 2. Prior treatment with a selective *RET* inhibitor(s) (including investigational selective *RET* inhibitor[s]). 3. Investigational agent or anticancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. In addition, no concurrent investigational anticancer therapy is permitted. 4. Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of selpercatinib. 5. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.	1. Prior systemic antitumour therapy (e.g., chemotherapy, biologic modifiers, or antiangiogenic therapy) within 4 weeks of randomisation (6 weeks for nitrosoureas or mitomycin C). 2. Radiation to ≥25% of bone marrow. 3. Treatment with other investigational agents within 4 weeks of randomisation. 4. Treatment with cabozantinib. 5. Brain metastases or spinal cord compression, unless completed radiation therapy ≥4 weeks prior to randomisation and stable without steroid and without anticonvulsant treatment for ≥10 days. Other criteria e.g., renal function, serious intercurrent illness, infection.

Trial	LIBRETTO-001 (NCT03157128)	EXAM (NCT00704730)
	6. Any unresolved toxicities from prior therapy greater than NCI CTCAE grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy. 7. Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Other criteria e.g., concurrent cardiovascular disease, infection, active second malignancy	
Location	65 centres in Australia, Canada, Denmark, Germany, Japan, Hong Kong, Israel, Singapore, France, Italy, Spain, South Korea, Switzerland, Taiwan, and the US (15 countries)	140 active enrolling clinical sites including, but not limited to, the US, Europe, Canada, Latin America, Asia- Pacific, and Australia (specific number of countries not recorded)
Randomisation stratified for *RET* mutation	NA	No
RET-mutation subgroup analysis pre-planned	NA	Yes
Primary outcome measure	ORR	PFS
Other key outcome measures	PFS, OS	ORR, OS
Treatment switching	NA	No

Source: Table 7, CS, Appendix D[29]

AE: adverse event; CNS: central nervous system; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MKI: multi-targeted kinase inhibitor; mRECIST: modified RECIST; MRI: magnetic resonance imaging; MTC: medullary thyroid cancer; NA: not applicable; NCI: National Cancer Institute; NSCLC: non–small cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetics; PTC: papillary thyroid cancer; RANO: response assessment in neuro-oncology; RECIST: Response Evaluation Criteria in Solid Tumours; RET: rearranged during transfection proto-oncogene gene; US: United States; WHO: World Health Organisation

Table 4.28: Comparison of baseline participant characteristics for LIBRETTO-001 and EXAM trials in RET-mutant MTC

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)
Male (n, %)	36 (65.5)	58 (65.9)	[redacted]	73 (68.2)
Age				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR (NR)
Median (min, max)	57 (17, 84)	58 (15, 82)	[redacted]	55 (20, 86)
Age category				
≤65 years	[redacted]	[redacted]	[redacted]	84 (78.5%)
>65 years	[redacted]	[redacted]	[redacted]	23 (21.5%)
Weight (kg), mean	[redacted]	[redacted]	[redacted]	74
Patients with measurable disease (n, %)	[redacted]	[redacted]	[redacted]	101 (94.4)
Sum of the longest diameter (mm)				
n	[redacted]	[redacted]	[redacted]	101
Mean (SD)				120.5 (80.5)
Median (min, max)				111.7 (10.7, 420.2)
WHO performance status (n, %)	[redacted]	[redacted]	[redacted]	NR
ECOG PS (n, %)	0: 11 (20) 1: 41 (74.5) 2: 3 (5.5)	0: 43 (48.9) 1: 42 (47.7) 2: 3 (3.4)	[redacted]	0: 66 (61.7) 1: 39 (36.4) 2: 2 (1.9)
Calcitonin (pg/mL)				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)
Median (min, max)	[redacted]	[redacted]	[redacted]	NR
Carcino-embryonic antigen (ng/mL)				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR
Median (min, max)	[redacted]	[redacted]	[redacted]	NR
***RET*-mutation status (n, %)**				
Positive	[redacted]	[redacted]	[redacted]	107 (100)
Negative	[redacted]	[redacted]	[redacted]	0 (0)
Unknown	[redacted]	[redacted]	[redacted]	0 (0)
RET M918T mutation status	33 (60%)	49 (55.7%)	[redacted]	81 (75.7%)
MTC disease type (n, %)				
Hereditary	[redacted]	[redacted]	[redacted]	NR
Sporadic/unknown				
Locally advanced				
Patients with prior anticancer therapy (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 85/219 (38.8%)
Patients with prior systemic therapy for MTC (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 81/219 (37.0%)
Prior therapies (n, %)				
1 or 2	[redacted]	[redacted]	[redacted]	NR
2 or more	[redacted]	[redacted]	[redacted]	NR

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)
3 or more	[redacted]	[redacted]	[redacted]	NR
Patients with prior thyroidectomy	[redacted]	[redacted]	[redacted]	NR
Prior TKI status (n, %)	55 (100)	7 (8)	[redacted]	23 (21.5)
No. of organs and anatomic locations involved at enrolment (n, %)	[redacted]	[redacted]	[redacted]	NR
Main sites of metastatic disease (n, %)				
Hepatic	[redacted]	[redacted]	[redacted]	NR
Lymph nodes				
Respiratory				
Bone				
Neck				
Smoking				
Never	[redacted]	[redacted]	[redacted]	55 (51.4)
Former	[redacted]	[redacted]	[redacted]	43 (40.2)
Current	[redacted]	[redacted]	[redacted]	9 (8.4)

Source: Table 9, CS, Appendix D[29]

[a]Cabozantinib and vandetanib-naïve patients, 81.8% of whom had no prior treatment

[b]Data for the *RET*-mutation-positive patients in the placebo arm of the EXAM trial are not available

[c]Includes 14 patients (6.2%) with non-measurable disease

ECOG PS: Eastern Cooperative Oncology Group Performance Status; Max: maximum; Min: minimum; MTC: medullary thyroid cancer; NR: not reported; *RET*: rearranged during transfection; SD: standard deviation; TKI: tyrosine kinase inhibitor

Table 4.29: Comparison of baseline participant characteristics in the LBRETTO-001, SELECT and Decision trials for RET fusion-positive TC

Characteristics	LIBRETTO-001	SELECT	DECISION
	Selpercatinib n=19	Placebo n=131	Placebo n=210
Median age, years (minimum to maximum)	54 (25 to 88)	61 (21 to 81)	63 (30 to 87)
Number (%) male	9 (47.4)	75 (57.3)	95 (45.2)
Race/Ethnicity			
White	14 (73.7)	103 (78.6)	128 (61.0)
Black of African American	1 (5.3)	4 (3.1)	5 (2.4)
Asian	[redacted]	24 (18.1)	52 (24.8)
Other	2 (10.5)	0	2 (1.0)
Missing or uncodeable	[redacted]	n/a	23 (11.0)
Region, n (%)			
Europe	[redacted]	64 (48.9)	125 (59.5)
North America	[redacted]	39 (29.8)	36 (17.1)
Other	[redacted]	28 (21.4)	49 (23.3)
Median time from diagnosis, months (range)	[redacted]	73.9 (6.0 to 484.8)	66.9 (6.6 to 401.8)
ECOG performance status, n (%)			
0	5 (26.3)	68 (51.9)	129 (61.4)
1	12 (63.2)	61 (46.6)	74 (35.2)
2	2 (10.5)	2 (1.5)	6 (2.9)
Not available	[redacted]	0	1 (0.5)
Histology, n (%)			
Papillary	13 (68.4)	68 (51.9)	119 (56.7)

Characteristics	LIBRETTO-001	SELECT	DECISION
	Selpercatinib n=19	Placebo n=131	Placebo n=210
Poorly differentiated	3 (15.7)	19 (14.5)	16 (7.6)
Follicular, not Hürthle cell	0	22 (16.8)	19 (9.0)
Hürthle cell	1 (5.3)	22 (16.8)	37 (17.6)
Other	2 (10.5)	0	5 (2.4)
Missing or non-diagnosed	0	0	14 (6.7)
Metastases, n (%)			
Locally advanced	[redacted]	0	8 (3.8)
Distant	[redacted]	131 (100)	202 (96.2)
Metastases site, n (%)			
Lung	[redacted]	124 (94.7)	181(86.2)
Lymph node	[redacted]	64 (48.9)	101(48.1)
Bone	[redacted]	48 (36.6)	56 (26.7)
Pleura	[redacted]	18 (13.7)	24 (11.4)
Head and neck	[redacted]	Not reported	34 (16.2)
Liver	[redacted]	28 (21.4)	30 (14.3)
Prior systemic therapy (%)	19 (100)	27 (20.6)	0

Source: Table 11, CS, Appendix D[29]
ECOG: Eastern Cooperative Oncology Group; *RET*: rearranged during transfection; TC: thyroid cancer

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 RET-mutant MTC

An unanchored matching-adjusted indirect comparison (MAIC) was conducted using individual patient data (IPD) from the any-line population of the LIBRETTO-001 trial (the IAS and SAS1 datasets combined, n=212) and aggregate data from the EXAM trial.[30, 32] The data from LIBRETTO-001 included both treatment-naïve and pre-treated patients (one or more lines of prior cabozantinib or vandetanib) and the data from EXAM also included both pre-treated and treatment-naïve patients as results for these groups were not reported separately.

The MAIC used propensity score matching (PSM) to weight patients in the LIBRETTO-001 trial so their summary baseline patient characteristics matched those reported in EXAM. The variables used in the matching model were age, weight, ECOG performance score, gender, smoking status and RET M918T mutation status as these were reported by both trials. Based on a meeting with a clinical expert in thyroid cancer, the company listed the following relevant prognostic factors: performance status, stage and grade at diagnosis, baseline CNS metastases, Cushing's disease, diarrhoea, prior therapy, and RET mutation type.[36] Of these, only performance status (ECOG) and RET mutation type (RET M918T mutation status) were included as matching variables in the MAIC.

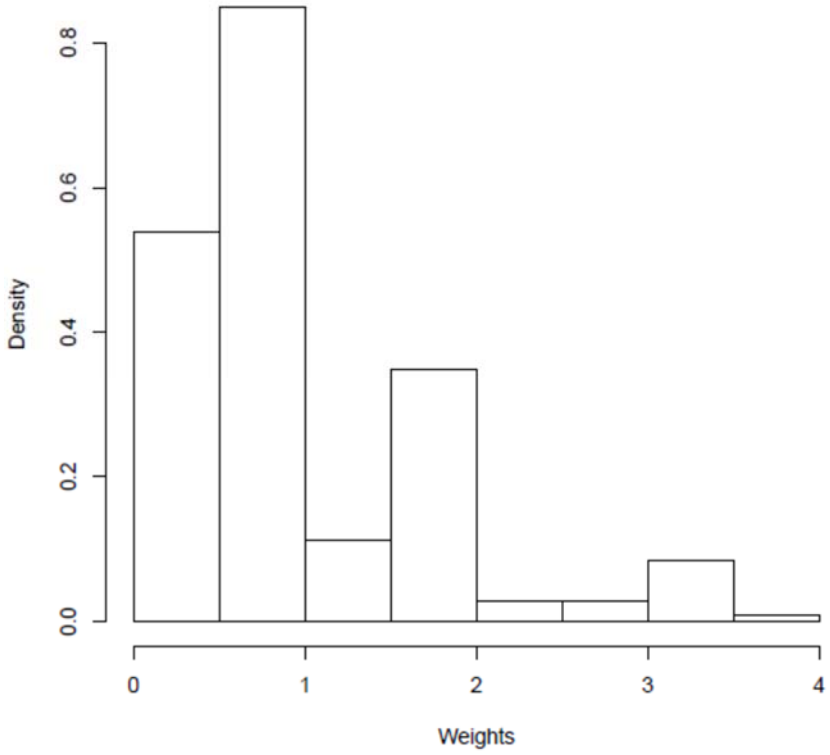
As this was an unanchored MAIC the guidance in NICE DSU TSD 18 recommends that the matching model includes all known prognostic variables and treatment-effect modifiers.[37] These were identified though the systematic literature review and validated with a clinical expert. Details of the relationship between each factor and outcomes and the corresponding references for each source were provided in Appendix D.[29] As only aggregate data, not IPD, were reported by EXAM, the logistic regression model was estimated using the method of moments. Details of the baseline characteristics of the treatment groups before and after matching are shown in Table 4.30. The distribution of the weights is shown in Figure 4.14. This does not suggest any concerns about the weighting.

Table 4.30: Baseline characteristics of LIBRETTO-001 and EXAM before and after matching

Characteristic	Before matching		After matching
	LIBRETTO-001 any-line (n=212)	**EXAM (n=107) *RET*-mutant cabozantinib**	**LIBRETTO-001 any-line (n_{eff}=[redacted])**
Age, mean (SD)	[redacted]	55.00 (20, 86)[a]	[redacted]
Weight (kg), mean (SD)	[redacted]	74.00 (20.19)	[redacted]
ECOG-0 (%)	[redacted]	61.68	[redacted]
Sex (% male)	[redacted]	68.22	[redacted]
Smoking (% never)	[redacted]	51.40	[redacted]
RET M918T mutation status (%)	[redacted]	74.56	[redacted]

Source: Table 34, CS
a Median (min, max)
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; SD: standard deviation; RET: rearranged during transfection.

Figure 4.14: Distribution of weights in the MAIC



Source: Figure 20, CS.[1]

PFS was analysed using a weighted Cox proportional hazards model adjusted for treatment group and using the weights from the PSM. PFS results were obtained from the EXAM trial by digitising the unweighted Kaplan-Meier curves from the cabozantinib or placebo groups. The proportional hazards assumption was tested but did not hold for the comparison of selpercatinib with cabozantinib, so stratified survival functions were also used.

OS was also analysed using a weighted Cox proportional hazards model adjusted for treatment group and *RET* M918T status. OS data were not available from EXAM for the *RET*-mutant subgroup so the data were obtained from the unweighted Kaplan-Meier curves from the *RET* M918T-positive group (81 cabozantinib and 45 placebo patients). Clinical experts were used to confirm that PFS outcomes in the placebo arm of the *RET* M918T-positive group of EXAM were similar to the *RET*-mutant group overall. OS for the *RET* M918T-positive group for cabozantinib was not used in the analysis as cabozantinib is more effective in this population compared to the overall *RET*-mutant population. OS data from LIBRETTO-001 are immature.

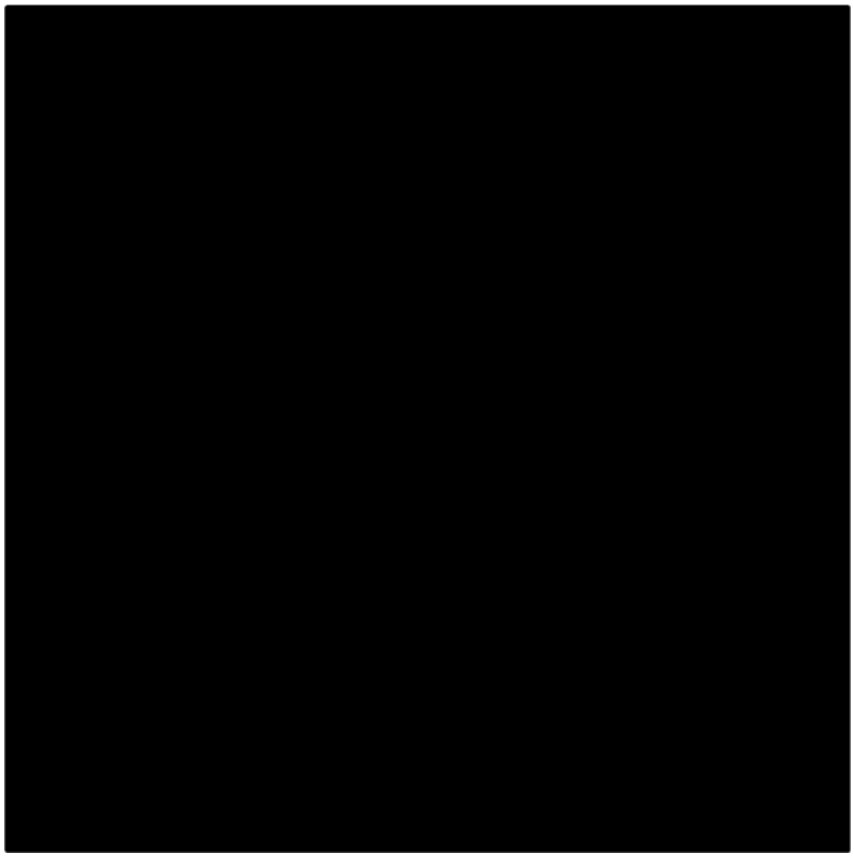
PFS and OS results from the MAIC comparing selpercatinib with cabozantinib and placebo are shown in Table 4.31 and KM curves are in Figures 4.15 and 4.16.

Table 4.31: PFS and OS for LIBRETTO-001 and EXAM before and after matching

	PFS		OS	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Selpercatinib versus cabozantinib				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted (matched)	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib versus BSC (placebo)				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted (matched)	[redacted]	[redacted]	[redacted]	[redacted]

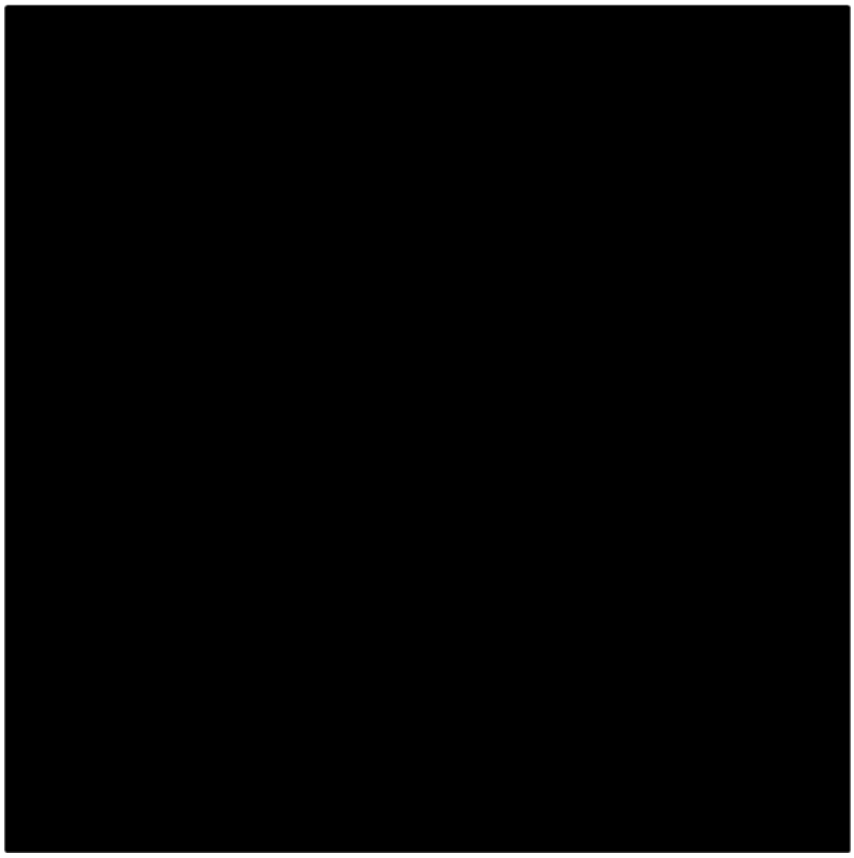
[a] The treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated because the data for cabozantinib were for patients with *RET* M918T. Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population.
Abbreviations: BSC: best supportive care; CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.
Source: Table 35, CS

Figure 4.15: PFS for selpercatinib (loxo) before and after weighting, cabozantinib and placebo



Source: Figure 21, CS
Test for PH assumption in PFS was rejected before and after matching for selpercatinib versus cabozantinib ($p<0.05$), but not for placebo ($p>0.05$).
Abbreviations: PFS: progression-free survival; IRC: independent review committee; Loxo: selpercatinib.

Figure 4.16: OS for selpercatinib (loxo) before and after weighting, cabozantinib and placebo



Source: Figure 21, CS
OS for cabozantinib is expected to be overestimated as the analyses use data for the *RET* M918T-positive population and cabozantinib is known to be more effective in this population than in the overall *RET*-mutation population (Kaplan-Meier OS data for the *RET*-mutant group in EXAM are not available).
Abbreviations: OS: overall survival; Loxo: selpercatinib.

4.4.2 RET fusion-positive TC

The only treatments recommended for patients with advanced *RET* fusion-positive TC are lenvatinib and sorafenib, patients who do not respond or have contraindications to these treatments receive palliative treatment with BSC. LIBRETTO-001 is the only trial of selpercatinib in this patient population and it is a single-arm trial. The systematic review did not identify any relevant RCTs of comparators in patients with *RET* fusion-positive TC. The company's clinical expert confirmed that it is not clear whether data for patients with TC are generalisable to those with *RET* fusion-positive TC. The DECISION and SELECT trials were identified for being a reasonable proxy to BSC (via placebo) in the *RET* fusion-positive TC who have received prior TKIs. Baseline characteristic are shown in Table 4.29 in Section 4.3. Important differences between the populations are: 100% of patients are *RET* fusion-positive in LIBRETTO-001 but this was unknown in the SELECT trial; SELECT only included confirmed progressive DTC but all subtypes were allowed in LIBRETTO-001; and differences in prior systemic therapy as selection was mostly first-line patients (100% of LIBRETTO-001 and 20.6% of SELECT had received at least one prior therapy). Subgroup results by line of therapy were not reported for OS in SELECT. OS was also affected by patient crossover in both trials as placebo patients could crossover to the intervention.

The placebo arm of SELECT was chosen as a suitable proxy for BSC in a previous NICE STA (TA535) which is confirmed by clinical expert opinion, suggesting that the trial population of SELECT is more comparable to the target population as at least one prior TKI was allowed. The placebo arm was considered to be the most suitable proxy for BSC in patients with *RET* fusion-positive TC.

A naïve indirect treatment comparison (ITC) was performed which compared PFS directly between the selpercatinib arm of LIBRETTO-001 and the placebo arm of SELECT, without any matching. This showed that selpercatinib improved PFS compared with BSC in the previously treated *RET* fusion-positive TC population. The median PFS were 20.07 months (95% CI 9.4 to not estimable) in the previously treated LIBRETTO-001 patients, 3.6 months (1.9 to 3.7) in the previously treated SELECT patients and 3.7 months (95% CI 3.5 to 4.5) in the SELECT ITT population.

ERG comment: As pointed out in the CS both the MAIC for the *RET*-mutant MTC population and the ITC for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators. An unanchored MAIC was used to compare selpercatinib with BSC and cabozantinib for OS and PFS. However, this can only include those prognostic factors and effect modifiers which are reported by both studies, other important factors may be missing and MAIC results are likely to be biased due to unobserved confounding. OS data were not available for the *RET*-mutant MTC population and had to be estimated using the results for the *RET* M918-positive population which is likely to underestimate OS for selpercatinib compared to cabozantinib.

OS and PFS results were not reported by treatment-naïve and previously treated patients in the EXAM trial so analyses by line of therapy were not possible. The results are based on subgroups with small numbers of patients, which also affects their reliability. The CS did not contain any discussion on the likely amount of residual systematic error in the MAIC but did present results from a naïve indirect treatment comparison (unweighted results) which were similar to the MAIC results. However, as both analyses used selpercatinib data from a single-arm study, the results may be unreliable.

A naïve ITC was performed for the *RET* fusion-positive TC population using single-arm selpercatinib and BSC (placebo) data from two studies. OS data are immature and the pre-treated subgroup from LIBRETTO-001 was small (19 patients). BSC data came from the SELECT study but this was not limited to patients with a *RET* fusion. OS was not analysed as it was affected by patient crossover from placebo to active treatment. Given that this analysis was based on small patient numbers and a comparison of single-arms without any attempts to balance the patient groups, the PFS results are also likely to be uncertain.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As discussed in Section 4.3 of this report the placebo arm from the ZETA trial fulfils the inclusion criteria for this appraisal and should have been included. Note that some authors were involved in both the ZETA and EXAM trials.

The ZETA trial is a multinational phase III, double-blind, parallel group RCT comparing vandetanib with placebo. Inclusion criteria were: adults who had measurable, unresectable locally advanced or metastatic, hereditary, or sporadic MTC; submission of a tumour sample was required except for patients with hereditary MTC who had a documented germline RET mutation; WHO PS of 0 to 2; serum calcitonin level ≥500 pg/mL, presence of measurable tumour and able to swallow medication.[33]

In comparison to the EXAM trial, patients in the ZETA trial did not have documented radiographic disease progression (as per Response Evaluation Criteria in Solid Tumours guidelines) at screening which were compared with images obtained within previous 14 months. There were no other differences in the inclusion criteria; the exclusion criteria were identical for the EXAM and ZETA trials (prior systemic anticancer therapy within four weeks before randomisation or significant cardiac, hematopoietic, hepatic or renal dysfunction). Confirmation of mutations in the *RET* gene was required in both trials.[30, 31, 33]

Table 4.32 provides a comparison of baseline participant characteristics, between the LIBRETTO-001, EXAM and ZETA trials. In the EXAM trial, data for the *RET*-mutation-positive patients in the placebo arm was not available, thus, the table provides information for patients in *RET*-mutant subgroup that received cabozantinib. Similarly, in the ZETA trial, data for confirmed *RET*-mutation positive patients in the placebo arm was not reported separately and data for all patients in the placebo group were reported in the table below. However, as 50% were confirmed positive and only 6% confirmed negative, and 44% unknown it is possible that between over 50% and 94% of patients in the placebo arm of the ZETA trial were RET-mutation positive.[33] The equivalent figures for the EXAM placebo group (ITT population) are: 55.9% positive, 9.9% negative and 34.2% unknown.[30]

Limited baseline characteristics for the ZETA trial were reported, and not taking RET mutations status into account (ITT population). The comparison between the EXAM, ZETA placebo group and LIBRETTO-001 trial reveals that:

- The ZETA placebo group is slightly younger than LIBRETTO-001; the value for the placebo arm of EXAM is almost identical to ZETA i.e. 53.8 vs. 53.3.[33]
- The percentage of male patients in the ZETA placebo group is lower than in EXAM RET mutant subgroup (but slightly higher than LIBRETTO-001 (any-line)); the value for the EXAM placebo group (ITT population) is 63.1%.
- Performance status 1 or 2 in the ZETA placebo group is comparable to the EXAM trial, but not to LIBRETTO-001 (performance criteria 0-2 based on WHO and ECOG are highly similar and comparison is possible).
- Fewer patients in the ZETA trial have *RET* M918T mutation status when compared to the EXAM RET mutation subgroup and LIBRETTO-001, although the value for the EXAM placebo group only was 40.5% vs. 43.2% for the ZETA placebo arm.
- Slightly fewer patients in the ZETA placebo arm had prior systemic therapy for MTC when compared to the EXAM cabozantinib group (ITT population).

Table 4.32: Comparison of baseline participant characteristics for LIBRETTO-001 and EXAM trials in RET-mutant MTC

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]	ZETA
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)	Placebo (n=100)
Male (n, %)	36 (65.5)	58 (65.9)	[redacted]	73 (68.2)	56 (56%)
Age					
Mean (SD)	[redacted]	[redacted]	[redacted]	NR (NR)	53.4 (NR)
Median (min, max)	57 (17, 84)	58 (15, 82)	[redacted]	55 (20, 86)	NR
Age category					
≤65 years	[redacted]	[redacted]	[redacted]	84 (78.5%)	NR
>65 years	[redacted]	[redacted]	[redacted]	23 (21.5%)	NR
Weight (kg), mean	[redacted]	[redacted]	[redacted]	74	NR
Patients with measurable disease (n, %)	[redacted]	[redacted]	[redacted]	101 (94.4)	NR
Sum of the longest diameter (mm)					
n	[redacted]	[redacted]	[redacted]	101	NR
Mean (SD)				120.5 (80.5)	NR
Median (min, max)				111.7 (10.7, 420.2)	NR
WHO performance status (n, %)	[redacted]	[redacted]	[redacted]	NR	0=58%; 1=38%; 2=4%
ECOG PS (n, %)	0: 11 (20) 1: 41 (74.5)	0: 43 (48.9) 1: 42 (47.7)	[redacted]	0: 66 (61.7) 1: 39 (36.4)	NR

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]	ZETA
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)	Placebo (n=100)
	2: 3 (5.5)	2: 3 (3.4)		2: 2 (1.9)	
Calcitonin (pg/mL)					
Mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Median (min, max)	[redacted]	[redacted]	[redacted]	NR	NR
Carcino-embryonic antigen (ng/mL)					
Mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Median (min, max)	[redacted]	[redacted]	[redacted]	NR	NR
***RET*-mutation status (n, %)**					
Positive	[redacted]	[redacted]	[redacted]	107 (100)	50 (50)
Negative	[redacted]	[redacted]	[redacted]	0 (0)	6 (6)
Unknown	[redacted]	[redacted]	[redacted]	0 (0)	44 (44)
RET M918T mutation status	33 (60%)	49 (55.7%)	[redacted]	81 (75.7%)	41 (43.2)[d]
MTC disease type (n, %)					
Hereditary	[redacted]	[redacted]	[redacted]	NR	5 (5)
Sporadic/unknown					95 (95)
Locally advanced					3 (3)
Patients with prior anticancer therapy (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 85/219 (38.8%)	NR
Patients with prior systemic therapy for MTC (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 81/219 (37.0%)	42 (42)

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]	ZETA
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)	Placebo (n=100)
Prior therapies (n, %)					
1 or 2	[redacted]	[redacted]	[redacted]	NR	NR
2 or more	[redacted]	[redacted]	[redacted]	NR	NR
3 or more	[redacted]	[redacted]	[redacted]	NR	NR
Patients with prior thyroidectomy	[redacted]	[redacted]	[redacted]	NR	NR
Prior TKI status (n, %)	55 (100)	7 (8)	[redacted]	23 (21.5)	NR
No. of organs and anatomic locations involved at enrolment (n, %)	[redacted]	[redacted]	[redacted]	NR	0 or 1: 8 (8%) 2 or more: 92 (92%)
Main sites of metastatic disease (n, %)					
Hepatic	[redacted]	[redacted]	[redacted]	NR	64 (64%)
Lymph nodes					68 (68%)
Respiratory					60 (60%)
Bone					40 (40%)

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[b]	ZETA
	Pre-treated (n=55)	Treatment-naive[a] (n=88)	Any-line[c] (n=212)	Cabozantinib (n=107)	Placebo (n=100)
Neck					17 (17%)
Smoking					
Never	[redacted]	[redacted]	[redacted]	55 (51.4)	NR
Former	[redacted]	[redacted]	[redacted]	43 (40.2)	NR
Current	[redacted]	[redacted]	[redacted]	9 (8.4)	NR

Source: Table 9, CS, Appendix D[29] and Wells et.al. 2012[33].
[a]) Cabozantinib and vandetanib-naïve patients, 81.8% of whom had no prior treatment; [b]) Data for the *RET*-mutation-positive patients in the placebo arm of the EXAM trial are not available; [c]) Includes 14 patients (6.2%) with non-measurable disease; [d]) Based on data for sporadic disease only (n=95 patients).
ECOG PS = Eastern Cooperative Oncology Group Performance Status; Max = maximum; Min = minimum; MTC = medullary thyroid cancer; NR = not reported; *RET* = rearranged during transfection; SD = standard deviation; TKI = tyrosine kinase inhibitor.

The primary and secondary endpoints of interest in the ZETA and EXAM trials were PFS and OS, respectively. The follow-up period was median 24 months in the ZETA trial and minimum 42 months in the EXAM trial.[30, 33]

In the EXAM trial, cabozantinib was favoured over placebo in all patients (median PFS 11.2 versus 4.0 months, respectively) and in the subgroup of *RET* M918T positive patients (median PFS 13.9 versus 4.0 months, respectively; $p<0.0001$ for both comparisons; Figure 4.17).[30]

In the ZETA trial, median PFS was 19.3 months in the placebo group and an estimated median of 30.5 months for the vandetanib group (HR 0.46; 95%CI 0.31 to 0.69; $p<0.001$; Figure 4.18). The PFS at six months was 83% and 63% for vandetanib and placebo respectively. In patients with sporadic MTC (n=95 patients in the placebo arm), a subgroup analysis for *RET* mutation positive and *RET* M918T mutation positive (n=45 and 41 patients in the vandetanib and placebo arm, respectively) showed a substantial response for vandetanib (Figure 4.19).[33] The ERG did find a recent publication for this trial that showed a median PFS of 8.4 months for the placebo arm in patients with both progression and symptoms at baseline.[38]

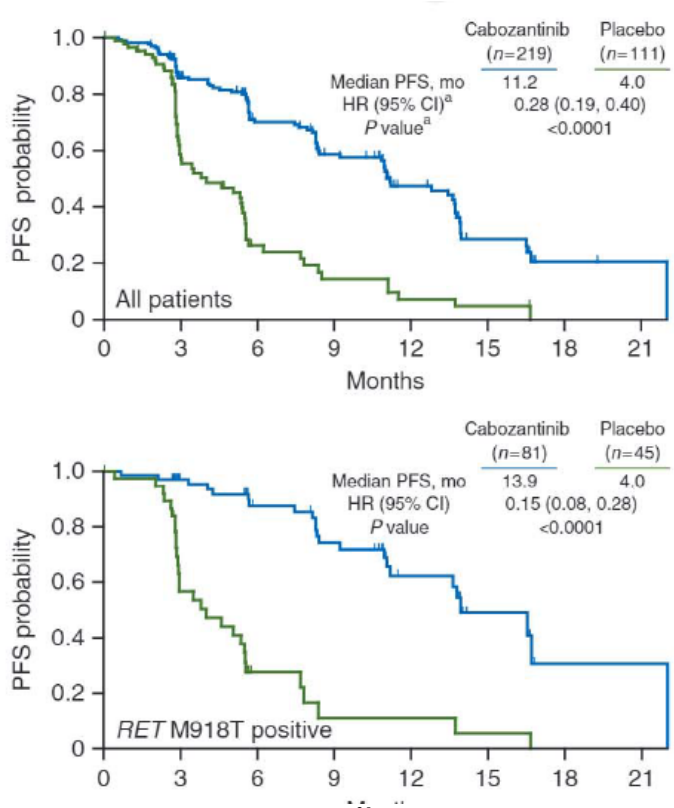
A naïve comparison of PFS Kaplan-Meier curves of progression-free survival in the EXAM and ZETA trials shows that PFS was considerably better in the placebo arm of the ZETA trial when compared with the EXAM trial (see Figures 4.17 and 4.18).

In the EXAM trial, the median OS with cabozantinib versus placebo for all patients was 26.6 versus 21.1 months ($p=0.24$), respectively; and for the *RET* M918T positive group 44.3 versus 18.9 months ($p=0.03$), respectively. Only the *RET* M918T positive subgroup showed a substantial benefit in OS for patients receiving cabozantinib when compared to placebo (Figure 4.20).[30]

In the ZETA trial, no median OS was provided and no results for OS based on the *RET*-mutation status were reported. At data cut-off after the median follow-up of 24 months, the authors state that the overall survival data were immature and the reported HR was (HR 0.89; 95% CI 0.48 to 1.65; Figure 4.21). The final survival analysis was planned when 50% of the patients have died.[33]

Looking at data from both Figures 4.20 and 4.21, OS for placebo in the ZETA trial is considerably better than OS for placebo in the EXAM trial; similarly, to the results of PFS, when compared with the EXAM trial.

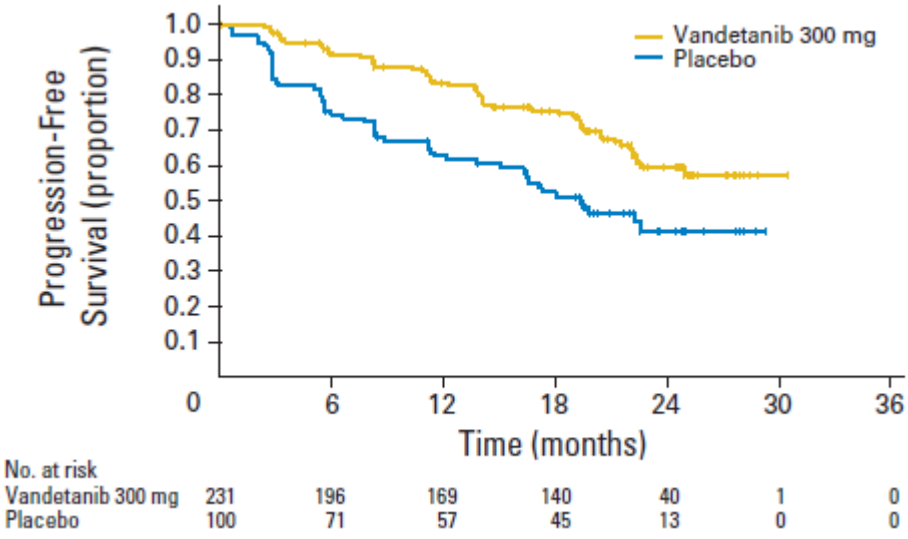
Figure 4.17: PFS for cabozantinib and placebo (EXAM trial)



Source: Schlumberger et al. 2017.[30]

Kaplan-Meier curve of progression-free survival (PFS) in the (A) overall intent-to-treat population and (B) in patients with RET M918T-positive disease. Analyses for the ITT population were stratified by randomisation stratification factors, and analyses for patients with RET M918T-positive disease were unstratified.

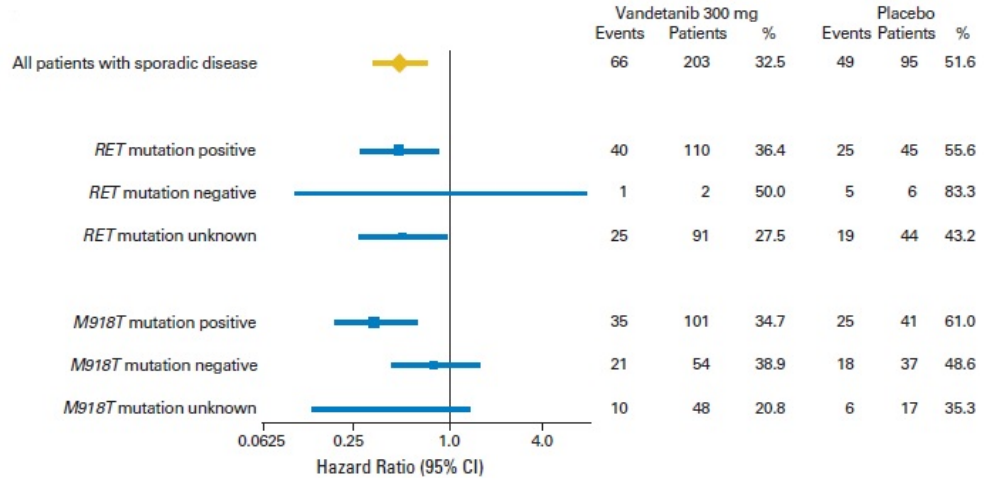
Figure 4.18: PFS for vandetanib and placebo (ZETA trial)



Source: Wells et al. 2012.[33]

Note: Kaplan-Meier curve of progression-free survival (PFS; intention-to-treat population; all randomly assigned patients); derived from all available centralized Response Evaluation Criteria in Solid Tumors (RECIST) assessments.

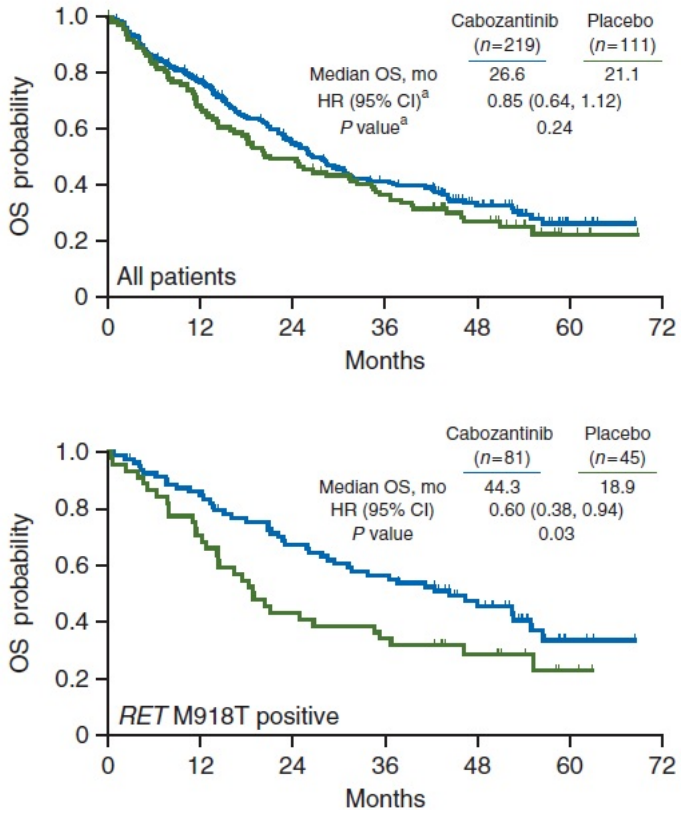
Figure 4.19: HRs for PFS for vandetanib and placebo (ZETA trial)



Source: Wells et al. 2012.[33]

Note: Forest plot of hazard ratios for PFS according to rearranged during transfection (RET) mutation status and M918T mutation status in patients with sporadic medullary thyroid carcinoma. A hazard ratio <1 favours vandetanib. The analyses were performed using a log-rank test with treatment as the only factor.

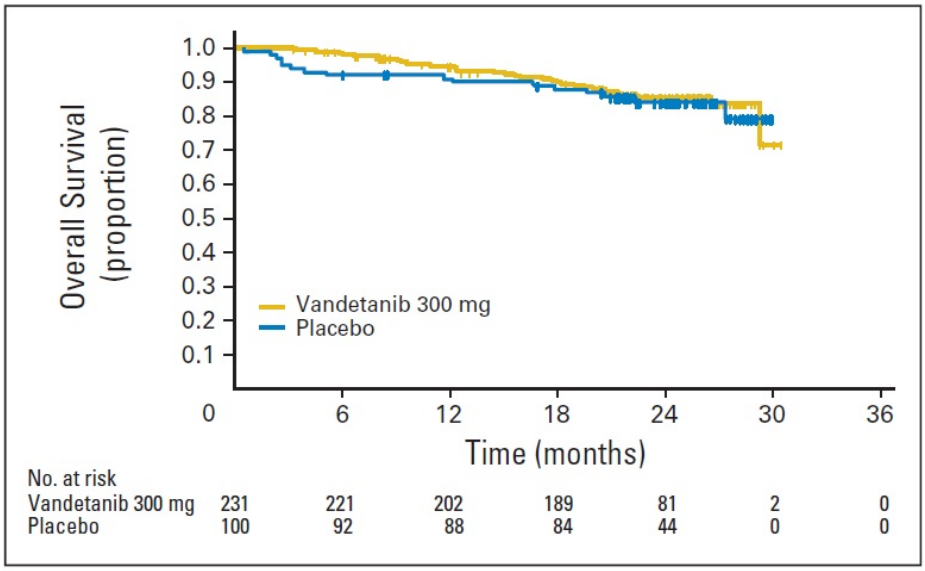
Figure 4.20: OS for cabozantinib and placebo (EXAM trial)



Source: Schlumberger et al. 2017.[30]

Kaplan-Meier curve of overall survival (OS) in the (A) overall intent-to-treat population and (B) in patients with RET M918T-positive disease. Analyses for the ITT population were stratified by randomisation stratification factors, and analyses for patients with RET M918T-positive disease were unstratified.

Figure 4.21: OS for vandetanib and placebo (ZETA trial)



Source: Wells et al. 2012.[33]
Note: Kaplan-Meier curve of overall survival (intention-to-treat population; all randomly assigned patients)

As shown above, neither the EXAM trial nor the ZETA trial is a perfect match for LIBRETTO-001 and the current decision problem. However, although it is impossible with the data available to compare the EXAM and ZETA RET mutation subgroup data, it is possible to compare the placebo groups for the ITT population. This shows that, although the eligibility criteria seemed to be the same for the trials and that there is some similarity in baseline characteristics, their outcomes, particularly in terms of placebo PFS are quite different. Given that it is unclear which of the trials provides a better match to the population consistent with the decision problem and that of LIBRETTEO-001, notwithstanding the effect of RET subgroup status, the better PFS for ZETA does highlight the possibility that the estimates used for BSC obtained from EXAM might be too low. This might mean that the effectiveness of selpercatinib relative to BSC might have been overestimated. It would therefore be useful for the committee to see the results of a MAIC comparing selpercatinib with BSC using the placebo arm of the ZETA trial instead of the EXAM trial. Results of such an analysis will be equally unreliable as the MAIC presented in the CS. Nevertheless, it is possible that the EXAM trial underestimated PFS in BSC patients, while the ZETA overestimated PFS in BSC patients. The actual PFS might well lie somewhere between the results of a MAIC using EXAM and one using ZETA.

If the committee agrees, the company should be asked to perform a MAIC using ZETA and to use those data in the economic model.

4.6 Conclusions of the clinical effectiveness section

The company presented one single arm study with data for selpercatinib: the LIBRETTO-001 study. LIBRETTO-001 is an ongoing, multicentre, single arm, open-label study with the intent of studying the pharmacokinetics, safety, and maximum tolerated dose of selpercatinib and to permit a preliminary efficacy and safety assessment in patients with RET-altered solid tumours.

The LIBRETTO-001 study included 702 patients ≥12 years old with locally advanced or metastatic solid tumours, including RET fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation) who progressed on or were intolerant to standard therapy,

or no standard therapy exists, or in the opinion of the Investigator, were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and an ECOG ≥2 or LPS≥40%.

As of the 16 December 2019 data cut-off, enrolled patients included: 226 patients with RET-mutant MTC (124 of these 226 were previously treated with cabozantinib and/or vandetanib) and 27 patients with RET fusion-positive thyroid cancer (19 of these 27 were previously treated). [redacted] patients in the MTC analysis sets were recruited from sites in the UK, but details of the cohorts in which they were enrolled is not available. Further details on how many patients from the TC analysis set are from the UK are not available.

RET-mutant MTC

For the RET-mutant MTC patient group, the integrated analysis set (IAS), consisted of patients who had received one or more lines of prior therapy of cabozantinib or vandetanib (n=124). The ORR was [redacted] by IRC assessment. As such, the majority of patients treated with selpercatinib experienced at least a partial response. For the [redacted] responding [redacted] patients, the median DOR by IRC [redacted], with [redacted] events observed and median DOR follow-up of [redacted] months. Median PFS by the IRC was [redacted], with [redacted] alive and progression-free by IRC at the data cut-off. The median OS was not reached [redacted], with [redacted] of patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted]

In the absence of randomised controlled trials of selpercatinib vs. any specified comparator, and because LIBRETTO-001[28] is a single arm study, an unanchored MAIC was used to generate relative efficacy estimates vs. cabozantinib and placebo (used a proxy for BSC) for the *RET*-mutant MTC population.

In addition to LIBRETTO-001,[28] the company stated that their SLR identified two relevant trials of comparator therapies (cabozantinib and vandetanib) at their recommended doses in patients with *RET*-mutant MTC (EXAM[30-32] and ZETA[33]). Vandetanib is not considered a relevant comparator in the UK and was not included in the scope for this appraisal,[23] hence, only LIBRETTO-001[28] and EXAM[30] were considered in the CS.

The company excluded the ZETA trial because vandetanib is not considered a relevant comparator in the UK. However, that is not a valid argument when single arms from trials have been selected. The placebo arm from the ZETA trial fulfils the inclusion criteria and should have been included. We will present some results from the ZETA in Section 4.5 of this report to show how this omission may have impacted results.

An unanchored matching-adjusted indirect comparison (MAIC) was conducted using individual patient data (IPD) from the any-line population of the LIBRETTO-001 trial (the IAS and SAS1 datasets combined, n=212) and aggregate data from the EXAM trial.[30, 32] The data from LIBRETTO-001 included both treatment-naïve and pre-treated patients (one or more lines of prior cabozantinib or vandetanib) and the data from EXAM also included both pre-treated and treatment-naïve patients as results for these groups were not reported separately. The baseline characteristics of the *RET*-mutant subgroups were not available for the placebo arm of the EXAM study, therefore the baseline characteristics of the cabozantinib group were assumed to be similar to those of the placebo arm and were use in the MAIC.[1]

The MAIC used propensity score matching (PSM) to weight patients in the LIBRETTO-001 trial so their summary baseline patient characteristics matched those reported in EXAM. The variables used in

the matching model were age, weight, ECOG performance score, gender, smoking status and RET M918T mutation status as these were reported by both trials. Based on a meeting with a clinical expert in thyroid cancer, the company listed the following relevant prognostic factors: performance status, stage and grade at diagnosis, baseline CNS metastases, Cushing's disease, diarrhoea, prior therapy, and RET mutation type.[36] Of these, only performance status (ECOG) and RET mutation type (RET M918T mutation status) were included as matching variables in the MAIC.

PFS and OS results from the MAIC comparing selpercatinib with cabozantinib and placebo are shown in Table 4.31 and KM curves are in Figures 4.15 and 4.16 (see Section 4.4.1 of this report).

RET fusion-positive TC

For patients with previously treated *RET* fusion-positive TC (n=19), the ORR was 78.9% (15/19; 95% CI: 54.4, 93.9) by IRC. The median DOR was 18.43 months by IRC (95% CI: 7.6, NE), with [redacted] events observed and median DOR follow-up of 17.51 months and [redacted] in response for at least 12 months. By Kaplan–Meier estimate, the probability of remaining in response at six and 12 months was [redacted] and [redacted], respectively. For the previously treated *RET* fusion-positive thyroid cancer patients followed for at least six months from first dose, the median PFS by IRC was 20.07 months (95% CI: 9.4, NE), with [redacted] alive and progression-free by IRC at the data cut-off, [redacted] events observed and median follow-up of 13.73 months. By Kaplan–Meier estimate, the probability of being progression-free at six and 12 months was [redacted] and 64.4% (95% CI: 37.0, 82.3), respectively. For previously treated *RET* fusion-positive thyroid cancer patients, the median OS was not reached [redacted], with [redacted] patients still alive and median follow-up of [redacted] months. At 12 months, the OS rate was [redacted].

The company's SLR did not identify any RCTs of relevant comparators, in patients with *RET* fusion-positive TC. Two phase III, double-blind, trials were identified that included a placebo arm that the company considered could be considered a reasonable proxy for BSC, in patients with *RET* fusion-positive TC who have received prior TKIs (DECISION[34] and SELECT[35]). A naïve indirect treatment comparison (ITC) was performed which compared PFS directly between the selpercatinib arm of LIBRETTO-001 and the placebo arm of SELECT, without any matching. This showed that selpercatinib improved PFS compared with BSC in the previously treated RET fusion-positive TC population. The median PFS were 20.07 months (95% CI 9.4 to not estimable) in the previously treated LIBRETTO-001 patients, 3.6 months (1.9 to 3.7) in the previously treated SELECT patients and 3.7 months (95% CI 3.5 to 4.5) in the SELECT ITT population.

ERG comment: As pointed out in the CS both the MAIC for the *RET*-mutant MTC population and the ITC for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators. An unanchored MAIC was used to compare selpercatinib with BSC and cabozantinib for OS and PFS. However, this can only include those prognostic factors and effect modifiers which are reported by both studies, other important factors may be missing and MAIC results are likely to be biased due to unobserved confounding. OS data were not available for the *RET*-mutant MTC population and had to be estimated using the results for the *RET* M918-positive population which is likely to underestimate OS for selpercatinib compared to cabozantinib.

OS and PFS results were not reported by treatment-naïve and previously treated patients in the EXAM trial so analyses by line of therapy were not possible. The results are also based on subgroups with small numbers of patients, which also affects their reliability. The CS did not contain any discussion

on the likely amount of residual systematic error in the MAIC but did also present results from a naïve indirect treatment comparison (unweighted results) which were similar to the MAIC results. However, as both analyses used selpercatinib data from a single-arm study, the results may be unreliable.

A naïve ITC was performed for the *RET* fusion-positive TC population using single-arm selpercatinib and BSC (placebo) data from two studies. OS data are immature and the pre-treated subgroup from LIBRETTO-001 was small (19 patients). BSC data came from the SELECT study but this was not limited to patients with a *RET* fusion. OS was not analysed as it was affected by patient crossover from placebo to active treatment. Given that this analysis was based on small patient numbers and a comparison of single arms without any attempts to balance the patient groups, the PFS results are also likely to be uncertain.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Searches were not performed to identify cost effectiveness studies. The company justified the absence of cost effectiveness searches as follows: *'As thyroid cancer is a rare type of cancer, and there are no other selective RET kinase inhibitors currently available to patients, it was not considered necessary to conduct a SLR to identify relevant previous economic evaluations*'.[1] A targeted literature review was conducted to identify NICE technology appraisals for patients with TC and MTC. No details of this targeted literature review were reported in the CS. Appendix G explained the reasoning behind the decision not to conduct searches for cost effectiveness studies and provided a table of economic evaluations identified in the searches for health-related quality of life and resource use data (Table 15 of the CS appendices).[29]

Appendices H and I of the CS reported the literature searches used to identify health-related quality of life, and resource use and cost data. One overarching search strategy was used to identify all health-related quality of life, and resource use and cost data. Searches were conducted on 12 August 2019 and 7-8 October 2019. A summary of the resources searched is provided in Table 5.1.

Table 5.1: Resources searched for health-related quality of life, and resource use and cost data.

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Not reported	Not reported	12 August 2019
	PubMed	Not reported	Not reported	12 August 2019
	EconLit	Not reported	Not reported	12 August 2019
	Cochrane Library	Not reported	Not reported	12 August 2019
Conference proceedings	ISPOR, ASCO, ESMO and IASLC via Embase	Not reported	Not reported	12 August 2019
HTA websites	UK - UYCRD	https://www.crd.york.ac.uk/CRDWeb/	All years	7-8 October 2019
	Tufts Medical Centre CEA	http://healtheconomics.tuftsmedicalcenter.org/cear4/Searchin		

Search strategy element	Resource	Host/source	Date range	Date searched
		gtheCEARegistry/SearchtheCEARegistry.aspx		
	US - ICER	https://icer-review.org/		
	UK - NICE	https://www.nice.org.uk/		
	UK - SMC	https://www.scottishmedicines.org.uk/		
	Canada - CADTH	https://www.cadth.ca/		
Bibliographic lists of seven relevant articles and systematic reviews were searched for relevant primary articles				
ISPOR = International Society for Pharmacoeconomics and Outcomes Research; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; IASLC = International Association for the Study of Lung Cancer; UYCRD = University of York's Centre for Research and Dissemination (including the National Health Service Economic Evaluation Database (NHS EED) and the HTA database); CEA = Cost Effectiveness Analysis Registry; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; CADTH = Canadian Agency for Drugs and Technologies in Health				

ERG comment:

- The company did not conduct literature searches for cost effectiveness studies. A targeted literature review to identify relevant NICE technology appraisals was conducted instead. Details of the targeted literature review searches were not reported in the CS.
- The selection of databases searched for health-related quality of life, and resource use and cost data were satisfactory, and searches were clearly reported and reproducible. The database name and date searched were provided. The database host and database date range were not provided.
- The Cochrane Library was searched, but as the NHS EED and HTA databases are no longer available, it was probably not worth searching.
- The CS reported that conference abstracts published in the two years prior to the database searches were identified through manual searching. However, it appears that conference abstracts were identified via the Embase searches, and not through manual searching. This was confirmed by the response to the ERG clarification letter.[24]
- HTA agency website searches were conducted, and full details of the search terms used, dates of searches, and results were reported.
- The database date ranges were not reported, but a publication date limit was used: '*January 2017 to present*'. The justification for this three-year date limit was to '*provide sufficient overlap'* with the three NICE technology appraisals used to provide data for the economic model.
- It is not clear if the search facets used to identify health-related quality of life and resource use/cost data were based on validated search filters, such as those published on the ISSG Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/. It is recommended practice to provide citation details of any study design filters used.[25]
- Truncation and proximity operators were used inconsistently.
- The results of the searches presented in the PRISMA diagram (Appendix H.2, Figure 2) appear to have been derived from a broader search including search terms for NSCLC. Full details of this broader search were not reported in the CS.
- Searches were conducted in August 2019 (for the database searches) and October 2019 (for the HTA agency searches) and were a year out of date. An update of the searches before submission

to NICE would have been appropriate and may have identified potentially relevant data published since October 2019.

5.1.2 Inclusion/exclusion criteria used in the study selection

The company's economic SLR aimed to identify HRQoL and resource use and cost data.[1] The company stated that as thyroid cancer is a rare type of cancer, and there are no other selective RET kinase inhibitors currently available to patients, it was not considered necessary to conduct a SLR to identify relevant previous economic evaluations.[29] However, they did a targeted literature review (TLR) of NICE technology appraisals to identify economic evaluations relating to the treatment of patients with TC and MTC in UK clinical practice.

The inclusion/exclusion criteria in the HRQoL and cost and resource use studies shown in Table 21 of Appendix H.[29]

ERG comment: Additional evidence relating to relevant comparators may have been missed by not conducting a full SLR for economic evaluation. No eligibility criteria were shown for economic evaluations beyond the statement that the search was for NICE technology appraisals for the treatment of patients with TC and MTC.

The HRQoL and cost and resource use criteria appear reasonable. No language restrictions were mentioned, although the CS does state that five of the 63 studies that were not eliminated at full text screening were non-English articles. The PRISMA diagram in Figure 2 of Appendix H indicates that these were excluded, based on language.[29]

5.1.3 Identified studies

The CS states that the economic evaluation TLR identified two relevant appraisals: cabozantinib for treating MTC (TA516), and lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535).[16, 18] The CS states that economic analyses and systematic reviews that were identified in this search were included at the first stage of screening, used for identification of primary studies, and then excluded. A summary of all of the economic evaluations identified in the SLR can be found in Table 15 of the CS appendices.[29]

Tables 22 and 24 of the CS appendices show the HRQoL and cost and resource use studies which were included in the SLR.[29]

ERG comment: The list of economic evaluations identified in the SLR contains economic evaluations which are not NICE appraisals. It is not clear how these were found in the TLR of previous NICE appraisals or whether they were excluded automatically or on the basis of some eligibility criteria.

The PRISMA diagram indicates that 292 records were included in the SLR.[29] However, Table 22 shows only four HRQoL studies were included and Table 24 shows only 30 cost and resource use studies included. The company confirmed that the PRISMA diagram combines articles identified for NSCLC and TC and that the unaccounted for included articles all related to NSCLC and were therefore not included in this appraisal. It is also concerning that the HRQoL study by Fordham et al., used by the company in the model was not identified in the HRQoL SLR as the SLR only searched for studies from January 2017, assuming any relevant studies published prior to this time would be captured in prior NICE appraisals.[39] It cannot be assumed that prior appraisals captured and reported all evidence relevant to this appraisal and therefore relevant evidence may have been missed.

5.1.4 Interpretation of the review

It was very difficult to follow the review given that it was conducted for both NSCLC and TC and no disaggregation was given in the PRISMA diagram. It is unclear to what extent information was missed due to the company decision not to conduct a full SLR for economic evaluations. Inclusion/exclusion criteria appeared reasonable for the HRQoL and cost and resource use SLR, however the company failed to include the language criteria which was clear from the text and PRISMA diagram. This criterion may have led to relevant information being missed. It is also concerning that the HRQoL study by Fordham et al.,[39] used by the company in the model, was not identified in the HRQoL SLR. It is unclear how many other studies may have been missed.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in ERG report)
Model	The company developed a de-novo partitioned survival model in Excel.	A standard approach was used, which aligns with previous appraisals TA516 and TA535 in advanced MTC and TC populations.[18, 20]	Section 5.2.2
States and events	The model contains three states: progression free, progressed disease and death. All patients enter the model in the progression free state and transition to either progressed disease or death according to the PFS and OS curves in the model.	The chosen structure represents the progression of the condition and aligns with previous appraisals TA516 and TA535 in advanced MTC and TC populations.[16, 18]	Section 5.2.2
Comparators	Both for the *RET*-mutant MTC and the *RET*-fusion positive TC population, the relevant comparator is BSC	The expected license for selpercatinib will be for patients requiring systemic treatment following prior treatment with cabozantinib and/or vandetanib or prior treatment with a multikinase inhibitor (MKI), for the *RET*-mutant MTC and the *RET* fusion-positive TC, respectively. For these patients, BSC is the only alternative.	Section 5.2.4
Treatment effectiveness	For patients with *RET*-mutant MTC, the effectiveness of selpercatinib on PFS and OS was based on data from LIBRETTO-001 (any-line population; n=212) and the effectiveness of BSC on PFS and OS was based on data from patients receiving placebo in EXAM (n=62 patients with *RET*-mutant MTC for PFS, and n=45 patients with *RET*-M918-positive MTC for OS).	No head-to head trials comparing the treatments under consideration were available. A MAIC was performed to match baseline characteristics for *RET*-mutant MTC, but this was not feasible for *RET*-fusion positive TC due to the small sample size (n=19) from LIBRETTO-001.	Section 5.2.6
Adverse events	Grade ≥3 adverse events with at least 2% difference in frequency between interventions in the model. The probabilities of AEs for	Grade ≥3 AE are expected to have the greatest impact on patients	Section 5.2.7

	Approach	Source/Justification	Signpost (location in ERG report)
	selpercatinib were based on the MTC safety analysis set of the LIBRETTO-001 trial (n=[redacted]). Probabilities of AE for BSC in RET-mutant MTC were taken from the EXAM trial and from SELECT for BSC in RET fusion-positive TC.		
Health-related QoL	HRQoL data was collected using the EORTC QLQ-C30 in the LIBRETTO-001 trial however this was not appropriately mapped to EQ-5D utilities that could be used in the model. Therefore the model used utility values from a vignette study by Fordham et al.	EQ-5D data was not collected in the trial. The mapping requested by the ERG at clarification did not produce plausible values that could be used in the model. The utility values from the study by Fordham et al. have been used in previous appraisals TA516 and TA535 in advanced TC and MTC populations and were considered reflective of the utility of RET fusion positive TC and RET-mutant MTC patients.[16]	Section 5.2.8
Resource utilisation and costs	The company base-case analysis included drug acquisition costs, pharmacist costs for drug dispensing, the costs for monitoring in the PF and PD health states, and the costs for palliative care during the last month of life. Costs were included from the NHS and PSS perspective.	According to NICE reference case.	Section 5.2.9
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section 5.2.5
Sensitivity analysis	Probabilistic and one-way sensitivity analysis.	According to NICE reference case.	Section 6.2

AE = adverse event; HRQoL = health related quality of life; MAIC = matching-adjusted indirect comparisons; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival; PSS = personal social services; QoL = quality of life; SLR = systematic literature review; ToT = time on treatment.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to NICE reference case
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A time horizon of 25 years is used in the model, which the company report can be considered lifetime. However, when the company's base-case Weibull curve is used for OS in the MTC population, approximately 10% of patients are still alive at 25 years.
Synthesis of evidence on health effects	Based on systematic review	No head-to-head evidence between selpercatinib and BSC was available. An unanchored MAIC was used to compare selpercatinib with BSC in the *RET*-mutant MTC population and a naïve ITC was performed for the *RET* fusion-positive TC population.
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALYs). The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects are expressed in QALYs. The EQ-5D was not collected in the LIBRETTO-001 trial. EORTC QLQ-C30 data was available but this was not appropriately mapped to EQ-5D utility values. Therefore, utilities in DTC patients from the literature were used.[39]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The EORTC QLQ-C30 patient reported trial data was not used in the model. The utility values used in the model were estimated using a vignette study, in which members of the general population valued health state descriptions designed to represent DTC cancer health states.[39] No patient reported data was included.

Element of health technology assessment	Reference case	ERG comment on company submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The utility values used in the model were valued in a representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (3.5%)	According to NICE reference case

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; UK = United Kingdom.

5.2.2 Model structure

The company constructed a de novo model in Microsoft Excel. The model is a cohort-based partitioned survival model consisting of three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death.[1] All patients enter in the PF state. The proportion of patients in the PF curve is defined by the PFS curve. The proportion of patients in the death state is defined by the OS curve and the proportion of patients in the PD state is defined by the proportion of patients alive minus the proportion progression free.

ERG comment: The model structure is considered appropriate for the decision problem.

5.2.3 Population

The patient population that is considered in the cost effectiveness analysis consists of adults and adolescents aged 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib, and adults with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with a multikinase inhibitor (MKI). It should be noted that the wording of the anticipated EU conditional marketing authorisation was changed between the time of the original CS and the time of providing the response to the ERG's clarification questions. In the original CS,[1] the relevant population was defined as: adults and adolescents aged 12 years and older with advanced *RET*-mutant MTC who require systemic therapy, and adults with advanced *RET* fusion-positive TC who require systemic therapy and who have progressed following prior systemic treatment.

The population that is defined in the updated anticipated EU conditional marketing authorisation is consistent with the following subset of patients that were included in the 16 December 2019 data cut-off from the LIBRETTO-001 trial: n=124 patients with advanced *RET*-mutant MTC who received one or more lines of prior cabozantinib or vandetanib and n=19 patients with advanced *RET* fusion-positive TC who received prior systemic therapy with lenvatinib or sorafenib. An additional subgroup in LIBRETTO-001 consisted of n=88 patients with *RET*-mutant MTC who were naïve to cabozantinib or vandetanib. This subgroup was consistent with the population as defined in the original submission, but not with the population as defined in the updated, anticipated EU conditional marketing authorisation. Despite it being inconsistent with the indicated population, this subgroup was still included in the revised company base-case in the estimation of the treatment effect (see Section 5.2.6).

The subgroup of patients with *RET*-mutant MTC from the any-line population in LIBRETTO-001 had a mean age of [redacted] years and consisted of [redacted]% females, as indicated by the company in response to the ERG's clarification questions. The original submission erroneously stated a mean age of [redacted] years and percentage of [redacted]% females, and these values were also used in both the original and revised company base-case analysis. The subgroup of patients with *RET* fusion-positive TC had a mean age of [redacted] years and consisted of [redacted]% females.

ERG comment: The population that is used to inform clinical effectiveness assumptions for RET-mutant MTC in the model consists of first-line and second-line patients and is therefore not consistent with the population as indicated by the updated marketing authorisation of only second-line patients. It is therefore uncertain to what extent the cost effectiveness results are applicable to the relevant population. The ERG prefers to use the MAIC-adjusted mean age as starting age in the model for *RET* fusion-positive TC, which is [redacted] years.

5.2.4 Interventions and comparators

Selpercatinib, the intervention under consideration, is self-administered orally as 160 mg (i.e. two capsules of 80 mg) twice daily in 28-day cycles until disease progression or unacceptable toxicity, or another reason for treatment discontinuation. In LIBRETTO-001 treatment with selpercatinib could continue after disease progression, after approval by the sponsor, if patients were still benefitting from it. Clinical expert opinion consulted by the company also indicated that treatment may continue beyond progression.[36] If necessary, doses can be reduced in steps of 40 mg.

For patients with advanced *RET*-mutant MTC who progress following, or are unresponsive to, prior treatment with cabozantinib or vandetanib, the only remaining treatment option is BSC. The evidence base for the clinical effectiveness of BSC in these was based on the subgroup of patients with *RET*-mutant MTC who received placebo in the EXAM trial (n=62) for PFS, and on the subgroup of patients with *RET*-M918T-positive MTC who received placebo in the EXAM trial (n=45) for OS. The EXAM trial was designed to evaluate the clinical effectiveness of cabozantinib in adults with advanced MTC and included a subgroup of patients with *RET*-mutant MTC who received cabozantinib (n=107). Although cabozantinib was included as a comparator in the original CS, in which the definition of the indicated population included patients with MTC who were naïve to cabozantinib or vandetanib, it is no longer relevant for the updated definition of the indicated population and therefore not considered as a comparator to selpercatinib in the current appraisal. However, the subgroup of patients with *RET*-mutant MTC who received cabozantinib in EXAM was still used in the revised company base-case for the purpose of calculating the propensity score weights (PSW) that are used in the matching-adjusted indirect comparison (MAIC) of selpercatinib versus BSC to match the baseline characteristics of the patients with *RET*-mutant MTC who received selpercatinib in LIBRETTO-001.

For patients with advanced *RET* fusion-positive TC who progress following, or are unresponsive to, prior treatment with an MKI, the only remaining treatment option is BSC. The evidence base for the clinical effectiveness of BSC in patients with *RET* fusion-positive TC whose disease has progressed following prior treatment was based on the patients from the ITT population in the SELECT trial who received placebo (n=131). The SELECT trial only included patients with differentiated thyroid cancer (DTC); which is the combination of papillary thyroid cancer, which accounts for 80-85% of all thyroid cancers in Europe, and follicular thyroid cancer, which accounts for 5-10% of all thyroid cancers in Europe.[3] For patients with other types of advanced TC, such as anaplastic or undifferentiated TC, who received prior treatment with an MKI, BSC also would be the only treatment option. In both trials, LIBRETTO-001 and SELECT, the majority of patients had the papillary form of thyroid cancer (68.4% and 51.9%, respectively). It is unknown what the proportion of patients with *RET*-fusions was in SELECT and 79.4% of patients in SELECT had not received prior systemic therapy. However, the treatment effect of placebo in SELECT was similar for first-line and pre-treated patients. Treatment effectiveness for OS of BSC in SELECT was confounded by crossover. Upon progression, 87.8% of patients in SELECT who were randomised to placebo crossed over to lenvatinib and 12.2% of patients received subsequent anti-cancer treatments that were not part of the trial protocols (e.g. pazopanib and sorafenib).[40]

For patients with advanced *RET*-mutant MTC and patients with advanced *RET* fusion-positive TC, the company stated that BSC is assumed to consist of monitoring and palliative care.[1] As indicated in Document B of the CS,[1] the company assumed that resource use in BSC is consistent with TA516[18] and that it is likely to be the same in the progression-free and the progressed disease health states. In contrast, the company discarded the BSC resource use estimates from TA516 in the model and instead assumed the same health state costs as for selpercatinib (i.e. which differ between the progression-free and progressed disease health states). The company indicated in response to the ERG's clarification questions that this was done based on clinical expert opinion, [24] who was shown the BSC resource use estimates from TA535.[16] The only documentation of clinical expert opinion consulted by the company that was available to the ERG indicated a concern that the BSC resource use that was assumed represented monitoring during active treatment. Given that the same resource use was assumed for selpercatinib and BSC, this concern was not resolved. As such, it is unclear what the company assumed that BSC consists of. The company considers that the placebo arms in EXAM and SELECT are suitable proxies for BSC, analogous to TA516 and TA535 respectively.[16, 18]

5.2.5 Perspective, time horizon and discounting

The analysis is performed from an NHS and PSS perspective, in line with the NICE reference case.[41] A time horizon of 25 years is used in the model, which represents a lifetime time horizon as per the NICE reference case.[41] All costs and benefits (i.e. life years and QALYs gained) are discounted at 3.5% per annum, which is in line with the NICE reference case.[41]

5.2.6 Treatment effectiveness and extrapolation

In the cost effectiveness model, health state occupancy was determined by the cumulative survival probabilities from OS and PFS curves.

For patients with *RET*-mutant MTC, the effectiveness of selpercatinib on PFS and OS was based on data from LIBRETTO-001 (any-line population; n=212) and the effectiveness of BSC on PFS and OS was based on data from patients receiving placebo in EXAM (n=62 patients with *RET*-mutant MTC for PFS, and n=45 patients with *RET*-M918-positive MTC for OS). Despite the relevant population for this appraisal consisting of second-line patients, the company used the any-line population from

LIBRETTO-001 since they consider it to provide a more robust sample size and to reduce possible bias that would be caused by comparing only pre-treated patients from LIBRETTO-001 with the mix of first-line and second-line patients from EXAM. The any-line population was adjusted in line with the EXAM population according to the proportion of patients who received prior TKI therapy in addition to other characteristics. Since the company anticipates that patients without prior TKI treatment perform better as they are at an earlier stage of disease, a comparison of only pre-treated patients from LIBRETTO-001 with the mixed population from EXAM could lead to an underestimation of the treatment effectiveness of selpercatinib relative to BSC.

Data on OS from patients with *RET*-M918-positive MTC receiving placebo in EXAM were used because no OS Kaplan-Meier (KM) data were available for the subgroup of *RET*-mutant patients in EXAM. The company notes that clinical experts were consulted on the comparability of the overall *RET*-mutant subgroup and the *RET* M918T-positive subgroup who confirmed that the treatment effectiveness of placebo may be similar in both subgroups. In absence of any trials comparing selpercatinib and BSC head-to-head and because LIBRETTO-001 is a single-arm trial, an unanchored MAIC was performed to match the population from LIBRETTO-001 to the *RET*-mutant MTC population receiving cabozantinib in EXAM using propensity score weighting. Details regarding the MAIC are described in Section 4.4. The propensity score weighting resulted in an exact match of the mean values for all included baseline characteristics, with an effective sample size for the LIBRETTO-001 population of n_{eff}=[redacted]. As described in Section 4.4.1, the matching was done using the baseline characteristics from the cabozantinib arm in EXAM because no baseline characteristics were available for the placebo arm.

For patients with *RET*-fusion positive TC, the effectiveness of selpercatinib on PFS and OS was based on data from LIBRETTO-001 (n=19) and the effectiveness of BSC on PFS and OS was based on data from patients receiving placebo in SELECT (n=131 patients with unknown *RET*-fusion status). A naïve indirect comparison without matching was performed, due to the small sample size of patients from LIBRETTO-001. OS data from SELECT were adjusted for confounding due to treatment crossover using a rank preserving structural failure time (RPSFT) model.

PFS data for patients receiving placebo in SELECT were also available for the subgroup of patients who were pre-treated with one prior TKI (n=27), in which treatment effectiveness was similar to the ITT population (i.e. in the pre-treated subgroup median PFS was 3.6 months (95% CI: 1.9 – 3.7) and the HR of lenvatinib versus placebo was 0.22 (95% CI: 0.12 – 0.41), in the ITT population median PFS was 3.6 months (95% CI: 2.2 – 3.7) and the HR of lenvatinib versus placebo was 0.21 (95% CI: 0.14 – 0.31)). No data on OS were available for the pre-treated subgroup in SELECT. For consistency, as well as considering the low number of patients in the pre-treated subgroup with PFS data available, the company used the ITT population from SELECT for both PFS and OS. Although, similar as for the RET-mutant MTC population, no head-to-head trials that compare selpercatinib and BSC were available and LIBRETTO-001 was a single-arm trial, a MAIC was not feasible due to the small number of patients from LIBRETTO-001 (n=19) and therefore a naïve indirect comparison was performed.

For the EXAM and SELECT trials pseudo patient-level data were derived from published KM curves and number of event information using the algorithm by Guyot et al. 2012.[42] An overview of the data sources that were used to inform the input parameters of the company base case regarding baseline characteristics, PFS and OS are shown in Table 5.4.

Table 5.4: Sources of clinical evidence for selpercatinib and best supportive care

Parameter	Selpercatinib	BSC
RET-mutant MTC		
Baseline characteristics	LIBRETTO-001 any-line population (n=212)	
PFS	Propensity score-weighted KM data from the *RET*-mutant MTC any-line population receiving selpercatinib in LIBRETTO-001, matched to the baseline characteristics of patients with *RET*-mutant MTC receiving cabozantinib in EXAM (n_{eff} = [redacted])	Unweighted KM data for the *RET*-mutant subgroup receiving placebo (n=62) in the EXAM trial
OS	Propensity score-weighted KM data from the *RET*-mutant MTC any-line population receiving selpercatinib in LIBRETTO-001, matched to the baseline characteristics of patients with *RET*-mutant MTC receiving cabozantinib in EXAM (n_{eff} = [redacted])	Unweighted KM data for the *RET*-M918T subgroup receiving placebo (n=45) in the EXAM trial
RET fusion-positive TC		
Baseline characteristics	LIBRETTO-001 pre-treated subgroup (n=19)	
PFS	KM data from pre-treated patients with *RET* fusion-positive TC receiving selpercatinib in LIBRETTO-001 (n=19)	KM data from the ITT population receiving placebo in SELECT (n=131)
OS	KM data from pre-treated patients with *RET* fusion-positive TC receiving selpercatinib in LIBRETTO-001 (n=19)	RPSFT-adjusted KM data from the ITT population receiving placebo in SELECT (n=131)

Based on Table 49 in the CS.[1]
CS= company submission; ITT = intention to treat; KM = Kaplan-Meier; MTC = medullary thyroid cancer; n_{eff} = effective sample size; OS = overall survival; PFS = progression-free survival, RET = rearranged during transfection; RPSFT = rank preserving structural failure time; TC = thyroid cancer; .

ERG comment: Several uncertainties were introduced through the data sources that were used to inform the survival analyses:

First, the assumptions on clinical effectiveness for patients with *RET*-mutant MTC were based on an analysis of data from a mixed population of first- and second-line patients. Although this was done consistently for both treatments under comparison, it was not consistent with the population of only second-line patients that was indicated by the marketing authorisation. Despite the inclusion of 'prior TKI use' as a matching variable for the MAIC, uncertainty remains in relation to whether similar results would have been obtained if only a population of second-line patients had been analysed. This is especially so given the large difference in PFS between the first-line patients and the second-line patients in LIBRETTO-001.

Second, there is uncertainty concerning the assumptions about clinical effectiveness for patients with *RET*-mutant MTC that inherently follows from the use of an unanchored MAIC. Despite the MAIC resulting in an exact match between the mean values for the baseline characteristics of patients from

LIBRETTO-001 and EXAM, uncertainty remains due to a) matching the IPD to only summary statistics and b) potential unobserved or unadjusted for confounding variables. In addition, the effective sample size from LIBRETTO-001 was reduced from n=212 to n=[redacted] due to the propensity score weighting that is applied for the MAIC. Lastly, in absence of baseline characteristics for the placebo arm in EXAM a compromise was made to match patients using data from the cabozantinib arm in EXAM instead of the placebo arm.

Third, there is uncertainty concerning the assumptions about the OS for patients with *RET*-mutant MTC receiving BSC as data was used from patients with *RET*-M918-positive MTC receiving placebo in EXAM. The company stated that clinical experts confirmed that the effectiveness of placebo may be similar in both groups, but no documentation of this was available to the ERG. On the contrary, in the documentation of clinical expert opinion consulted by the company that was available to the ERG,[36] the clinical experts noted that M918 status is a prognostic variable and they expected the *RET*-M918-positive group to do worse than the overall *RET*-mutant group. Thus, it is uncertain whether similar OS would have been obtained for all *RET*-mutant patients receiving placebo.

Fourth, there is substantial uncertainty with regards to the comparative effectiveness of selpercatinib versus BSC in patients with *RET*-fusion positive TC, as the PFS and OS of both treatments are compared from separate studies, with no attempt of matching or use of any other method to correct for confounding. Whilst the reason why this was done (the small sample of patients from LIBRETTO-001 with *RET*-fusion positive TC (n=19)) is justifiable, it should be recognised that such naïve indirect comparison leads to uncertainty regarding the accuracy of the estimated difference in PFS and OS.

Fifth, there is uncertainty about the assumptions on clinical effectiveness of BSC for patients with *RET*-fusion positive TC due to the use of data from patients in SELECT of whom the *RET*-fusion status was unknown. It is unknown whether these patients are representative for *RET*-fusion positive patients. This was also confirmed by clinical experts consulted by the company.[36]

Sixth, there is uncertainty regarding the assumptions on clinical effectiveness of BSC for patients with *RET*-fusion positive TC due to the use of data from SELECT that only included patients with DTC. It was unknown to what extent these data are representative for patients with other types of TC. The company indicated that the prognosis for other types of TC is generally known to be worse.

Seventh, there is uncertainty about the assumptions on clinical effectiveness of BSC for second-line patients with *RET*-fusion positive TC due to the use of data from a mix of first- and second-line patients in SELECT. For PFS, the company provided results based on only second-line patients that demonstrate that these were similar to the mixed population. For OS, it remains uncertain whether similar results would have been obtained if only data from second-line patients were used.

Eighth, there is uncertainty about the assumptions on OS for patients with *RET*-fusion positive TC receiving BSC due to the use of OS data from SELECT that were adjusted for confounding due to treatment crossover using a rank preserving structural failure time (RPSFT) model. These adjusted data were also used in TA535 and were preferred by the Assessment Group (AG) of that appraisal.[16] The AG in TA535 noted, following clinical advice consulted by the AG, that it was reasonable to assume that patients in SELECT who switched from the placebo arm to receive the experimental treatment (i.e. lenvatinib) would experience the same treatment effect as patients who were originally randomised to the experimental arm.[16] As such, the use of a RPSFT model could be considered as appropriate. However, a caveat to the use of the RPSFT model-adjusted OS results is that it requires the assumption that post-progression anti-cancer treatments, other than those permitted by treatment crossover, represent routine clinical practice.[16] As stated by the AG in TA535, it is unknown whether the post-

study anti-cancer treatments administered to patients in SELECT reflect the treatments that would be offered to patients in the NHS.[16]

5.2.6.1 Survival extrapolations

Since the follow-up time in all relevant trials was shorter than the model time horizon, extrapolation from the observed OS and PFS data was required.

For the extrapolation of survival data, a range of standard parametric distributions, including exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma, as well as flexible (i.e. spline) models were fitted using both stratified and unstratified approaches (the latter only for *RET*-mutant MTC, see explanation below). This was done in accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance on survival analyses.[43] The choice of survival model was based on curve fit as indicated by the estimated Akaike information criterion (AIC) and Bayesian information criterion (BIC), visual inspection, and clinical plausibility (as determined in TA516 and TA535 for BSC)[16, 18]. In the model, PFS was bound by OS as a minimum to prevent logical inconsistencies.

RET-mutant MTC

For PFS, a range of stratified and unstratified parametric functions were fitted to the weighted KM data of the any-line population of patients with *RET*-mutant MTC from LIBRETTO-001 that were generated in the MAIC and unweighted, pseudo patient-level KM data of patients with *RET*-mutant MTC receiving placebo in EXAM. The AIC and BIC values for the PFS extrapolations are shown in Table 5.5, and the extrapolated curves are shown for selpercatinib and BSC in Figure 5.1 and Figure 5.2, respectively.

Table 5.5: AIC and BIC values of the PFS extrapolations for selpercatinib and BSC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value indicates a better curve fit.
Source: Table 1 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; PFS = progression-free survival.

The AIC and BIC results indicated a similar statistical fit between the PFS survival functions, therefore the choice of survival curve for the company's base-case model was guided by visual fit. The company considered all functions to provide a very similar visual fit to the Kaplan–Meier data for BSC. The loglogistic was selected, as is shown in Figure 5.3, as it provided a good visual fit to the early KM-data and showed little variation in the long-term extrapolation as compared to the original analysis presented in the CS. This was aligned with the base case curve selected by the ERG in TA516. A range of alternative survival functions was explored in scenario analyses.

ERG comment: Whilst statistical and visual fit are relevant to assess the fit of various survival functions to the observed data, for the unobserved part of the extrapolation clinical plausibility is the most important factor to consider in choosing the base case curve. In the updated survival analyses for *RET*-mutant MTC that were provided to the ERG as an addendum to the response to the clarification letter,[44] consultation of clinical expert opinion was not mentioned. This in contrast to the original CS,[1] in which a MAIC was performed for the same population without using 'prior TKI use' as a matching variable that led to a very similar PFS curve, that stated that the loglogistic was selected based on clinical expert opinion. Due to the similarity of the curves between the original and updated analyses, the ERG assumed that the clinical plausibility of the PFS curves from the updated analysis is the same as in the original CS.[1] However, no documentation of clinical expert opinion consulted by the company on this matter was available to the ERG (i.e. neither for the original, nor for the updated survival analyses). The ERG agreed with the choice for the loglogistic curve for PFS for their base-case but also considered it important to emphasise the uncertainty that was demonstrated by the large variation in PFS curves for selpercatinib using alternative parametric functions. In contrast, using alternative parametric functions demonstrated relatively much less variation in PFS curves for BSC. Therefore, the ERG performed scenario analyses using a variety of parametric functions to explore how the uncertainty regarding PFS propagates into the cost effectiveness results.

Figure 5.1: Extrapolations for progression-free survival: selpercatinib

Source: Figure 1 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
KM = Kaplan Meier.

Figure 5.2: Extrapolations for progression-free survival: BSC

Source: Figure 2 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
BSC = best supportive care; KM = Kaplan Meier.

Figure 5.3: Loglogistic curves for progression-free survival: selpercatinib and BSC

Source: Figure 3 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
BSC = best supportive care; KM = Kaplan Meier.

For OS, a range of stratified and unstratified parametric functions were fitted to the weighted KM data of the any-line population of patients with *RET*-mutant MTC from LIBRETTO-001 that were generated in the MAIC and unweighted, pseudo patient-level KM data of patients with *RET*-M918T-positive MTC receiving placebo in EXAM. The AIC and BIC values for the PFS extrapolations are shown in Table 5.6, and the extrapolated curves are shown for selpercatinib and BSC in Figure 5.4 and Figure 5.5, respectively.

Table 5.6: AIC and BIC values of the OS extrapolations for selpercatinib and BSC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value indicates a better curve fit.
Source: Table 2 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; PFS = progression-free survival.

According to the company, the proportional hazards (PH) assumption was not violated. This was based on the *RET*-M918T subgroup KM data for placebo from EXAM and the PH assumption was also considered to hold for the RET mutant population for EXAM. Therefore, unstratified PH functions were explored across treatment arms. Given the large degree of uncertainty due to LIBRETTO-001 OS data immaturity, the company considered it an advantage of using unstratified PH functions that they allow for less flexibility across interventions and comparator arms. The company considered the Weibull curve to provide a plausible estimate of the OS treatment effect of selpercatinib relative to BSC, and therefore selected the Weibull curve that is shown in Figure 5.6 for the company base case. A range of

alternative survival functions, including those which relax the PH assumptions, was explored in scenario analyses.

ERG comment: The ERG considered the Weibull curve to provide an overly optimistic estimate of OS for selpercatinib, with [redacted] of patients still alive after 25 years. The ERG also considered that too much emphasis was placed by the company on the results of the statistical test for the PH assumption. In light of the limited evidence that is available, the ERG considered the PH assumption as too strong. In the original CS,[1] the Weibull OS curve was substantially lower than in the updated analyses and clinical expert opinion (of which no documentation on this matter was available to the ERG) consulted by the company indicated that the curve in the original CS may already overestimate OS for selpercatinib. For these reasons, the ERG explored alternative curves that included stratified functions and concluded that the stratified Weibull function provided the best visual fit, best long-term plausibility for BSC, and the most reasonable estimate of the benefit of selpercatinib relative to BSC in light of the limited evidence and immature data that is available.

Figure 5.4: Extrapolations for overall survival: selpercatinib

Source: Figure 4 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
KM = Kaplan Meier.

Figure 5.5: Extrapolations for overall survival: BSC

Source: Figure 5 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
BSC = best supportive care; KM = Kaplan Meier.

Figure 5.6: Weibull curves for overall survival: selpercatinib and BSC

Source: Figure 6 in the updated survival analysis that were provided as an addendum to the main response to the clarification letter.[44]
BSC = best supportive care; KM = Kaplan Meier.

RET fusion-positive TC

For PFS, a range of stratified parametric functions were fitted to the KM data of the pre-treated population of patients with *RET* fusion-positive TC from LIBRETTO-001 and pseudo patient-level KM data of the ITT population of patients receiving placebo in SELECT. To be consistent with the results from analyses performed by the assessment group (AG) in TA535 which indicated that the proportional hazards (PH) assumption was not valid for PFS, unadjusted OS or RPSFT model-adjusted OS in the SELECT trial, unstratified models were not explored by the company for the current appraisal. The AIC and BIC values for the PFS extrapolations are shown in Table 5.7, and the extrapolated curves are shown for selpercatinib and BSC in Figure 5.7 and Figure 5.8, respectively.

Table 5.7: AIC and BIC values of the PFS extrapolations for selpercatinib and BSC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value indicates a better curve fit.
Source: Table 54 in the CS.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; PFS = progression-free survival.

The AIC and BIC results indicated a similar statistical fit between the PFS survival functions, therefore the choice of survival curve for the company's base-case model was guided by visual fit, clinical plausibility and external validation with the outcomes observed in LIBRETTO-001 and SELECT. The stratified Weibull curve was selected based on feedback from clinical experts and is shown in Figure 5.9. A range of alternative stratified and spline-knot curves is explored in scenario analyses.

ERG comment: The ERG agrees with the company that clinical expert opinion may guide the choice of extrapolation curves for PFS when a similar fit and plausibility between several curves is indicated by AIC and BIC values, visual fit, and consistency with external data. As such, the ERG agrees with the choice for a stratified Weibull curve based on feedback from clinical experts. However, no documentation of clinical expert opinion consulted by the company on this matter was available to the ERG.

Figure 5.7: Extrapolations for progression-free survival: selpercatinib

Source: Figure 35 in the CS.[1]
CS = company submission; KM = Kaplan Meier.

Figure 5.8: Extrapolations for progression-free survival: BSC

Source: Figure 36 in the CS.[1]
BSC = best supportive care; CS = company submission; KM = Kaplan Meier.

Figure 5.9: Stratified Weibull curves for progression-free survival: selpercatinib and BSC

Source: Figure 37 in the CS.[1]
BSC = best supportive care; CS = company submission; KM = Kaplan Meier.

For OS, a range of parametric functions were fitted to OS data from pre-treated *RET* fusion-positive TC patients in LIBRETTO-001 and the RPSFT-adjusted KM data from the ITT population receiving placebo in SELECT. The AIC and BIC values for the OS extrapolations are shown in Table 5.8, and the extrapolated curves are shown for selpercatinib and BSC in Figure 5.10 and Figure 5.11, respectively. The company explored an additional option for the extrapolation of OS using piecewise exponential functions fitted to data for 0 to six months and for six months onwards, analogous to the approach used in TA535.[16] The piecewise exponential curves are also shown in Figure 5.12.

Table 5.8: AIC and BIC values of the OS extrapolations for selpercatinib and BSC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value indicates a better curve fit.
Source: Table 55 in the CS.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; OS = overall survival.

The AIC and BIC results indicated a similar fit between the OS survival functions, therefore the choice of survival curve for the company's base-case model was guided by visual fit, clinical plausibility and external validation with the outcomes observed in LIBRETTO-001 and SELECT. The company considered the results of the extrapolations using stratified functions as implausible, due to the curves often crossing or converging early along the time horizon. Based on feedback from clinical experts and for consistency with TA535, the piecewise exponential model was used to extrapolate OS in the company base-case analysis. A range of alternative, stratified curves is explored in scenario analyses.

Figure 5.10: Extrapolations for overall survival: selpercatinib

Source: Figure 38 in the CS.[1]
CS = company submission; KM = Kaplan Meier.

Figure 5.11: Extrapolations for overall survival: BSC

Source: Figure 39 in the CS.[1]
BSC = best supportive care; CS = company submission; KM = Kaplan Meier.

Figure 5.12: Piecewise exponential curves for overall survival: selpercatinib and BSC

Source: Figure 40 in the CS.[1]
BSC = best supportive care; CS = company submission; KM = Kaplan Meier.

ERG comment: Due to the very limited sample size (n=19) as well as data being very immature, there was much uncertainty regarding the OS estimates for selpercatinib. The ERG agrees that the extrapolations for OS using stratified functions produced implausible results, due to the early crossing or converging of curves that would indicate favourable results for BSC or only a marginal benefit of selpercatinib. The company chose to use the piecewise exponential function for OS extrapolations instead, based on clinical feedback and consistency with TA535. The ERG agrees that clinical plausibility is the most important factor to guide the choice of OS survival functions in this situation, but the documentation of clinical expert opinion consulted by the company on this matter was not available to the ERG. The AG in TA535 demonstrated a very clear and consistent linear trend for the cumulative mortality hazard from 1.5 years from diagnosis based on an analysis of an external dataset (SEER database), that led to their choice for an exponential curve to extrapolate OS.[16] The AG in TA535 also demonstrated that exponential trends could be observed in the data for lenvatinib and BSC from SELECT and concluded that this was the case for lenvatinib throughout the entire trial period (i.e. starting from timepoint 0) and for BSC starting from six months and onwards.[16] As such, the ERG agrees that a piecewise exponential function fitted to data from 0 to six months and from six months onwards is appropriate for BSC. For selpercatinib, a similar piecewise approach was adopted as for BSC. This implies the assumption that all patients receiving selpercatinib will survive up to six months since in the limited data that are available all patients survive up to this point in time. The ERG considers it likely that this assumption would not hold if more data were available on OS for selpercatinib. The ERG therefore agrees that the current approach is consistent with the approach for BSC and the currently available data but anticipates that a different (e.g. non-piecewise) approach for selpercatinib might be more appropriate once additional data from LIBRETTO-001 are available from a later data cut-off.

5.2.7 Adverse events

The company included grade ≥3 adverse events with at least 2% difference in frequency between interventions in the model.[1] The probabilities of AEs for selpercatinib were based on the MTC safety analysis set of the LIBRETTO-001 trial (n=[redacted]). Probabilities of AE for BSC in RET-mutant MTC were taken from the EXAM trial and from SELECT for BSC in RET fusion-positive TC.[31, 35] AEs incidences for patients with RET-mutant MTC and RET fusion-positive TC are displayed in Tables 56 and 57 of the CS respectively.

ERG comment: Some of the AEs included in Tables 56 and 57 of the CS, labelled as included in the model, were in fact not included as their incidence varied by less than 2% across the different treatment arms.

It should be noted that the MTC safety analysis set of the LIBRETTO-001 trial (n=[redacted]) also includes [redacted] patients who had non-measurable disease, according to Figure 6 of the CS, and were outside of the LIBRETTO-001 population used to inform efficacy in the model.[1]

No adjustment was made for AEs so this represents a naïve comparison between selpercatinib and placebo in the two included populations. It is unclear how differences in the study populations would have affected AE results, but the AE incidence has only a negligible impact on the overall costs and QALYs and hence on the ICER.

5.2.8 Health-related quality of life

HRQoL data were collected in the LIBRETTO-001 study for patients with *RET*-mutant MTC using the EORTC QLQ-C30.[1] HRQoL was measured prior to receiving drug on the first day of treatment, at the start of each four-weekly treatment cycle (within seven days of each subsequent radiologic assessment, preferably prior to learning the results of the radiologic disease assessment), and at the end of treatment visit. Few data were collected for patients in the progressed health state.

No EQ-5D data were available from LIBRETTO-001 and no mapping was conducted to map the EORTC QLQ-C30 to EQ-5D utilities as no algorithm was identified in MTC patients specifically.[1]

The SLR conducted by the company did not identify any health state utility values (HSUVs) specific to patients with *RET*-mutant MTC or *RET* fusion-positive TC. In the base-case, utility values are assumed to be the same as those used in TA535 and TA516, sourced from a vignette study conducted by Fordham et al. 2015 to estimate patient utilities in DTC, shown in Table 5.9.[16, 18, 39] Clinical expert opinion considered that the Fordham utilities were reasonable for patients with *RET*-altered tumours, and that HRQoL in this population may be expected to be similar to that of the wider patient population with the same tumour type.[36] Alternative utility estimates used in previous thyroid cancer submissions in the UK identified by the company and tested in sensitivity analyses are displayed in Table 5.9.

Table 5.9: Health state utility value estimates

HSUV Source	Progression free	Progressed	Dead
Fordham et al. (company BC)	0.80 (0.19)	0.50 (0.28)	0
SMC cabozantinib	0.796	0.624	0
SMC sorafenib	0.80	0.64	0

Source: Tables 58 and 59 of the CS.[1]
BC = base-case; HSUV = health state utility value; SMC = Scottish Medicines Consortium.

The company incorporated a decline in utility due to ageing in their base-case, using an annual adjustment factor via a multiplicative approach derived from Ara and Brazier et al. 2010.[45]

Disutilities were applied to those patients experiencing the Grade 3+ AEs which were included in the model.[1] As in TA516 it was assumed that all included AEs resulted in a utility decrement of 0.11, based on Beusterien et al. 2009. The impact of AEs on HRQoL was assumed to last one month (30.44 days).[18, 46]

ERG comment: The ERG did not consider the company's argument that mapping of the available EORTC QLQ-C30 data collected in LIBRETTO-001 to the EQ-5D could not be performed, because no mapping algorithm estimated in MTC patients specifically was identified, was sufficient to exclude the possibility of mapping. While it is desirable to match the population in which the mapping was conducted as closely as possible to the trial population, it is rare that a perfect match is available. Mapping from a similar cancer population would provide an estimate of EQ-5D utilities and make use of valuable data in the trial population rather than having to rely on estimates from the literature in different populations. Therefore at clarification, the ERG requested that the company map the HRQoL data from the LIBRETTO-001 study to the EQ-5D using the mapping algorithm which they considered most representative of the population considered in this appraisal.[47] The company responded with mapped EQ-5D (presumably 3L) results, which had been estimated using a mapping algorithm developed by Khan et al.2016 in a non-small cell lung cancer population.[48] The study by Khan et al. offered several alterative models, from which the company selected the beta-binomial, as it offered the

best fit for the EQ-5D-3L. The ERG agrees with this choice from the models available within the Khan study.

However, the company and ERG note that the resulting EQ-5D-3L estimates which the company provided, shown in Table 17 of the clarification response, were highly implausible, with mean utilities >[redacted] for pre- and post-progression in all subgroups tested.[24] From Table 5 in the Khan paper the ERG can see that the highest EQ-5D-3L value obtainable from the beta-binomial model (estimated by assuming perfect health and 0 symptoms on the EORTC QLQ-C30) is 0.901.[48] Therefore, it is impossible that these means could be obtained from correct estimation of the beta-binomial model provided in the Khan study, suggesting that either an error occurred in the company's computation of the mapping or the reporting of the mapping coefficients in the Khan publication are incorrect. The company also stated that the random effects linear regression model from Khan was also tried, but again resulted in unrealistic values (not reported).[24] The ERG attempted to replicate EQ-5D-5L estimates for the maximum and minimum possible scores on the QLQ-C30 cited in the paper using the provided coefficients, but were unable to replicate these findings suggesting possible inconsistencies in the paper. However, in such a case the ERG would argue that another mapping algorithm publication should have been used to obtain EQ-5D estimates from the trial data rather than the model relying solely on utilities from the literature.

The ERG identified several alternative mapping algorithms between the QLQ-C30 and the EQ-5D-3L including one by Kontodimopoulos et al. 2009 estimated in patients with gastric cancer and another by Marriott et al. 2017 in a colorectal cancer population.[49, 50] The ERG did not have the required QLQ-C30 data per health state with which the EQ-5D health state utility values required for the model could be calculated. However, the baseline QLQ-C30 data provided by the company in their response to clarification could be used to estimate an approximation of the EQ-5D progression free utility value, as all patients were considered progression free at baseline. This data was mapped using the linear mixed regression model coefficients reported by Marriott et al. and the ordinary least squares model from Kontodimopoulos et al., resulting in baseline EQ-5D-3L utilities of [redacted] and [redacted] respectively.

The company's base-case utility values obtained from the literature were based on a study by Fordham et al. 2015 which estimated utilities for patients with radioactive iodine-refractory differentiated thyroid cancer by creating vignette health state descriptions which were valued by 100 members of the UK general population using time trade-off interviews.[39] This study meets the NICE reference case in terms of valuation of HRQoL (UK general population), but not in terms of the measurement of HRQoL. The reference case states that HRQoL should be measured in patients, however in the Fordham study no patients provided a measurement of their HRQoL. Additionally, the vignettes are lengthy, meaning that the members of the general population valuing them have to remember 10 or 11 different aspects of a hypothetical health state, simultaneously imagine how it would be to live in this state and retain this imagined state through the valuation exercise. This process is repeated for a series of different hypothetical states, which may become confused. This will encourage focusing effects and will affect the estimates produced. It is unclear how reflective these utility values are of patients with RET-mutant MTC or RET-positive TC, as the study covers a different thyroid cancer population (DTC) and HRQoL was not measured directly in patients.

The company identified several sets of utility values that had been used in previous thyroid cancer appraisals at the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG), shown in Table 59 of the CS.[1] These included utility values of 0.796 and 0.624 in progression free and progressed patients respectively used in the SMC's appraisal of cabozantinib in patients with progressive, unresectable, locally advanced MTC. Limited information was available

about these utilities other than that they were estimated from published trial data in non-specified thyroid cancer in which SF-36 outcomes had been converted to utilities by mapping to EQ-5D and converting to SF-6D values. It was also stated that the trial population in which HRQoL was measured was made up of stage 1 and 2 TC patients, which would be a less severe population than considered in this appraisal.

The SMC appraisal of sorafenib in patients with progressive, locally advanced or metastatic, DTC, refractory to radioactive iodine also provided an alternative set of utility values, derived from EQ-5D data from the DECISION study.[1] Progression free patients receiving sorafenib and BSC had utility values of 0.72 and 0.8 respectively, while progressed patients had a utility of 0.64. These utility values again represent a different TC population (DTC) which may not be fully reflective of the populations in this appraisal. While EQ-5D trial data may be preferable to utilities from a vignette study in terms of the meeting NICE reference case requirements, the limited information available about the collection of HRQoL in DECISION means that these HSUVs are also associated with substantial uncertainties. It is unknown how many patients/observations provided data for each health state, the drop-out rate around progression and how long after progression HRQoL was measured, among other issues. These piece of information all provide indications of how reflective of each health state the utilities are likely to be, particularly for progressed disease which can be substantially affected by such issues. Given the uncertainty associated with these utilities as well as the vignette study the ERG did not feel that they could be certain that either of the alternative sets of utilities available represents a better source than the company's chosen base-case.

The ERG's mapping of the baseline QLQ-C30 data was able to provide some validation of the progression-free utility value of 0.80 assumed from Fordham et al, as well as the alternative PFS utility values identified (0.796 and 0.8). However, given that the ERG does not have access to the LIBRETTO-001 QLQ-C30 data from progressed patients, the assumed progressed disease value of 0.5, or the alternative progression values of 0.624 and 0.64 could not be validated. Given the uncertainties relating all available sets of utility values identified from previous SMC appraisals, the ERG did not change the base-case source of utility values from the company submission, instead choosing to present the alternatives as scenario analyses (assuming the BSC utility for PFS patients in the scenario using utilities from the sorafenib appraisal).

The company reported in the CS that all included AEs were assumed to be associated with a disutility of 0.11.[1] However, in the model, in the previously treated TC population a disutility of 0.38 was applied for diarrhoea, while in the MTC population this remained consistent with the CS reporting at 0.11. When the ERG queried at clarification whether the 0.38 applied for TC patients was correct, the company replied "*Where no specific utility decrement was identified, the estimate for any AE used in NICE TA516 (Assessment Group model) based on Beusterien et al. (2009) was applied* **(0.11).** *An estimate specifically for diarrhoea was identified in TA535 (Table 19, page 536 of the Committee Papers). This decrement (0.38), as included in the model, is the correct value*."[24] The ERG considers that the discrepancy across indications for this value is likely due to an attempt by the company to maintain consistency with the approach in the relevant previous TA for each indication, with TA535 specific to advanced TC and TA516 specific to MTC. However, the ERG questions whether the impact of diarrhoea would really be more than three times larger in patients with TC than those with MTC. However, given the very limited impact of this disutility on the ICER (a change of £[redacted] on an ICER of approximately £[redacted]), this issue was not considered important and no base-case change was made.

Both the duration of AEs of one month and the assumption that all AEs were associated with a disutility of 0.11 (except diarrhoea in previously treated TC) were based on assumptions from TA516.[18]

Additional evidence to support these assumptions was requested at clarification, but nothing further was provided.[24] However given the limited impact of AE disutilities on the model results, this is not considered an issue of importance.

5.2.9 Resources and costs

5.2.9.1. Drug acquisition costs

The drug acquisition costs for selpercatinib and cabozantinib were based on their list prices, [redacted]

The list price for selpercatinib is [redacted] for a pack of 60 capsules, which amounts to [redacted] per capsule. The same list price applies to capsules of 80 mg and 40 mg selpercatinib. The company assumed that a proportion of patients had dose reductions, such that a mean dose intensity of [redacted] for selpercatinib was applied in the model that matched the mean dose intensity for selpercatinib in LIBRETTO-001. As a result, the company assumed that [redacted] of patients receiving selpercatinib had their dose reduced from 160 mg to 120 mg (i.e. one capsule of 80 mg and one capsule of 40 mg). In sum, the cost per four-week treatment cycle for selpercatinib was [redacted] for patients with and without dose reductions. Drug acquisition costs were applied once in every four weeks in the company base-case model, to account for drug wastage in relation to patients discontinuing within the four-week interval (i.e. here the company base-case model deviated from what is written in Document B of the CS,[1] which stated that the company base-case assumed no drug wastage). An overview of drug acquisition costs for selpercatinib is provided in Table 5.13 for patients without and with dose reductions.

An important factor for total drug acquisition costs is time on treatment. The company assumed that time on treatment was equal to PFS, even though patients could continue treatment after progression in LIBRETTO-001 and clinical expert opinion indicated that treatment may continue after progression. In their response to the clarification letter,[24] the company provided the mean number of days between meeting the PFS endpoint and treatment discontinuation for patients discontinuing treatment in LIBRETTO-001. These data are shown in Table 5.10. For patients who discontinued treatment in LIBRETTO-001, the mean time between meeting the PFS endpoint and treatment discontinuation was [redacted] days for pre-treated MTC patients (n=124) and [redacted] days for pre-treated TC patients (n=19).

Table 5.10: Mean time (days) between meeting the PFS endpoint and treatment discontinuation for patients discontinuing treatment in LIBRETTO-001

	Pre-treated MTC (n=124)	Any-line MTC (n=[redacted])	Pre-treated TC (n=19)
Discontinued treatment during trial follow-up, n (%)	[redacted]	[redacted]	[redacted]
Time between PFS and treatment discontinuation			
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]

Source: Table 19 in the response to the clarification letter.[24]
CI = confidence interval; max = maximum; min = minimum; MTC = medullary thyroid cancer; PFS = progress-free survival; SD = standard deviation; TC = thyroid cancer.

The company performed extrapolations of time to treatment discontinuation (TTD), in line with the approach for PFS and OS extrapolations, using a range of standard parametric distributions. This resulted in estimated curves for *RET*-mutant MTC that the company deemed implausible in comparison to the loglogistic PFS curve using all parametric distributions, and only the Weibull and gamma distributions resulted in estimated curves for *RET* fusion-positive TC that the company deemed plausible in comparison to the stratified Weibull PFS curves. The results of the TTD extrapolations are shown in Table 5.11 for *RET*-mutant MTC and in Table 5.12 for *RET* fusion-positive TC.

Table 5.11: PFS (loglogistic) and time on treatment extrapolations for selpercatinib in *RET*-mutant MTC

Time (years)	PFS	Exponential	Weibull	Lognormal	Loglogistic	Gompertz	Gamma	Spline knot 1	Spline knot 2	Spline knot 3
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 18 in the response to the clarification letter.[24]
MTC = medullary thyroid cancer; PFS = progression-free survival; RET = rearranged during transfection; TTD = time to discontinuation.

Table 5.12: PFS (stratified Weibull) and time on treatment extrapolations for selpercatinib in *RET* fusion-positive TC

Time (years)	PFS	Exponential	Weibull	Lognormal	Loglogistic	Gompertz	Gamma
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time (years)	PFS	Exponential	Weibull	Lognormal	Loglogistic	Gompertz	Gamma
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 20 in the response to the clarification letter.[24]
PFS = progression-free survival; RET = rearranged during transfection; TC = thyroid cancer; TTD = time to discontinuation.

ERG comment: To have drug acquisition cost estimates that are better in line with clinical practice, the ERG prefers to consider that treatment may continue beyond progression instead of assuming that time on treatment is equal to PFS. The ERG implemented this by shifting the time on treatment curves that are based on PFS in the company model by four weeks for *RET*-mutant MTC and by nine weeks for *RET* fusion-positive TC. The ERG included a scenario analysis that assumed that time on treatment is equal to PFS, in line with the assumption for the company base case model.

Table 5.13: Drug acquisition costs for selpercatinib and cabozantinib (patients without dose reductions)

Regimen	Regimen description	Capsule strength (mg)	Capsules per pack	Pack cost (£)	Capsule cost (£)	Capsules per dose	Doses per week	Capsules per 4 week treatment cycle	Costs per 4 week treatment cycle
Patients without dose reductions									
Selpercatinib	160 mg, orally, twice daily	80	60	£[redacted]	£[redacted]	2	14	112	£[redacted]
Patients with dose reductions									
Selpercatinib	120 mg, orally, twice daily	80	60	£[redacted]	£[redacted]	1	14	56	£[redacted]
		40	60	£[redacted]	£[redacted]	1		56	

Based on Table 60 and 61 in the CS.[1]
CS = company submission; mg = milligram.

5.2.9.2 Pharmacist drug dispensing costs

The company included the costs for the dispensing of selpercatinib, based on the assumption that this would require 12 minutes of a hospital pharmacist's time. It is indicated in the model that this assumption is based on TA520.[51] The model also indicates that an hourly wage of £46 is assumed for a pharmacist, based on Table 9 in Personal Social Services Research Unit (PSSRU) 2019.[52] As such, the company calculated a cost of £9.20 per drug dispense. In the company base-case model, the application of the drug dispensing costs coincides with the application of drug acquisition costs once in every four weeks (i.e. this deviates slightly from what is written in Document B of the CS,[1] which states that the drug dispensing costs are applied once every 30 days).

ERG comment: As indicated in the electronic model, pharmacy dispensing costs were sourced from TA520.[51] In TA520, reference was given to a hospital-based pharmacist for which the hourly wage of a Band 6 radiographer is applied from PSSRU 2016. Following the same approach using the values reported in PSSRU 2019 led to an hourly wage of £49, or £9.80 per 12 minutes of a pharmacist's time. This value was preferred by the ERG for their base-case model.

5.2.9.3 Costs of best supportive care

For resource use in BSC, the company assumed no additional costs other than the health state costs for PF and PD. However, in Table 63 in Document B of the CS cost estimates, in the form of unit costs and frequencies of usage, are provided for BSC that were sourced from TA516.[1, 18] Since these were not actually used in the model it is unclear to the ERG what the purpose of providing this information was, and therefore these costs are not further summarised here. Clinical expert opinion was consulted by the company on BSC resource use estimates, for which documentation was provided.[36] In response to a clarification question by the ERG regarding what information was provided to the expert, the company indicated that this pertained to the BSC resource use estimates from TA535 (i.e. not TA516 as indicated in Document B of the CS)[1].[16] The clinical expert indicated a concern that the estimates for BSC resource use pertained to monitoring during active treatment.[36] The company noted in their response to clarification questions that the expert indicated that BSC resource use was included in the health state costs (which are based on TA516,[36] as explained in Section 5.2.9. 3). This information was not provided in the documentation of clinical exert opinion that was made available to the ERG. The implementation of BSC costs in the model contrasts with Document B of the CS,[1] which states that BSC resource use was assumed to consist of monitoring and palliative care and that it is likely to be the same in the progression-free and progressed health states.

ERG comment: The ERG noted that the implementation of BSC costs in the electronic model is not consistent with the explanation that was provided in Document B of the CS.[1] The ERG prefers that BSC costs are assumed to be the same in the PF and PD health states, since the relevant population for this appraisal consists of patients who have progressed disease by definition. Therefore, the ERG applied the costs of the PD health state to patients receiving BSC in both the PF and PD health states. Costs for palliative care were not included in the costs of the PF and PD health states but were applied as transition costs upon death (as explained in Section 5.2.9.4).

5.2.9.4 Health state costs

The costs related to health care resources used in the PF and PD health states were sourced by the company from TA516, which in turn were sourced from clinical experts consulted by the AG in TA516.[18] The unit costs were updated using NHS reference costs 2018/2019. The unit costs as used in the model for the valuation of health care resources in the PF and PD health states are shown in Table 5.14, alongside the alternative costs that the ERG considers to be better in line with TA516 (see ERG

comment below) or that the ERG considered were incorrectly sourced from the NHS reference costs 2018/2019. The frequencies of usage for each health care resource as used in the model are shown in Table 5.15, alongside the alternative values that the ERG considers were incorrectly sourced from TA516 (see ERG comment below).

Table 5.14: Unit costs for health care resources in the PF and PD health states

Resource	Company submission		ERG alternatives	
	Description (Currency code)	Unit cost (£)	Description (Currency code)	Unit cost (£)
Consultant-led outpatient visit	Consultant-led, non-admitted face to face attendance, follow up (general surgery; WF01A)	133.05	Consultant-led, non-admitted face to face attendance, follow up (medical oncology; WF01A)	194.17
Nurse-led outpatient visit	Non-consultant-led, non-admitted face to face attendance, follow up (general surgery; WF01A)	100.04	Non-consultant-led, non-admitted face to face attendance, follow up (medical oncology; WF01A)	147.38
ECG	Outpatient (medical oncology), electrocardiogram monitoring or stress testing (EY51Z)	196.61	Outpatient (medical oncology), electrocardiogram monitoring or stress testing (EY51Z)	195.61
Blood test	Directly accessed pathology, phlebotomy (DAPS08)	3.71	-	-
CT scan	Outpatient, Computerised Tomography Scan of more than Three Areas (RD27Z)	124.43	-	-

Based on the electronic model from the CS,[53, 54] TA516,[18] and NHS Reference costs 2018 / 2019.[55]
CS = company submission; CT = computerised tomography; ECG = electrocardiogram; ERG = evidence review group.

Table 5.15: Frequencies of usage for health care resources in the PF and PD health states

Resource	Annual frequency (range)	
	PF	PD
Consultant-led outpatient visit	12 (4–16)	6 (4–12)
Nurse-led outpatient visit	4 (0–6)	6 (0–6)
ECG	12	6
Blood test	12	6
CT scan	4	4

Based on the electronic model,[53, 54] and TA516.[18]
CS = company submission; CT = computerised tomography; ECG = electrocardiogram; ERG = evidence review group.

The costs of one month of palliative care and palliative chemotherapy are applied to all patients upon transitioning to the Death health state. The cost assumptions and unit costs for palliative care and

chemotherapy were sourced from TA516. In Table 65 in Document B of the CS,[1] the company provides the values as used in TA516 (i.e. not updated to 2019 costs). In the model the company uses an updated value for the costs of palliative care, but not for palliative chemotherapy. The values as used in the model by the company are shown in Table 5.16, alongside the value for palliative chemotherapy that was updated by the ERG.

Table 5.16: Palliative care and chemotherapy costs

Resource	Company submission		ERG updated value	
	Unit cost (£)	Source	Unit cost (£)	Source
Palliative care	5,718	TA516; PSSRU 2019	-	-
Palliative chemotherapy	827	TA516	314	TA516; NHS Reference costs 2018 / 2019

Based on the electronic model,[53, 54] TA516,[18] and NHS Reference costs 2018 / 2019.[55]
CS= company submission; ERG = evidence review group; NHS = national health services; PSSRU = personal social services research unit.

ERG comment: Analogous to TA516, the company included costs for both consultant-led and nurse-led (i.e. non consultant-led) outpatient visits. In contrast to TA516, in which the unit costs for these resources were based on those for a medical oncology setting, the company based these unit costs on a general surgery setting. This was corrected by the ERG, so that the unit costs are in line with those used in TA516. In Table 64 in the CS,[1] the company provided no entry for costs of an electrocardiogram (ECG), but the electronic model did include these costs. These were in line with the costs estimates for vandetanib in TA516 in the first and subsequent years to the PF and PD health states, respectively (i.e. 12 and 6, respectively). The ERG updated the value for the costs of palliative chemotherapy according to the NHS Reference costs 2018/2019.

5.2.9.5 Adverse event costs

The unit costs for adverse events were sourced from the NHS Reference costs 2018/2019 when available,[55] or based on assumptions made by the company. The company stated in the CS that the unit costs for adverse events were consistent with those used in TA516 and TA535. An overview of the unit costs for adverse events as used in the company base-case, including the corresponding (ERG-corrected) currency codes and descriptions for costs that were sourced from the NHS reference costs 2018/2019,[55] as well as the source that was used as a basis for the assumptions, are shown in Table 5.17.

Table 5.17: Adverse event unit costs as used in the company base-case

Adverse event	Unit cost (£)	Currency code and description*	Source for assumptions
Diarrhoea	£1,218.01	FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2#; Elective inpatient	TA516
Hand foot syndrome	£1,027.93	JD07K: Skin Disorders without Interventions, with CC Score 0-1; Elective Inpatient	Assumed by company%
Hypertension	£1,134.52	EB04Z: Hypertension; Elective Inpatient	TA516

Adverse event	Unit cost (£)	Currency code and description*	Source for assumptions
ECG QT prolonged	£1,027.53	EB07E: Arrhythmia or Conduction Disorders, with CC Score 0–3; Elective Inpatient	TA516
Decreased weight	£1,613.91	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient	Assumed by company
Abdominal pain	£740.83	FD05B: Abdominal Pain without Interventions; Elective Inpatient	Assumed by company%
Haemorrhage	£500.00	-	Assumed by company
Dysphagia	£915.75	CB02F: Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0; Elective Inpatient	Assumed by company%
Fatigue	£0.00	-	TA516$
Decreased appetite	£1,613.91	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient	TA516$
Rash	£1,027.93	JD07K: Skin Disorders without Interventions, with CC Score 0-1; Elective Inpatient	TA516
Asthenia	£0.00	-	TA516$
Mucosal inflammation	£1,223.18	FD01J: Gastrointestinal Infections without Interventions, with CC Score 0-1; Elective Inpatient	Assumed by company%
Vomiting	£1,613.91	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Elective Inpatient	Assumed by company
Dyspnoea	£1,063.91	DZ19N: Other Respiratory Disorders without Interventions, with CC Score 0-4; Elective Inpatient	TA516
Headache	£0.00	-	Assumed by company
Back pain	£1,393.30	HC32K: Low Back Pain without Interventions, with CC Score 0-2; Elective Inpatient	TA516
Syncope	£864.83	EB08E&: Syncope or Collapse, with CC Score 0-3; Elective Inpatient	TA516
Alanine aminotransferase	£0.00	-	Assumed by company
Aspartate aminotransferase	£0.00	-	Assumed by company
Hyponatraemia	£785.84	SA09L: Other Red Blood Cell Disorders with CC Score 0-1; Elective Inpatient	Assumed by company

Adverse event	Unit cost (£)	Currency code and description*	Source for assumptions
Lymphopenia	£2,621.33	SA17H: Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2; Elective Inpatient	Assumed by company
Pneumonia	£1,488.23	DZ11V: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3; Elective Inpatient	Assumed by company%
Hypocalcaemia	£785.84	SA09L: Other Red Blood Cell Disorders with CC Score 0-1; Elective Inpatient	Assumed by company
Dehydration	£500.00	-	Assumed by company
Weight increased	£500.00	-	Assumed by company

Based on Table 66 in the CS,[1] corrected by the ERG.
* From the NHS Reference costs 2018 / 2019.[55]
#In the CS this incorrectly referred to "Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, with CC Score 9+".[1]
%In the CS this incorrectly referred to TA516.[1]
$The CS did not refer to TA516 for this assumption, but the same assumption was used in TA516.[1, 18]
&The currency code was not provided in the CS.[1]
CS= company submission; ERG = evidence review group; NHS = national health services.

ERG comment: The AE costs were sourced from TA516 and pertain mostly to the costs that apply to an 'elective inpatient setting'. The ERG cannot confirm that these costs are also consistent with those used in TA535. As was also indicated by the company in response to the ERG's clarification questions, the AG in TA516 considered that the costs of a 'non-elective inpatient' setting may be more appropriate. Therefore, the ERG has replaced the AE costs with values that pertain to those in a 'non-elective short stay' setting. These unit costs are shown in Table 5.18 below.

Table 5.18: Adverse event unit costs as preferred by the ERG

Adverse event	Unit cost (£)	Currency code and description*
Diarrhoea	£412	FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; Non-elective short stay
Hand foot syndrome	£328	JD07K: Skin Disorders without Interventions, with CC Score 0-1; Non-elective short stay
Hypertension	£339	EB04Z: Hypertension; Non-elective short stay
ECG QT prolonged	£363	EB07E: Arrhythmia or Conduction Disorders, with CC Score 0–3; Non-elective short stay
Decreased weight	£397	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Non-elective short stay
Abdominal pain	£375	FD05B: Abdominal Pain without Interventions; Non-elective short stay
Haemorrhage	£500	-

Adverse event	Unit cost (£)	Currency code and description*
Dysphagia	£371	CB02F: Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0; Non-elective short stay
Fatigue	£0	-
Decreased appetite	£397	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Non-elective short stay
Rash	£328	JD07K: Skin Disorders without Interventions, with CC Score 0-1; Non-elective short stay
Asthenia	£0	-
Mucosal inflammation	£392	FD01J: Gastrointestinal Infections without Interventions, with CC Score 0-1; Non-elective short stay
Vomiting	£397	FD04E: Nutritional Disorders without Interventions, with CC Score 0-1, Non-elective short stay
Dyspnoea	£327	DZ19N: Other Respiratory Disorders without Interventions, with CC Score 0-4; Non-elective short stay
Headache	£0	-
Back pain	£357	HC32K: Low Back Pain without Interventions, with CC Score 0-2; Non-elective short stay
Syncope	£328	EB08E: Syncope or Collapse, with CC Score 0-3; Non-elective short stay
Alanine aminotransferase	£0	-
Aspartate aminotransferase	£0	-
Hyponatraemia	£364	SA09L: Other Red Blood Cell Disorders with CC Score 0-1; Non-elective short stay
Lymphopenia	£426	SA17H: Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2; Non-elective short stay
Pneumonia	£433	DZ11V: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3; Non-elective short stay
Hypocalcaemia	£364	SA09L: Other Red Blood Cell Disorders with CC Score 0-1; Non-elective short stay
Dehydration	£500	-
Weight increased	£500	-

Based on Table 66 in the CS,[1] adapted by the ERG.
* From the NHS Reference costs 2018 / 2019.[55]
CS= company submission; ERG = evidence review group; NHS = national health services.

5.2.9.6 Genetic testing costs

The company did not include the costs for genetic testing in their submission, neither for their base case nor for a scenario analysis. The company justified this with reference to *RET* next generation sequencing (NGS) and fluorescent in situ hybridisation (FISH) testing being included in the 2019/2020 National Genomic Test Directory for Cancer. The company stated that the transition to NGS testing, completed at Genomic Hubs, will facilitate routine *RET* testing alongside other oncogenic drivers, and therefore it is not anticipated that approval of selpercatinib would result in any additional costs to the healthcare

system. However, the final scope as issued by NICE for the current appraisal specifically mentioned that the "the economic modelling should include the costs associated with diagnostic testing for *RET* mutation/fusion in people with advanced MTC/advanced TC who would not otherwise have been tested".[23] The aspects regarding 'Economic analysis' as specified in the final scope were not reported by the company in Table 1 (i.e. which provides the details of the decision problem as addressed in the CS in relation to the final scope) of the CS.[1]

ERG comment: Since it was anticipated that the number of patients who at the time of this appraisal receive routine genetic testing would be almost zero, the ERG preferred to include the costs of genetic testing in their base case analysis.

The ERG has used the distribution of the different types of TCs of patients with *RET* fusions in LIBRETTO-001 (i.e. n=27) in combination with the prevalence estimates of *RET* fusions for each type of TC from Kohno et al. 2020 to calculate the total number of patients that need to be tested to identify the sample of 27 patients with *RET* fusion-positive TC.[56] This resulted in a total estimated number of 791 patients, as shown in Table 5.19. For patients with MTC the prevalence of *RET* mutations was estimated as 66.67%,[56] so that an estimated number of 185 patients with MTC need to be tested to identify the sample of 124 patients with *RET* mutant MTC.

Table 5.19: Estimated total number of genetic tests performed to identify patients with *RET*-mutant MTC and *RET* fusion-positive TC in LIBRETTO-001.

Type of TC	**Number of patients included in LIBRETTO-001**	**Prevalence of RET mutations in MTC / RET fusions in TC**	**Number of patients needed to test**
RET-mutant MTC			
Medullary TC	124	66.67%	186
RET fusion-positive TC			
Papillary TC	21	4.62%[#]	454
Hürthle cell TC	1	1.85%	54
Anaplastic TC	2	0.93%	215
Poorly differentiated TC	3	4.47%	67
Total	27	-	791

Based on information provided in the CS,[1] and Kohno et al. 2020.[56]
[#]Weighted average of 2 samples (prevalence of 2.32% in n=560 and prevalence of 7.20% in n=500).
CS= company submission; MTC = medullary thyroid cancer; *RET* = rearranged during transfection; TC = thyroid cancer.

The cost of NGS genetic testing was sourced by the ERG from Hamblin et al. 2017,[57] which provided an estimate of £367 (updated from 2013 to 2019 using the NHSCII 'Pay and prices' from PSSRU 2019)[52]. Hence, the cost of using NGS testing to identify a single patient with *RET* mutant MTC was estimated as 186*£367/124 = £551 and the cost to identify a single patient with *RET* fusion-positive TC was estimated as 791*£367/27 = £10,752. In a scenario analysis, the ERG used an alternative cost of NGS genetic testing that was sourced from Schwarze et al. 2020,[58] which provided an estimate of £6,479 (updated from 2016 to 2019 using the NHS Cost Inflation Indices (NHSCII) 'Pay and prices' from Personal Social Services Research Unit (PSSRU) 2019,[52] and based on an assumed annual sample throughput of 2000) per cancer case (i.e. comprising matched tumour and germline samples). Using this estimate, the cost of using NGS testing to identify a single patient with *RET* mutant MTC was estimated as 186*£6,479/124 = £9,719 and the cost to identify a single patient with *RET* fusion-positive

TC was estimated as 791*£6,479/27 = £189,811. In light of the uncertainty that follows from the large difference between the two estimates for genetic testing costs, the ERG preferred the lower cost estimate for their base-case to be conservative regarding this aspect. An important difference between the cost estimates pertains to whether only sequencing costs are taken into account as in Hamblin et al. 2017,[57] or whether it also includes analysis, interpretation and reporting of results as in Schwarze et al. 2020.[58] Another reason for why the cost estimate from Schwarze et al. 2020[58] is higher is due to it including testing of both tumour and germline samples. The ERG would advise that further expert opinion is sought regarding the applicability of either cost estimate to the context of the current appraisal.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

6.1.1 RET-mutant MTC

The company base-case incremental cost effectiveness results, provided in the response to the clarification letter,[24] for patients with *RET*-mutant MTC are provided in Table 6.1 and show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental cost of [redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 6.1: Company base-case deterministic cost effectiveness results (discounted) RET-mutant MTC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source: electronic model from the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

6.1.2 RET fusion-positive TC

The company base-case incremental cost effectiveness results for patients with *RET* fusion-positive TC are provided in Table 6.2 and show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental cost of [redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 6.2: Company base-case deterministic cost effectiveness results (discounted) RET fusion-positive TC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source: Table 71 in the CS.[1]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed to assess the sensitivity of the cost effectiveness results to the uncertainty associated with model input parameters. Random samples were drawn simultaneously from the assigned probability distribution for each input parameter. The probability distributions were informed using the standard errors (SEs) from the same data sources that informed the mean values when available, or by assuming SEs that represent 10% of the mean value when no measure of uncertainty was available.

6.2.1.1 RET-mutant MTC

The company base-case probabilistic results for patients with *RET*-mutant MTC are presented in Table 6.3, and the cost effectiveness plane (CE-plane) and cost effectiveness acceptability curve (CEAC) are presented in Figure 6.1 and Figure 6.2, respectively. Selpercatinib was associated with a [redacted] probability of being cost effective versus BSC at the common threshold ICERs of £30,000 and £50,000 per QALY gained.

Table 6.3: Company base-case probabilistic cost effectiveness results (discounted) RET-mutant MTC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

Source: Table 24 in the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY(s) = quality adjusted life year(s).

Figure 6.1: Cost effectiveness plane RET-mutant MTC

Source: Figure 10 in the response to the clarification letter.[24]
Generated using 1,000 iterations from the PSA.
PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

Figure 6.2: Cost effectiveness acceptability curve RET-mutant MTC

Source: Figure 11 in the response to the clarification letter.[24]
Generated using 1,000 iterations from the PSA.
PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

6.2.1.2 RET-fusion positive TC

The company base-case probabilistic results for patients with *RET* fusion-positive TC are presented in Table 6.4, and the cost effectiveness plane (CE-plane) and cost effectiveness acceptability curve (CEAC) are presented in Figure 6.3 and Figure 6.4, respectively. Selpercatinib was associated with a [redacted] probability of being cost effective versus BSC at the common threshold ICERs of £30,000 and £50,000 per QALY gained.

Table 6.4: Company base-case probabilistic cost effectiveness results (discounted) RET-fusion positive TC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

Source: Table 74 in the CS.[1]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY(s) = quality adjusted life year(s).

Figure 6.3: Cost effectiveness plane RET-fusion positive TC

[redacted]

Source: Figure 45 in the CS.[1]
Generated using 1,000 iterations from the PSA.
PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

Figure 6.4: Cost effectiveness acceptability curve RET-fusion positive TC

Source: electronic model from the response to the clarification letter.[24]
Generated using 1,000 iterations from the PSA.
PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

ERG comment: An error was found in the formulae for creating random values for the parameters of the OS and PFS curves. In most instances, instead of multiplying the Cholesky decomposition matrix with random draws from a standard Normal distribution, the matrix was multiplied with random draws from a uniform distribution between 0 and 1. This has been corrected for the ERG analyses in Section 7 of this report.

6.2.2 Deterministic sensitivity analysis

The company performed a deterministic, one-way sensitivity analysis (OWSA) to assess the impact of varying each parameter independently at both the upper and lower bounds of the 95% confidence interval that surrounds its mean estimate. Similar to the PSA, an SE that represents 10% of the mean value was assumed when no measure of uncertainty was available.

6.2.2.1 RET-mutant MTC

For patients with *RET*-mutant MTC, the tornado plot in Figure 6.5 shows the deviations from the base-case ICER for the 25 parameters of which the impact of their uncertainty was the largest.

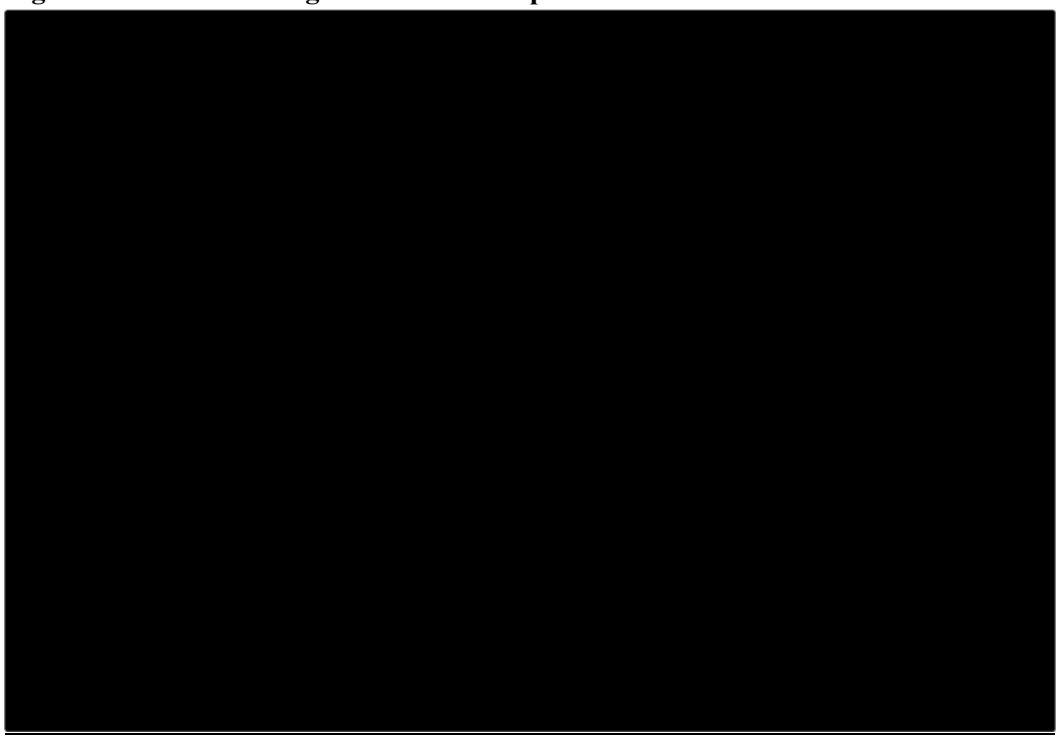
Figure 6.5: Tornado diagram RET-mutant MTC

Source: Figure 12 in the response to the clarification letter.[24]
BSC = best supportive care; ECG = electrocardiogram; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year.

6.2.2.2 RET-fusion positive TC

For patients with *RET*-fusion positive TC, the tornado plot in Figure 6.6 shows the deviations from the base-case ICER for the 25 parameters of which the impact of their uncertainty was the largest.

Figure 6.6: Tornado diagram *RET*-fusion positive TC



Source: Figure 49 in the CS.[1]

BSC = best supportive care; ECG = electrocardiogram; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year.

ERG comment: The parameters included in the OWSA did not include the parameters of the PFS and OS curves, and thus, these analyses give a very limited view on the individual contribution of each input parameter on the overall parametric uncertainty.

6.2.3 Scenario analysis

The company explored a number of scenario analyses in which model assumptions or parameters were altered, including various alternatives for the extrapolation of survival curves. None of the variations in the parameters that were assessed by the company led to a change in the ICER that exceeded 10%. The largest impact was due to variation in the estimates used for health state costs and utilities.

6.2.3.1 RET-mutant MTC

The results of the scenario analyses for patients with *RET*-mutant MTC are presented in Table 6.5.

Table 6.5: Results of scenario analyses (RET-mutant MTC)

Scenario	ICER (£/QALY)	% ICER change
Base case	[redacted]	-
Discount rate 1.5% (benefits)	[redacted]	-16.73%
Discount rate 6%	[redacted]	14.36%
Undiscounted health outcomes and costs	[redacted]	-19.58%
Utilities, SMC sorafenib [redacted]PF: 0.72 PD: 0.64	[redacted]	-11.21%
Utilities, SMC cabozantinib[redacted]PF: 0.796 PD: 0.624	[redacted]	-12.72%
Disutility, SMC lenvatinib [redacted]-0.042 (all treatments)	[redacted]	-0.04%
Drug wastage not included	[redacted]	-11.87%
Curve choice: PFS – Exponential	[redacted]	63.81%
Curve choice: PFS – Weibull	[redacted]	-5.17%
Curve choice: PFS – lognormal	[redacted]	3.16%
Curve choice: PFS – Gompertz	[redacted]	-26.22%
Curve choice: PFS – Gamma	[redacted]	-2.99%
Curve choice: PFS – spline knot 1	[redacted]	-8.34%
Curve choice: PFS – spline knot 2	[redacted]	-22.89%
Curve choice: PFS – spline knot 3	[redacted]	-32.26%
Curve choice: PFS – stratified Weibull	[redacted]	35.09%
Curve choice: PFS – stratified lognormal	[redacted]	104.62%
Curve choice: PFS – stratified loglogistic	[redacted]	73.80%
Curve choice: PFS – stratified Gompertz	[redacted]	-7.49%

Scenario	ICER (£/QALY)	% ICER change
Curve choice: PFS – stratified gamma	[redacted]	42.80%
Curve choice: PFS – stratified spline knot 1	[redacted]	26.98%
Curve choice: PFS – stratified spline knot 2	[redacted]	-4.02%
Curve choice: PFS – stratified spline knot 3	[redacted]	19.36%
Curve choice: OS – Exponential	[redacted]	-4.58%
Curve choice: OS – Gompertz	[redacted]	-5.80%
Curve choice: OS – spline knot 1	[redacted]	-5.09%
Curve choice: OS – spline knot 2	[redacted]	-10.00%
Curve choice: OS – spline knot 3	[redacted]	17.95%
Curve choice: OS – stratified Weibull	[redacted]	114.34%
Curve choice: OS – stratified Gompertz	[redacted]	770.62%
Curve choice: OS – stratified spline knot 1	[redacted]	145.15%
Curve choice: OS – stratified spline knot 2	[redacted]	923.57%
Curve choice: OS – stratified spline knot 3	[redacted]	-

Source: Table 1 in the updated base case scenario analyses provided in the clarification response.[59]
ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; SMC = Scottish Medicine Consortium.

ERG comment: For reasons that were not explained, the company's scenario analyses did not include the full set of alternative curves as presented in Section 5.2.6 of this report.

6.2.3.2 RET fusion-positive TC

The results of the scenario analyses for patients with *RET* fusion-positive TC are presented in Table 6.6.

Table 6.6: Results of scenario analyses (RET fusion-positive TC)

Scenario	ICER (£/QALY)	% ICER change
Base case	[redacted]	-
Discount rate 1.5% (benefits)	[redacted]	-8.6%
Discount rate 6%	[redacted]	7.3%
Undiscounted health outcomes and costs	[redacted]	-10.9%
Utilities, SMC sorafenib [redacted]PF: 0.72 [redacted]PD: 0.64	[redacted]	0.6%
Utilities, SMC cabozantinib [redacted]PF: 0.796 [redacted]PD: 0.624	[redacted]	-5.5%
Disutility, SMC lenvatinib [redacted]-0.042 (all treatments)	[redacted]	-0.3%

Scenario	ICER (£/QALY)	% ICER change
Drug wastage excluded	[redacted]	-12.1%
Curve choice: PFS – stratified lognormal	[redacted]	10.4%
Curve choice: PFS – stratified loglogistic	[redacted]	11.8%
Curve choice: PFS – stratified Gompertz	[redacted]	-1.3%
Curve choice: PFS – stratified gamma	[redacted]	1.0%
Curve choice: OS – stratified Weibull	[redacted]	103.6%
Curve choice: OS – stratified Gompertz	[redacted]	155.8%
Curve choice: OS – stratified lognormal	[redacted]	337.9%
Curve choice: OS – stratified loglogistic	[redacted]	185.6%
Curve choice: OS – stratified gamma	[redacted]	81.6%

Source: Table 76 in the CS.[1]
ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; SMC = Scottish Medicine Consortium.

The largest impact on the ICER was caused by assuming different parametric functions for the extrapolations of PFS and OS, demonstrating a substantial variation due to the uncertainty in the clinical data.

6.3 Model validation and face validity check

The company reported that the model was built to align with the NICE reference case and preferred methods and that the chosen structure closely aligns with previous NICE appraisals in TC, TA516 and TA535).[16, 18, 60]

The face validity of the model was tested by having the model structure, source data and statistical analysis design reviewed by external experts, including a health economist and UK clinical experts in TC.[1]

Internal validity was examined by an independent reviewer not involved in the model development using quality-control procedures for verification of input data and coding.[1] These procedures included verification of all input data with original sources and programming validation. Any discrepancies were discussed, and the model input data were updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code. In addition, the model was validated by an independent health economist.

The company state that cross validity should be investigated by comparing results with other models analysing the same problem.[1] But because no economic evaluations were identified in *RET*-altered TC, cross validation was not possible.

External validity was examined by comparing model predictions with outcomes in studies used to build the model (i.e., dependent, external validity) and with outcomes in studies not used to build the model (i.e., independent, external validity), with results presented in Appendix J of the CS.[29] LIBRETTO-001 survival data was too immature for external validation of selpercatinib, except for PFS in RET fusion positive TC. However, data were available for the RET-mutant subgroup from EXAM to validate the modelled mPFS results for placebo (BSC). mPFS was reported to be consistent with the placebo (BSC) ITT population from SELECT for the pre-treated RET fusion-positive TC population. However, these

data were in a non-RET specific population, therefore firm interpretations of external validity for this patient group cannot be drawn.

Trial OS data were only available for RET M918T-positive subgroup from EXAM for BSC, which suggested an overestimation of predicted OS in the model for RET mutant MTC. However, the RET M918T subgroup cannot be directly compared to the RET-mutant target population, therefore, no firm conclusions can be drawn. Clinical expert feedback was reported to confirm that the RET M918T data for placebo were generalisable to the overall RET-mutant population. It was not possible to assess validity of predicted mOS versus trial data for either selpercatinib or BSC due to immature data

ERG comment: No details of expert or reviewer comments or findings in relation to face or internal validity were provided. Therefore, the ERG cannot verify what was found or whether any issues or discrepancies remain following these forms of validation.

External validation results displayed in Table 6.7 show that, where evaluable, median PFS and OS results from the model provided with the original CS align fairly closely with the relevant trial results. Model results between the model provided in the original CS and in response to clarification also align, with the exception of selpercatinib results in the RET mutant-MTC group, particularly for OS. A dramatic difference in median selpercatinib OS in RET mutant-MTC is observed, going from [redacted] months in the any line original CS model to [redacted] months in the updated pre-treated clarification response model. Given that the trial result is not available for this it is not possible to externally validate these dramatically different results.

Table 6.7: External validation results

Technology	Trial median PFS (months)	Median PFS CS model (months)	Median PFS clarification response model (months)	Trial median OS (months)	Median OS CS model (months)	Median OS clarification response model (months)
RET-mutant MTC (any line in CS model, previously treated in clarification response model)						
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	4	[redacted]	[redacted]	18.9 (M918T subgroup)	[redacted]	[redacted]
RET fusion-positive TC						
Selpercatinib	20.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	3.6 (SELECT ITT)	[redacted]	[redacted]	NE (20.3-NE)	[redacted]	[redacted]
Source: Table 27 and Table 28 of the CS Appendices and the model received in response to clarification.[24, 29]						

Difference in the population represented in trial results and the population intended to receive selpercatinib in practice limits the applicability of many of the available external validity results. Despite mentioning that a relevant aspect of external validity is comparing model outcomes with outcomes in studies not used to build the model, this does not seem to have been performed.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In response to the ERG's clarification questions, the company implemented the following changes in the model:

- Cabozantinib was no longer considered as a relevant comparator for *RET*-mutant MTC, following the updated marketing authorisation that indicated selpercatinib as a treatment for only second-line patients.
- OS and PFS curves for selpercatinib were based on re-weighted KM data from a MAIC that was adjusted for prior TKI use.
- The company corrected an error with the drop-down function for the user to select the time horizon.
- The company corrected an error in the general population mortality calculations.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[61]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

The following errors were corrected by the ERG in the model provided in response to the clarification letter:

- The ERG corrected the following unit costs that were not updated or were incorrectly sourced by the company: pharmacist hourly wage (see Section 5.2.9.2), consultant-led outpatient visit, nurse-led outpatient visit, electrocardiogram and palliative chemotherapy (see Section 5.2.9.4).
- The ERG corrected an error in the PSA for the *RET*-mutant MTC population by drawing random values for the PFS and OS curves using a multiplication of the Cholesky matrix with '=norminv' instead of (erroneously) with '=rand()'.

7.1.2.2 Fixing violations

No violations were applicable to this appraisal.

7.1.2.3 Matters of judgement

The ERG's preferences regarding reasonable alternative assumptions led to the following changes to the company model:

- The ERG used the stratified Weibull function for OS in *RET*-mutant MTC, instead of the Weibull that the company used (see Section 5.2.6.1).
- The costs of genetic testing were included (i.e. only for the selpercatinib arm, not for BSC; see Section 5.2.9.6).
- For BSC, the PD health state costs instead of PF health state costs were applied to patients in the PF health state (see Section 5.2.9.3).
- AE costs that were based on an assumed 'elective inpatient' setting were changed to those based on an assumed 'non-elective short stay' setting (see Section 5.2.9.5).
- The starting age in the model for the *RET*-mutant MTC population was changed to 55.0 years (see Section 5.2.3).
- The company's assumption that time on treatment was equal to PFS was changed, so that time on treatment was in line with data from LIBRETTO-001 and clinical expert opinion (see Section 5.2.9.1).

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
OS in *RET*-mutant MTC	Weibull	Stratified Weibull	Section 5.2.6.1
Genetic testing costs	Excluded	Included	Section 5.2.9.6
BSC costs	PF and PD health state costs	PD health state costs	Section 5.2.9.3
AE costs	'Elective inpatient' setting	'Non-elective short stay' setting	Section 5.2.9.5
Starting age	55.7 for the *RET*-mutant MTC population	55.0 for the *RET*-mutant MTC population	Section 5.2.3
Time on treatment	Equal to PFS	Treatment continuation beyond progression, in line with data from LIBRETTO-001.	Section 5.2.9.1

AE = adverse event; BSC = best supportive care; ERG = evidence review group; MTC = medullary thyroid cancer; OS = overall survival; PD = progressed disease; PF =progression-free; PFS = progression-free survival; RET = rearranged during transfection

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the cost effectiveness analyses. These uncertainties were related to the company's extrapolations of OS and PFS, given the substantial uncertainty shown by the range of extrapolations provided, alternative utility values, genetic testing costs, and time on treatment.

7.1.3.1 Scenario set 1: Overall survival

For OS in RET-mutant MTC the ERG ran scenarios using several potential plausible curves which surrounded their base-case stratified Weibull curve (stratified gamma, stratified loglogistic, stratified spline 1 knot), as well as the company's preferred Weibull curve. The majority of the remaining curves,

which provided similar or more optimistic extrapolations than the company's preferred Weibull, were considered to fit poorly to the last part of the KM curve, failing to account for the substantial drop towards the end of follow-up. Therefore, these curves were not considered in scenarios. It should be noted that of the MTC OS scenarios tested, the stratified loglogistic estimates a notable proportion of long-term survivors which is likely to be implausible, while the stratified spline 1 knot curves cross slightly at 150 months before converging.

For OS in the RET fusion-positive TC population, most extrapolations resulted in crossed curves which was considered likely to be implausible. Therefore, the ERG only ran one scenario using the stratified gamma as this was the only extrapolation other than the company base-case which avoided this issue.

7.1.3.2 Scenario set 2: Progression-free survival

For PFS in RET-mutant MTC, again the company's updated survival analyses showed substantial uncertainty with a wide range of extrapolations. While all extrapolations except the spline 3 knot fit well to the BSC KM data, uncertainty towards the end of the KM curve generates a much broader potentially plausible range for selpercatinib. Given the level of uncertainty, the ERG did not change the company's base-case choice of the loglogistic curve and ran scenarios for all remaining curves with the exception of the spline 3 knot and the stratified lognormal and stratified loglogistic which the latter curves suggesting substantial proportions of selpercatinib patients remaining progression free at 300 months which was not considered plausible. These scenarios provide the committee with a range of potentially plausible ICERs.

For PFS in the RET fusion-positive TC population, all PFS extrapolations were considered potentially plausible. Therefore, the ERG made no base-case change and ran all alternative curves as scenarios.

7.1.3.3 Scenario set 3: Utility scenarios

The ERG conducted several scenario analyses, changing the assumed utility values and disutilities in the model. The ERG tested the impact of using two sets of alterative HSUVs in the model, one set assumed from the SMC appraisal of cabozantinib in advanced MTC and one set assumed from the SMC appraisal of sorafenib in metastatic DTC refractory to radioactive iodine. The ERG also tested the impact of assuming a disutility of 0.11 for diarrhoea in the TC population instead of the assumed disutility of 0.38, as 0.11 matched the assumed disutility of diarrhoea in the MTC population as well as the assumed disutility for all other Grade 3+ AEs in both populations.

7.1.3.4 Scenario set 4: Genetic testing costs

As prescribed per the final scope by NICE,[23] the ERG included genetic testing costs in their base case and performed a scenario analysis in which these costs are excluded (as per the company base case). In addition, the ERG performed a scenario using an alternative cost estimate for the costs of NGS testing. Instead of the estimate of £367 that was used in the base case, which was sourced by the ERG from Hamblin et al. 2017,[57] an alternative cost of £6,479 for the scenario analysis was obtained from Schwarze et al. 2020,[58] as described in detail in Section 5.2.9.6.

7.1.3.5 Scenario set 5: Time on treatment

In line with data from LIBRETTO-001 and clinical expert opinion, the ERG assumed that treatment with selpercatinib could continue beyond progression as explained in Section 5.2.9.1. The ERG performed a scenario analysis in which time on treatment for selpercatinib was assumed to be equal to PFS, as per the company base case.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

7.2.1.1 RET-mutant MTC

The ERG preferred base-case incremental cost effectiveness results for patients with *RET*-mutant MTC are provided in Table 7.2 and show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental cost of [redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 7.2: ERG base-case deterministic cost effectiveness results - RET-mutant MTC (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

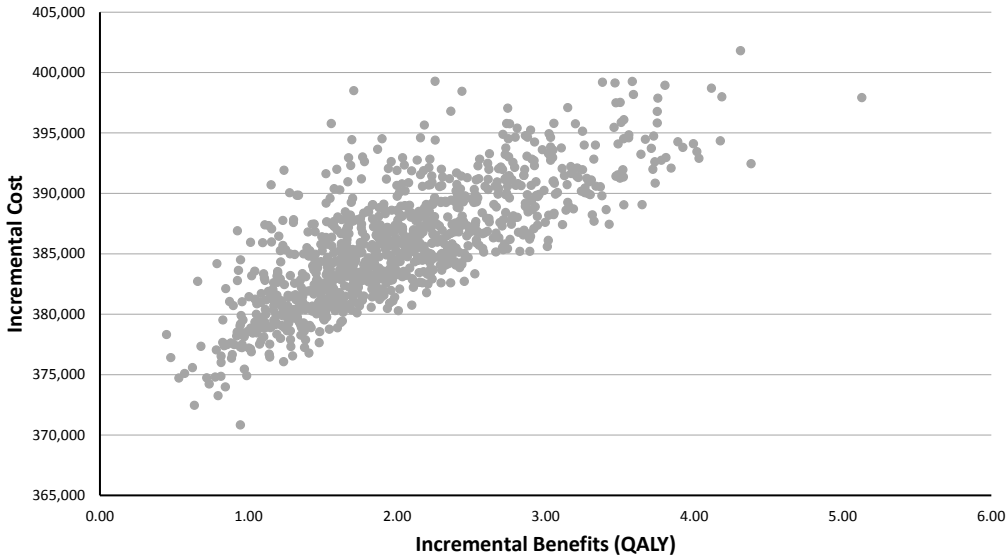
The PSA results in Table 7.3 are similar to the deterministic results. Figure 7.1 displays the cost effectiveness plane, where all simulations fall in the north-east quadrant. Figure 7.2 shows the CEAC. At the common threshold ICERs of £30,000 and £50,000 per QALY gained, selpercatinib has a [redacted] probability of being cost effective versus BSC.

Table 7.3: ERG base-case probabilistic cost effectiveness results - RET-mutant MTC (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

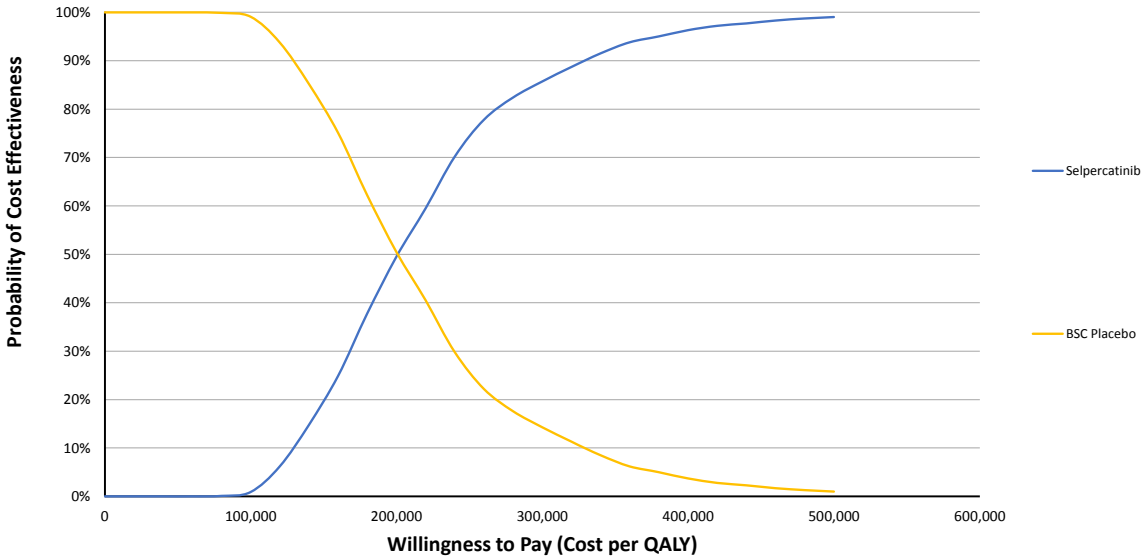
Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

Figure 7.1: ERG preferred cost effectiveness plane - RET-mutant MTC



Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]

Figure 7.2: ERG preferred cost effectiveness acceptability curve - RET-mutant MTC



Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]

7.2.1.2 RET fusion-positive TC

The ERG preferred base-case incremental cost effectiveness results for patients with *RET* fusion-positive TC are provided in Table 7.4 and show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental cost of [redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (i.e. an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 7.4: ERG base-case deterministic cost effectiveness results - RET fusion-positive TC (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

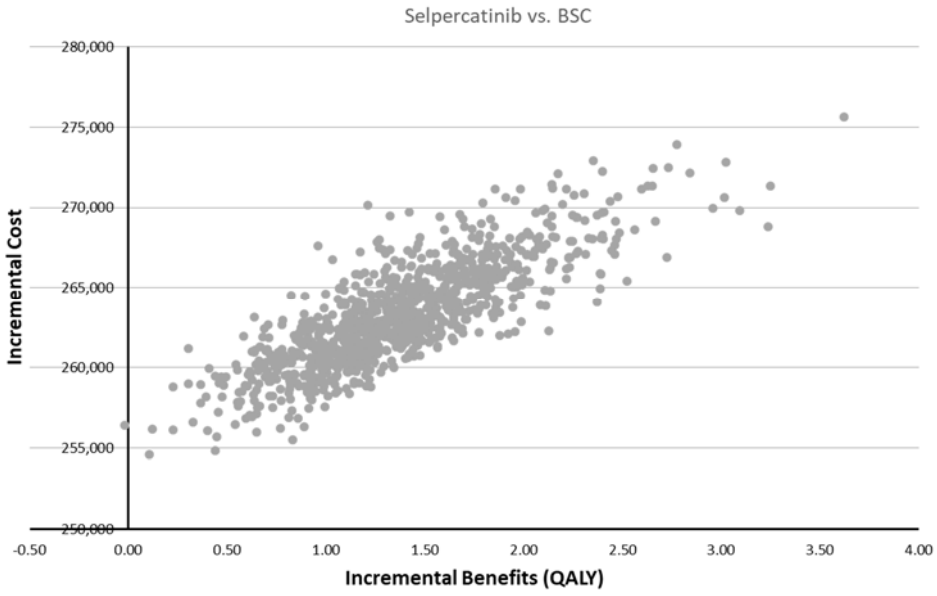
The PSA results in Table 7.5 are similar to the deterministic results. Figure 7.3 displays the cost effectiveness plane, where all simulations fall in the north-east quadrant. Figure 7.4 shows the CEAC. At the common threshold ICERs of £30,000 and £50,000 per QALY gained, selpercatinib has a [redacted] probability of being cost effective versus BSC.

Table 7.5: ERG base-case probabilistic cost effectiveness results - RET fusion-positive TC (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				

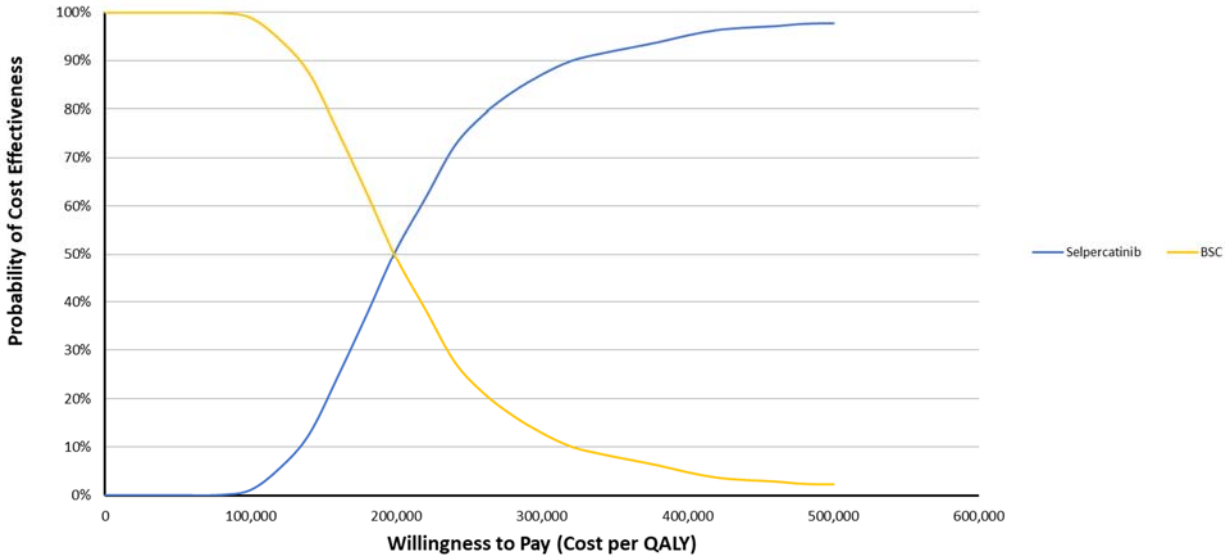
Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

Figure 7.3: ERG preferred cost effectiveness plane - RET fusion-positive TC



Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]

Figure 7.4: ERG preferred cost effectiveness acceptability curve - RET fusion-positive TC



Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Scenario set 1: Overall survival

Results of the OS scenarios are displayed in Table 7.6. In the TC population, the only alternative extrapolation which did not result in crossing curves was the stratified gamma, for which the selpercatinib extrapolation was much less optimistic than the base-case piecewise exponential, resulted in a large increase in the ICER, which increased from [redacted] to [redacted]. This demonstrates the substantial uncertainty in this assumption, which is understandable given the very limited sample size.

In the MTC population, the ERG considered that the company's base-case Weibull (ICER = [redacted]) was likely to be overoptimistic as it did not follow the drop in the KM curve towards the end of follow up. Therefore, the ERG considered the stratified Weibull more plausible, as well as those alternative extrapolations closest to the stratified Weibull, which are considered in scenarios. These potentially plausible extrapolations result in a potentially plausible range of ICERs of [redacted] to [redacted], again demonstrating the substantial uncertainty in the survival analyses presented. It should be noted that of the MTC OS scenarios tested, the stratified loglogistic estimates a proportion of long-term survivors which could be implausible.

Table 7.6: OS scenarios

OS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
RET-mutant MTC							
Weibull (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Stratified Weibull (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive TC							
Piecewise exponential (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BC = base-case; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; OS = overall survival; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.

7.2.2.2 Scenario set 2: Progression free survival

For PFS in RET-mutant MTC, again the company's updated survival analyses showed substantial uncertainty with a wide range of extrapolations (Table 7.7). While all extrapolations except the spline 3 knot fit well to the BSC KM data, uncertainty towards the end of the KM curve generates a much broader potentially plausible range for selpercatinib. Therefore, all but one extrapolation was tested as scenarios. These scenarios demonstrate the substantial uncertainty in the PFS of MTC with a range of potentially plausible ICERs from [redacted] to [redacted].

In the RET fusion-positive TC population, there was again uncertainty on which set of curves best reflected the population in the long term and therefore all alternatives were run. The results demonstrate that this parameter choice has less of an impact on results than the other elements of survival in the model, with a range of ICERs from [redacted] to [redacted].

Table 7.7: PFS scenarios

PFS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
RET-mutant MTC							
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline 3 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline 2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline 2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive TC							
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BC = base-case; ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; PFS = progression free survival; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.

7.2.2.3 Scenario set 3: Utilities

Changing the assumed HSUVs from Fordham et al. to one of the alternative sets from the SMC appraisals identified in the CS had a limited impact on the ICER in the MTC population, reducing the ICER from [redacted] to [redacted] using the SMC cabozantinib utilities and to [redacted] using the SMC sorafenib utilities (Table 7.8). In the RET-fusion-positive TC population, switching between the same sets of utility values had a larger impact on the ICER, reducing it from [redacted] to [redacted] using the SMC cabozantinib utilities and to [redacted] using the SMC sorafenib utilities. Changing the AE disutility for diarrhoea from 0.38 to 0.11 reduced the ICER by approximately [redacted], demonstrating that this is not an important issue.

Table 7.8: Utility scenarios

Utility values	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
RET-mutant MTC							
Fordham et al. (PFS=0.8, PD=0.5) (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMC cabozantinib (PFS=0.796, PD=0.624)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMC sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility values	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
(PFS=0.80, PD=0.64)							
RET fusion-positive TC							
Fordham et al. (PFS=0.8, PD=0.5) (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMC cabozantinib (PFS=0.796, PD=0.624)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMC sorafenib (PFS=0.80, PD=0.64)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All AE disutilities 0.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
AE = adverse event; Incr. = incremental; PD = progressed disease; PFS = progression free survival; QALYs = quality adjusted life years; SMC = Scottish Medicines Consortium; RET = rearranged during transfection; TC = thyroid cancer.

7.2.2.4 Scenario set 4: Genetic testing costs

The results of a scenario analysis in which genetic testing costs are excluded and a scenario analysis using an alternative cost estimate of £6,479 for the costs of NGS testing are shown in Table 7.9. The exclusion of genetic testing costs and the use of the higher estimate had only a slight impact on the results for the *RET*-mutant MTC population and led to a variation in the ICER from £[redacted] per QALY gained when genetic testing costs were excluded to £[redacted] per QALY gained when the higher estimate was used for the *RET* fusion-positive TC population.

Table 7.9: Genetic testing costs scenarios

Genetic testing costs	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
***RET*-mutant MTC**							
ERG preferred base-case: Genetic testing costs Hamblin et al., 2017[57]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic testing costs excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic testing costs Schwarze et al., 2020[58]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Genetic testing costs	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
***RET* fusion-positive TC**							
ERG preferred base-case: Genetic testing costs Hamblin et al., 2017[57]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic testing costs excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic testing costs Schwarze et al., 2020[58]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]
BC = base-case; ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.

7.2.2.5 Scenario set 5: Time on treatment

The results of a scenario analysis in which it was assumed that time on treatment for selpercatinib was equal to PFS are shown in Table 7.10. When time on treatment was assumed to be equal to PFS, the ICER reduced from £[redacted] to £[redacted] per QALY gained for the *RET*-mutant MTC population and from £[redacted] to £[redacted] per QALY gained for the *RET* fusion-positive TC population.

Table 7.10: Time on treatment scenario

Time on treatment	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
***RET*-mutant MTC**							
ERG preferred base-case: Time on treatment in line with LIBRETTO-001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment equal to PFS in line with company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**							
ERG preferred base-case: Time on treatment in line with LIBRETTO-001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment equal to PFS in line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time on treatment	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
with company base-case							
Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24] BC = base-case; ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.							

7.3 ERG's preferred assumptions

Table 7.11 below displays the step-by-step changes which the ERG made to the company base-case alongside the cumulative impact of each change added to the previous changes on results. In the RET-mutant MTC population, the change which had the largest impact on results was extrapolating OS using the stratified Weibull curve instead of the Weibull, which added approximately £100,000 to the ICER. All other ERG changes had minimal impact on the ICER.

In the RET fusion-positive TC population the change which had the largest impact was assuming treatment continuation beyond progression, in line with the data from LIBRETTO-001, which increased the ICER by approximately £15,000, followed by the inclusion of genetic testing costs which increased the ICER by approximately £8,000. Other changes had a minimal impact.

Table 7.11: ERG's preferred model assumptions (cumulative)

Preferred assumption	Section in ERG report	Selpercatinib		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
***RET*-mutant MTC**								
Company original base-case	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company post-clarification base-case	7.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Errors corrected by ERG	7.1.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Stratified Weibull for OS	5.2.6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Genetic testing costs included	5.2.9.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Only PD health state costs for BSC	5.2.9.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ AE costs based on 'non-elective short stay' setting	5.2.9.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Starting age 55.0 for the RET-mutant MTC population	5.2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Treatment continuation beyond progression	5.2.9.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**								
Company original base-case	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company post-clarification base-case	7.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in ERG report	Selpercatinib		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
+ Errors corrected by ERG	7.1.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Genetic testing costs included	5.2.9.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Only PD health state costs for BSC	5.2.9.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ AE costs based on 'non-elective short stay' setting	5.2.9.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Treatment continuation beyond progression	5.2.9.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[24]

AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; MTC = medullary thyroid cancer; OS = overall survival; PD = progressed disease; QALY = quality-adjusted life year; RET = rearranged during transfection; TC = thyroid cancer.

7.4 Conclusions of the cost effectiveness section

The main issue in the cost effectiveness analysis are the uncertainties in the estimates of relative treatment effectiveness for both populations, as this has a direct and potentially large impact on the ICERs.

For the population of patients with *RET*-mutant MTC comparative effectiveness was estimated through a MAIC. As also discussed in section 4, this analysis was affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators.

For example, the basis for the MAIC was data from a mixed population of first- and second-line patients. Although this was done consistently for both treatments under comparison, it was not consistent with the population of only second-line patients that was indicated by the marketing authorisation. It is unclear if similar results would have been obtained if only a population of second-line patients had been analysed. This is especially so given the large difference in PFS between the first-line patients and the second-line patients in LIBRETTO-001.

Also, uncertainty remains due to potential unobserved or unadjusted for confounding variables. When confounding variables were adjusted for, in absence of baseline characteristics for the placebo arm in EXAM a compromise was made to match patients using data from the cabozantinib arm in EXAM instead of the placebo arm. Furthermore, OS data for BSC were not available for the RET-mutant MTC population in EXAM and had to be estimated using the results for the *RET* M918-positive population. However, it is unclear to what extent OS is the same in *RET*-M918-positive patients and the overall *RET*-mutant group.

For the population of patients with *RET*-fusion positive TC comparative effectiveness was estimated through a naïve indirect comparison. This in itself is a major limitation, and other limitations can also be identified.

For the selpercatinib, data was only available for 19 patients, which limits the confidence in any conclusions drawn from that data. For the BSC group, data was used from the SELECT trial. However, data was used from patients with DTC of whom the *RET*-fusion status was unknown, and it is unclear whether these patients are representative for *RET*-fusion positive TC patients. The company indicated that the prognosis for other types of TC than DTC is generally known to be worse. Also, the BSC patients in the SELECT trial were permitted to cross-over after progression, limiting the unbiased estimation of OS, despite the use of a rank preserving structural failure time model to adjust for the cross-over.

Other issues were also identified within the cost effectiveness analyses which are important to note, although secondary to the key issues of the extent to which the analyses conducted are able to reflect the relative efficacy in both populations.

The OS and PFS data were extrapolated using parametric survival curves. In both populations, due to the immature data, many curves were reasonable in comparison to the observed data, whilst often varying widely for the part beyond the last observed data. For the unobserved part of the extrapolation clinical plausibility is the most important factor to consider in choosing the base-case curve. However, no documentation of clinical expert opinion consulted by the company on this matter was available to the ERG. In most instances, the ERG had little reason to deviate from the choices made by the company. For the OS in the *RET*-mutant MTC population though, the ERG considered the unstratified Weibull curve to provide an overly optimistic estimate of OS for selpercatinib, with 10% of patients still alive after 25 years. The ERG also considered that given the limited evidence that is available, the PH

assumption as too strong. In the original CS,[1] the Weibull OS curve was substantially lower than in the updated analyses and clinical expert opinion (of which no documentation on this matter was available to the ERG) consulted by the company indicated that the curve in the original CS may already overestimate OS for selpercatinib. For these reasons, the ERG explored alternative curves that included stratified functions and concluded that the stratified Weibull function provided the best visual fit, best long-term plausibility for BSC, and the most reasonable estimate of the benefit of selpercatinib relative to BSC in light of the limited evidence and immature data that is available.

In the LIBRETTO-001 study it was observed that some patients continued treatment after progression. However, in the model the company assumed that time on treatment was equal to PFS. The ERG has changed this so that time on treatment was in line with data from LIBRETTO-001 and clinical expert opinion.

Regarding health care resource use and costs, some minor issues were found with regards to unit costs used and the costs of BSC. The main issue where the company base-case model and the one based on the ERG's preferred assumptions deviate is regarding the genetic testing costs. These were not included by the company but were included by the ERG to be in line with the decision problem as formulated in the final scope by NICE.

HRQoL data were collected in the LIBRETTO-001 study for patients with *RET*-mutant MTC using the EORTC QLQ-C30. The company did not initially map this data to the EQ-5D, stating that no mapping algorithms estimated in patients with TC were available. At clarification, the ERG requested that the company map this data using a mapping algorithm estimated in a different cancer population. The company conducted a mapping which returned implausible utilities which could not be used in the model. Therefore, the company assumed HSUVs from the literature obtained from a vignette study by Fordham et al., in which vignettes describing potential health states for patients with DTC were valued using by members of the general population. However, this study did not measure HRQoL in patients, instead using vignettes assumed to accurately describe the health of such patients. However other HSUVs available from the literature were also associated with their own uncertainties relating to the population studied and methods used. Therefore, the company's base-case utility values were maintained in the base-case, with alternatives tested in scenarios.

The company base-case incremental deterministic results (after clarification) indicate that selpercatinib is more costly and more effective than BSC. For *RET*-mutant MTC patients the incremental costs are £[redacted] and the incremental QALY [redacted] resulting in an ICER of £[redacted] per QALY gained. For patients with *RET* fusion-positive TC the incremental costs are [redacted] and the incremental QALY [redacted], resulting in an ICER of [redacted] per QALY gained versus BSC. Selpercatinib was associated with a [redacted] probability of being cost effective versus BSC at the common threshold ICERs of £30,000 and £50,000 per QALY gained for both populations.

The ERG preferred base-case incremental cost effectiveness results for patients with *RET*-mutant MTC show that over a lifetime time horizon, treatment with selpercatinib leads to total incremental costs of [redacted], whilst yielding [redacted] extra QALYs, resulting in an ICER of [redacted] per QALY gained versus BSC. For the population with *RET* fusion-positive TC the incremental costs are [redacted], the QALY gain [redacted] and de resulting ICER £[redacted] per QALY gained. Like in the company base case selpercatinib was associated with a [redacted] probability of being cost effective versus BSC at the common threshold ICERs of £30,000 and £50,000 per QALY gained for both populations.

The ERG scenarios with the largest impact on the results were those exploring various OS curves. Looking at plausible alternatives, we find ICERs ranging from approximately [redacted]

for the *RET*-mutant MTC population and from approximately [redacted] for the *RET* fusion-positive TC population. For the PFS curves the ranges were somewhat smaller, and for the alternative utility values and the prolonged time to treatment discontinuation the impact on the ICERs was minimal. When for the costs of genetic testing the higher cost per test is used, the ICER in the *RET* fusion-positive TC population goes up to approximately [redacted]

Nevertheless, given the problems with the estimation of the effect of treatment with selpercatinib based on only a single-arm study, all ICERs mentioned are potentially biased, reflecting a level of uncertainty much larger than that indicated by all sensitivity and scenario analyses. Unfortunately, given the data currently available, these uncertainties cannot be resolved.

8. END OF LIFE

According to the company, selpercatinib should be considered as an end of life treatment for adult patients with RET fusion-positive TC who require systemic therapy and whose disease has progressed following prior systemic treatment and for adults and people aged 12 years and over with advanced RET-mutant MTC who require systemic therapy who have previously received or who are ineligible for cabozantinib, given (a) these patients have a short life expectancy, normally less than two years and (b) there is sufficient evidence to indicate that the selpercatinib offers an extension to life of at least an additional three months, compared with current NHS treatment (CS, Section B.2.12.1).

For the first EOL criterion (short life expectancy, normally less than 24 months), the company refers to evidence from the EXAM[30] and SELECT[35] trials. These were discussed by NICE appraisal committees in TA516[18] and TA535[16], respectively. In both appraisals the committee concluded that the interventions did not meet the criterion for short life expectancy, and therefore the end-of-life criteria did not apply. The committee came to the same conclusion in the appraisal of vandetanib (TA550).[17] However, in the previous appraisals the population included in the scope was different from the population in this appraisal. In this appraisal it is "people with advanced RET fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment and people with advanced RET mutation-positive medullary thyroid cancer (MTC) who require systemic therapy". In the previous appraisals it was "adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine" (TA535[16]) and "adults with unresectable locally advanced or metastatic medullary thyroid carcinoma" (TA516[18] and TA550[17]).

In addition, model results in this appraisal show mean undiscounted life years of greater than two in both indications, suggesting that the life expectancy criterion is not met.

Therefore, the company needs to show that life expectancy in the population for this appraisal is less than 24 months given that cabozantinib, lenvatinib and sorafenib have been recommended in previous appraisals and therefore constitute current best practice.

For the second EOL criterion (an extension to life of at least three months), the company relies on evidence from the economic model that is based on results from highly uncertain MAIC analyses. Therefore, there is no robust evidence that selpercatinib offers an extension to life of at least an additional 3 months compared with current NHS treatment.

ERG comment: The ERG is not convinced there is robust evidence to say that selpercatinib meets the end-of-life criteria.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 8 January 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Major Comments

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 states "*The anticipated EU marketing authorisation wording for the selpercatinib indications of interest for this submission are (Response to Clarification, Question A7):* "[redacted]" "[redacted]"."	This statement should read: "*The EU marketing authorisation wording for the selpercatinib indications of interest for this submission are:* *"Selpercatinib as monotherapy is indicated for the treatment of adults with advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with a lenvatinib and/or sorafenib"* *"Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib"."*	Positive CHMP opinion has now been received confirming licence wording. Therefore, CIC highlighting is no longer required for either of these indications.	Not a factual error. We used the information we had when we finished our report. The information has now been updated.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response

Page 32 states *"A conditional marketing authorisation application for selpercatinib for the treatment of RET-fusion positive TC and RET-mutant MTC was submitted to the European Medicines Agency (EMA) on* [redacted] *and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in* [redacted] *(CS, Table 2, page 18)."*	This statement should read: *"A conditional marketing authorisation application for selpercatinib for the treatment of RET-fusion positive TC and RET-mutant MTC was submitted to the European Medicines Agency (EMA) on 20th December 2019 and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 10th December 2020."*	Confidentiality highlighting should be removed here and the date updated, as positive CHMP opinion has now been received.	Again, not a factual error, but the report has been updated.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 38 states "*it is interesting that the included study designs are 'randomised, controlled, prospective clinical trials, systematic reviews (including meta-analyses) and single-arm trials or RCTs in RET-altered tumours (any tumour site, any intervention, any line of therapy)'. That means the LIBRETTO-001 trial does not fulfil the inclusion criteria. Given that the LIBRETTO-001 study was included, all single arm studies in the relevant population should have been included."*	This statement should be removed.	The LIBRETTO-001 trial fulfils the eligibility criteria as it is a single-arm trial, which is included in the eligibility criteria. In total, nine single arm studies were included in the SLR, as detailed in Appendix D.1.3, on page 21 of the CS.	Agree, sentence removed.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 71 states *"The company was asked to provide adverse events specifically for the two populations described in the scope and for the population used in the MAIC instead of the data presented in the CS[1] (overall OSAS and RET-mutant MTC populations). Data for the exact patient populations requested in the Clarification letter was not available, and instead, the company provided safety data for:*"	Please change to: *"The company was asked to provide adverse events specifically for the two populations described in the scope and for the population used in the MAIC instead of the data presented in the CS[1] (overall OSAS and RET-mutant MTC populations). The company provided safety data for all patients with available safety data in line with patient populations requested in the Clarification letter, albeit constituting a larger pool of patients than those informing the MAIC:*"	This statement is subject to misinterpretation, as the reader may come to the wrong conclusion that the company did not provide data on the correct patient populations. The safety data provided in the response to clarification is in line with the two populations described in the scope and used in the MAIC, however it represents the available safety data collected from all relevant patients at the time of the 16 December data cut-off, hence the higher patient numbers.	Not a factual error – no change made.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.4.1, page 87, the ERG present the MAIC analysis that was reported in Section B.2.8.1 of the company submission. This MAIC no longer informs the cost-effectiveness results for the base case analysis for *RET*-mutant MTC.	The correct analysis is the MAIC including any-line patients adjusted for prior TKI use presented in CQ response A21 on page 24. The company suggests that this is highlighted in the report and direct the reader to the results in the CQ response.	The MAIC presented in CQ response A21 on page 24 is the analysis used to generate the base case cost-effectiveness results, and therefore this should be made clear in this section for the benefit of the reader.	Not a factual error – no change made.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 96 states *"A comparison of PFS Kaplan-Meier curves of progression-free survival in the EXAM and ZETA trials shows that PFS was considerably better in the placebo arm of the ZETA trial when compared with the EXAM trial (see Figures 4.17 and 4.18)."* And page 99 states *"This shows that, although the eligibility criteria seemed to be the same for the trials and that there is some similarity in baseline characteristics, their outcomes, particularly in terms of placebo PFS are quite different."*	Please amend the first statement to: *"A naïve comparison of PFS Kaplan-Meier curves of progression-free survival in the EXAM and ZETA trials shows that PFS was considerably better in the placebo arm of the ZETA trial when compared with the EXAM trial (see Figures 4.17 and 4.18)."* Please amend the second statement to: *"However, although it is impossible with the data available to compare the EXAM and ZETA RET mutation subgroup data, it is possible to compare the placebo groups for the ITT population, albeit naïvely."*	The ERG should acknowledge that the comparison between EXAM and ZETA trials is naïve, given the considerable limitations associated with naïve comparisons. The conclusions drawn by the ERG are therefore subject to considerable uncertainty.	The word 'naïve' has been added on page 96.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 96 states *"Looking at data from both Figures 4.20 and 4.21, OS for placebo in the ZETA trial is considerably better than OS for placebo in the EXAM trial;"*	Please change to: "*Looking at data from both Figures 4.20 and 4.21, OS for placebo in the ZETA trial appears to be considerably better than OS for placebo in the EXAM trial. However, it should be acknowledged that OS is confounded by crossover in the ZETA trial, which may go some way to explaining the apparent difference in OS."*	The ERG should acknowledge that the OS data for ZETA is confounded by crossover, as this is essential context when interpreting the differences in OS between the EXAM and ZETA trials.	Not a factual error – No change made.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 105 states "*The PRISMA diagram indicates that 292 records were included in the SLR. However, Table 22 shows only four HRQoL studies were included and Table 24 shows only 30 cost and resource use studies included. Therefore it is unclear what happened to the remaining HRQoL and cost and resource use shown as included in the PRISMA diagrams studies*."	Please change to: *"The PRISMA diagram indicates that 292 records were included in the SLR, which combines articles identified for NSCLC and TC. The Company confirmed that Table 22 presents the four HRQoL studies identified for TC, and Table 24 shows the 30 cost and resource use studies included for TC. The remaining articles relate to NSCLC and were therefore not included."*	The PRISMA diagram presents the findings for both NSCLC and TC. Table 22 and Table 24 present only those relevant to TC, and therefore the remaining studies were all excluded because they were relevant to NSCLC only.	Given the company's clarification the ERG has made the following amendment in their report: The PRISMA diagram indicates that 292 records were included in the SLR. However, Table 22 shows only four HRQoL studies were included and Table 24 shows only 30 cost and resource use studies included. The company confirmed that the PRISMA diagram combines articles identified for NSCLC and TC and that the unaccounted for included articles all related to NSCLC and were therefore not included in this appraisal.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 105 and 106 state "*It is also concerning that the HRQoL study by Fordham et al., used by the company in the model was not identified in the HRQoL SLR. It is unclear how many other studies may have been missed.*"	This statement should be removed, or amended to acknowledge the reason that Fordham *et al.* (2015) was not included in the SLR – this study falls outside the time limit of January 2017.	The Fordham *et al.* (2015) study falls outside the time limit of the SLR of January 2017. Any relevant HRQoL studies published prior to this time limit, such as Fordham *et al.* (2015), were assumed to have been captured in the prior NICE appraisals. The four HRQoL studies	Given the company's clarification the ERG has made the following amendment in their report: It is also concerning that the HRQoL study by Fordham et al., used by the company in the model was not identified in the

		presented in Table 22 of the appendices are the only HRQoL studies identified in the time frame that fulfilled eligibility criteria for TC. Therefore this statement should be removed as it implies that studies were erroneously overlooked.	HRQoL SLR as the SLR only searched for studies from January 2017, assuming any relevant studies published prior to this time would be captured in prior NICE appraisals. It cannot be assumed that prior appraisals captured and reported all evidence relevant to this appraisal and therefore relevant evidence may have been missed.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 113 states *"Despite the relevant population for this appraisal consisting of second-line patients, the company used the any-line population from LIBRETTO-001 since they consider it to provide a more robust sample size and to reduce possible bias that would be caused by comparing only pre-treated patients from LIBRETTO-001 with the mix of first-line and second-line patients from EXAM."*	Please add additional statement to the statement on page 113 to: *"Despite the relevant population for this appraisal consisting of second-line patients, the company used the any-line population from LIBRETTO-001 since they consider it to provide a more robust sample size and to reduce possible bias that would be caused by comparing only pre-treated patients from LIBRETTO-001 with the mix of first-line and second-line patients from EXAM. The any-line population was adjusted in line with the EXAM population according to the proportion of patients who received prior TKI therapy in addition to other characteristics."*	The population used in the *RET*-mutant MTC MAIC included first- and second-line patients adjusted for prior TKI use, in line with the MAIC presented in the response to clarification A21. This important context should be reported when discussing the comparison between LIBRETTO-001 and EXAM.	The ERG agrees with the amendment as proposed by the company and has changed the report text accordingly.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 122 states "*The ERG considered the Weibull curve to provide an overly optimistic estimate of OS for selpercatinib, with [redacted] of patients still alive after 25 years .*"	Please change to: "*The ERG considered the Weibull curve to provide an overly optimistic estimate of OS for selpercatinib, with [redacted] of patients still alive after 25 years .*"	The stated predicted survival using the unstratified Weibull are from the without prior TKI adjusted analysis for OS. Please update the figure to reflect the predicted survival when the unstratified Weibull is applied to the prior TKI adjusted analysis for OS used in the company base case.	The ERG agrees with the amendment as proposed by the company and has changed the text in the report accordingly. In addition, the ERG has corrected the title of Figure 5.6 by replacing 'Piecewise exponential' with 'Weibull'.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 177 states *"In this appraisal it is 'people with advanced RET fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment and people with advanced RET mutation-positive medullary thyroid cancer (MTC) who require systemic therapy'"* Page 177 also states "*Therefore, the company needs to show that*	The first statement should be amended to the new licence wording to: "*In this appraisal it is 'people with advanced RET fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment with lenvatinib and/or sorafenib and people with advanced RET mutation-positive medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib'.* The second statement should be amended to: "*Therefore, the company needs to show that life*	The description of the population in this appraisal should reflect the updated licence wording, which restricts the use of selpercatinib to patients who have received prior MKIs. This is an important distinction between this appraisal and the previous appraisals of first-line treatments. Current MKIs cabozantinib, lenvatinib and sorafenib are first-line treatments. This should be	Not a factual error – the information was based on information we had when we completed our report. No change made.

life expectancy in the population for this appraisal is less than 24 months given that cabozantinib, lenvatinib and sorafenib have been recommended in previous appraisals and therefore constitute current best practice."	*expectancy in the population for this appraisal (i.e. the second line setting) is less than 24 months given that cabozantinib, lenvatinib and sorafenib have been recommended in previous appraisals, and therefore constitute current past practice in the first-line setting."*	clearly stated to avoid implying that the company need to show that life expectancy for patients receiving these therapies is less than 24 months.	

Section 2: Minor Comments

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 57 states *"The CS notes that median DOR was not reached by the 16 December 2019 (the CS mentions the date as 17 December 2020, but this is probably an error)"*	The second statement should be amended to: *"The CS notes that median DOR was not reached by the 16 December 2019 (the CS mentions the date as 17 December 2020, but confirmed this was an error)"*	Thank you for highlighting. This was an error.	The report has been updated.

Section 3: Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
Page 32 states "[redacted]And	Marketing authorisation has been granted. Please remove confidentiality highlighting for marketing authorisation throughout.	*"Selpercatinib as monotherapy is indicated for the treatment of adults with advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with a multiple kinase inhibitor"* *And "Selpercatinib as monotherapy*	This has been updated.

[redacted]		*is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib"*	
Page 39 states: "*Multicentre, open-label, Phase I/II study in patients with advanced solid tumours, with RET activations (N=*<missing AIC>*)."*	Missing AIC highlighting.	*"Multicentre, open-label, Phase I/II study in patients with advanced solid tumours, with RET activations (N=[redacted])."*	This has been updated.
Page 64 states "*The mean baseline score for global health status/QoL subscale was* <missing AIC> *(SD=*<missing AIC>*).*	Incorrect AIC highlighting (missing underline).	"*The mean baseline score for global health status/QoL subscale was [redacted] (SD=[redacted]).*	This has been updated.
Page 137 states: "*However, given the very limited impact of this disutility on the ICER (a change of* <missing CIC> *on an ICER of approximately* <missing CIC>*), this issue was not considered important and no base-case change was made.*	Missing CIC highlighting.	"*However, given the very limited impact of this disutility on the ICER (a change of [redacted] on an ICER of approximately [redacted]), this issue was not considered important and no base-case change was made.*	This has been updated.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for the treatment of advanced RET-fusion positive thyroid cancer and advanced RET-mutant medullary thyroid cancer [ID3744]

Company response to the ERG Report

May 2021

File name	Version	Contains confidential information	Date
ID3744_Eli Lilly_Selpercatinib in TC_Company Response to the ERG Report_ACIC	Final	No – Fully Redacted	17th May 2021

Lilly thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the issues raised in the Evidence Review Group (ERG) report. Since the original submission on 6th October 2020 there have been a number of changes relating to the marketing licence, price and pack sizes for selpercatinib, summarised in Table 1 below.

Table 1: Licencing, list price and method of administration for selpercatinib.

<table>
<tr><td>Marketing authorisation</td><td colspan="2">Date and type of authorisation in GB[1]
26th February 2021, Conditional
Wording[2]
Selpercatinib as monotherapy is indicated for the treatment of adults with:
advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib
Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.</td></tr>
<tr><td>Pharmaceutical formulation and method of administration</td><td colspan="2">Method of administration
Oral
Dosage
The recommended dose of selpercatinib based on body weight is 160 mg orally (2 x 80 mg capsules) twice daily (BID) for adults ≥50 kg. For adults <50 kg, the recommended dose of selpercatinib is 120 mg orally BID. Treatment should be continued until disease progression or unacceptable toxicity[2]</td></tr>
<tr><td rowspan="8">List price</td><td>Strength, form, and pack size</td><td>List price (£)</td></tr>
<tr><td>60 capsule bottle of 80 mg selpercatinib</td><td>£4,680.00</td></tr>
<tr><td>60 capsule bottle of 40 mg selpercatinib</td><td>£2,340.00</td></tr>
<tr><td>112 capsule blister of 80mg selpercatinib</td><td>£8,736.00</td></tr>
<tr><td>168 capsule blister of 40mg selpercatinib</td><td>£6,552.00</td></tr>
<tr><td>56 capsule blister of 80mg selpercatinib</td><td>£4,368.00</td></tr>
<tr><td>56 capsule blister of 40mg selpercatinib</td><td>£2,184.00</td></tr>
<tr><td colspan="2">The cost of a 28-day cycle of selpercatinib is £8,736.00</td></tr>
<tr><td>PAS price</td><td colspan="2">The PAS price of a 60 capsule bottle of 80 mg selpercatinib is [redacted] or [redacted] for 60 capsule bottle of 40mg. The cost of a 28-day cycle of selpercatinib is [redacted]</td></tr>
</table>

The Company have provided a concise response focussing on the key issues identified in the ERG report that have a material impact on decision-making:

- Section 1: Company response to key issues raised by the ERG
- Section 2: Summary of key issues where the Company have aligned with ERG preferences or where uncertainty cannot be resolved
- Section 3: Summary of additional changes to the economic model

Full details of updates made to the revised base case of the model have been presented in Appendix A and revised base case, deterministic and probabilistic sensitivity analyses and scenario analyses have been presented in Appendix C.

1 Company response to key issues

1.1 Issue 1: Appropriateness of cabozantinib as a comparator

The ERG requested that an economic analysis be provided for selpercatinib versus cabozantinib in the updated licence population. However, the final licence for selpercatinib states for patients with *RET*-mutant medullary thyroid cancer (MTC): 'selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced *RET* mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib'.[2]

Cabozantinib,[3] but not vandetanib,[4] is recommended in England for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. For patients who have progressed on cabozantinib, the only remaining treatment option is best supportive care (BSC). Given the updated licence specifies that selpercatinib can only be used following either cabozantinib and/or vandetanib, the Company do not consider cabozantinib to be a relevant comparator for this appraisal.

1.2 Issue 2: Immaturity of effectiveness data

As outlined in the ERG report, several outcomes of the LIBRETTO-001 study are immature, such as overall survival (OS), progression-free survival (PFS) and duration of response (DOR). Since the original Company submission, additional efficacy data from a March 2020 data cut have become available. Summary tables presenting key clinical data from the 16th of December 2019 and 30th March 2020 data cut are presented below to allow for easy comparison. For the 30th March 2020 data cut-off, results are presented for patients who had been enrolled at the time of the 16th December 2019 data cut-off, but with additional follow-up. Results are also presented for all patients enrolled as of the 30th March 2020 data cut-off. Data are presented in full for all patients enrolled as of the 30th March 2020 data cut-off in Appendix A.

These data represent a larger sample size and longer duration of follow up and show that, directionally, there is no difference in efficacy between the 30th March 2020 and 19th December 2019 data cut-offs. Whilst these data corroborate and therefore provide additional confidence in the results of the 16th December 2019 data cut, they have not been used to conduct additional match-adjusted indirect treatment comparisons (MAIC) and naïve indirect treatment comparisons (ITC) for the *RET*-mutant MTC and *RET* fusion-positive TC populations, respectively, nor to inform the revised base case, due to time constraints and as only a small number of additional

events had occurred. As such, these data would have minimal impact on the resulting cost-effectiveness results.

A summary of the key clinical data from the 16th of December 2019 and 30th March 2020 data cut-off for the integrated analysis set (IAS; including patients who are previously treated with cabozantinib and/or vandetanib) and the supplementary analysis set 1 (SAS1; including patients who are cabozantinib and/or vandetanib naïve) are presented in Table 2 and Table 3 respectively. Full details of the efficacy data for each endpoint are presented in Appendix A.1.

Table 2: Objective response rate, progression-free survival, and overall survival previously treated (IAS) *RET*-mutant MTC by IRC Assessment, 30th March 2020 data cut-off

	All Patients Enrolled as of 17 June 2019		All Patients Enrolled as of 30 March 2020
Data Cut-Off Date:	**16 December 2019 Additional 6 Months Follow-up**	**30 March 2020 Additional 9.5 Months Follow-up**	**30 March 2020**
No. of Eligible Patients[a]	124	124	143
Objective Response Rate (CR + PR)			
N (%)	[redacted]	[redacted]	[redacted] (69.2)
95% CI	[redacted]	[redacted]	61.0, 76.7
Duration of Response (months)			
Median	[redacted]	[redacted]	NE
95% CI	[redacted]	[redacted]	19.1, NE
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Duration of Follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Progression-free Survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate of Progression-free Survival (%)			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Overall Survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate (%) of Overall Survival			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a] Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP).
+ = Censored Observation

Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MTC: medullary thyroid cancer; NE: not estimable; No.: number; PR: partial response.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Table 3: Objective response rate, progression-free survival, and overall survival cabozantinib/vandetanib naive (SAS1) *RET*-mutant MTC by IRC Assessment, 30th March 2020 data cut-off

	All Patients Enrolled as of 17 June 2019		All Patients Enrolled as of 30 March 2020
Data Cut-Off Date:	**16 December 2019 Additional 6 Months Follow-up**	**30 March 2020 Additional 9.5 Months Follow-up**	**30 March 2020**
No. of Eligible Patients[a]	88	88	[redacted]
Objective Response Rate (CR + PR)			
N (%)	64 (72.7)	[redacted]	[redacted]
95% CI	(62.2, 81.7)	[redacted]	[redacted]
Duration of Response (months)			
Median	21.95	[redacted]	[redacted]
95% CI	NE, NE	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Duration of Follow-up (months)			
Median	7.79	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Progression-free Survival (months)			
Median	23.56	[redacted]	[redacted]
95% CI	NE, NE	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate of Progression-free Survival (%)			
12 months or more	92.4	[redacted]	[redacted]
95% CI	82.1, 96.8	[redacted]	[redacted]
Overall Survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate (%) of Overall Survival			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a] Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP).
+ = Censored Observation
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MTC: medullary thyroid cancer; NE: not estimable; No.: number; PR: partial response.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

A summary of the key clinical data from the 16th of December 2019 and 30th March 2020 data cut off for the pre-treated *RET* fusion-positive TC group are presented in Table 4. Full details of the efficacy data for each endpoint are presented in Appendix A.2.

Table 4: Objective response rate, progression-free survival, and overall survival pre-treated *RET* fusion-positive TC by IRC Assessment, 30th March 2020 data cut-off

	All Patients Enrolled as of 17 June 2019		All Patients Enrolled as of 30 March 2020
Data Cut-Off Date:	**16 December 2019 Additional 6 Months Follow-up**	**30 March 2020 Additional 9.5 Months Follow-up**	**30 March 2020**
No. of Eligible Patients[a]	19	19	22
Objective Response Rate (CR + PR)			
N (%)	15 (78.9)	[redacted] (78.9)	[redacted] (77.3)
95% CI	(54.5, 93.9)	54.4, 93.9	54.6, 92.2
Duration of Response (months)			
Median	18.43	18.43	18.43
95% CI	7.6, NE	7.6, NE	10.1, NE
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Duration of Follow-up (months)			
Median	17.51	[redacted]	[redacted]
25th, 75th Percentiles	[redacted]	[redacted]	[redacted]
Progression-free Survival (months)			
Median	20.07	[redacted]	[redacted]
95% CI	9.4, NE	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate of Progression-free Survival (%)			
12 months or more	64.4	[redacted]	[redacted]
95% CI	37.0, 82.3	[redacted]	[redacted]
Overall Survival (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Rate (%) of Overall Survival			
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a] Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib to the data cut-off date (per RET-mutant MTC SAP).
+ = Censored Observation
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MTC: medullary thyroid cancer; NE: not estimable; No.: number; PR: partial response.

1.3 Issue 5: Extrapolation of survival data

The ERG highlighted that there was considerable uncertainty in the extrapolation of survival data, given the immaturity in survival outcomes for *RET*-mutant MTC OS. The Company have since sought additional clinical expert feedback to evaluate survival extrapolations for OS specifically for the *RET*-mutant MTC population, and to identify the most plausible extrapolation. The choice of extrapolation for the revised base case and the accompanying justification is presented in Appendix B.1.

1.4 Issue 7: Genetic testing cost

The ERG highlighted that the genetic testing costs should be included in the model, as specified in the final scope by NICE, and that a scenario should be performed that excludes them. The ERG also acknowledged the uncertainty regarding the cost of genetic testing and provided the following estimates: Hamblin *et al.* (2017), provided an estimate of £367 and Schwarze *et al.* (2020), provided an estimate of £6,479.

A figure of [redacted] per test specifically attributed to the *RET*-fusion or *RET*-mutant portion of a multi-gene testing NGS panel was provided by NHS England, which has been included in the model. Diagnostic costs of [redacted] per advanced *RET*-mutant MTC patient, and [redacted] per advanced *RET* fusion-positive TC patient have been applied. Further details on how these costs have been calculated and applied in the model can be found in Appendix B.6.

1.5 End-of-life criteria

Short life expectancy, normally less than 24 months

The Company acknowledges the ERG's view that the first end-of-life (EOL) criterion (short life expectancy, normally less than 24 months) relies on evidence from the Company's economic model which is based on the result of the uncertain indirect treatment comparisons. As highlighted, OS data are not available for patients with *RET*-altered TC following prior treatment, therefore OS data for patients receiving placebo (which can be considered a proxy for BSC) in the *RET* M918T-positive subgroup of the EXAM trial and the intention-to-treat (ITT) population of the SELECT trial for *RET*-mutant MTC and *RET* fusion-positive TC patients were used in the model, respectively. These estimates provided the best proxy for BSC in patients with *RET*-altered TC, however they may overestimate the survival of pre-treated patients of relevance to this submission, as described below.

RET-mutant MTC

- In the *RET* M918T positive subpopulation of the EXAM trial, to which the LIBRETTO-001 trial was match-adjusted in the MAIC, median overall survival in the placebo arm was 18.9 months (n=45) while median OS for the ITT population treated with placebo was 21.1 months (n=111).[6] These results suggests that the median overall survival of patients receiving placebo in the *RET* M918T positive subgroup and the ITT population in the EXAM trial is below the two year limit specified in the EOL criterion. The economic model using the updated survival extrapolations predicted a median OS of [redacted] months, which also falls below the two year limit, indicating that the majority of patients receiving BSC have a life expectancy under two years.

- Whilst the NICE appraisal committee in TA516 concluded cabozantinib did not meet the EOL criteria, the Company notes that this decision was based on the ITT placebo arm of the EXAM trial, which included predominantly patients naïve to multikinase inhibitor (MKI) treatment and only 21% who had received prior MKI treatment.[3] The population of relevance for this submission includes *RET*-mutant pre-treated patients, representing a population who may have worse prognosis than the ITT placebo arm of the EXAM trial.
- The model predicted mean undiscounted life years of [redacted] for *RET*-mutant MTC patients receiving BSC. However, these results may be skewed by a small proportion of patients with long term survival; [redacted]% of patients treated with BSC are predicted to be alive at 10 years based on the base case stratified gamma curve. It should also be noted that, whilst the *RET* M918T-positive subgroup of the EXAM trial was considered the best available proxy for BSC in patients with pre-treated *RET*-mutant MTC, this population also included a proportion of patients naïve to MKI treatment. As discussed in Appendix B.1, given OS was based on a mixed treatment population of pre-treated and patients naïve to systemic therapy, the most plausible extrapolation was specifically chosen to reflect a proportion of patients with non-progressive stable disease expected to have better survival outcomes in the long-term. Whilst this permitted the fairest comparison between selpercatinib and BSC in terms of the resulting ICER, it should be noted that, in absolute terms, this extrapolation may overestimate the survival of a fully pre-treated *RET*-mutant patient population.
- The ERG note that the placebo arm from the ZETA trial may also provide a reasonable proxy for BSC.[7] However, no data for OS is available for the placebo arm of the study and its interpretation is confounded for reasons discussed in Issue 3, Appendix 2.
- Taking all of these points into consideration, the available evidence suggests that the majority of patients with pre-treated *RET*-mutant MTC receiving BSC are expected to have a life expectancy under two years.

RET fusion-positive TC

- No RCT data were identified in patients with *RET* fusions and, in the absence of data for patients with known *RET* status, two trials were identified that included a placebo arm that could be considered a reasonable proxy for BSC: DECISION and SELECT.[8, 9] Median OS was not reached in either of these clinical trials and OS in the model was based on OS Kaplan–Meier curves from the ITT population of the SELECT trial, which included only DTC patients, did not limit to patients with a *RET* fusion and included predominantly first-line patients. However, the model-predicted median OS of [redacted] months, indicating that the majority of patients receiving BSC have a life expectancy under two years. Mean undiscounted life years were [redacted], which falls marginally above the two year threshold, but may be skewed by a small proportion of patients with longer term survival.
- Whilst the NICE appraisal Committee in TA535 concluded that lenvatinib did not meet the EOL criteria, it should be acknowledged that the population of relevance in TA535 did not restrict to pre-treated patients, nor to patients with *RET* fusions. This therefore represents a population with better prognosis than the population of relevance for this submission. Whilst the ITT population of the SELECT trial was considered the best available proxy for *RET* fusion-positive TC patients receiving BSC in this submission (in the absence of more relevant data), it should be noted that this population included predominantly (79.4%) patients naïve to treatment with a tyrosine kinase.[10] Therefore, as for the *RET*-mutant MTC population described above, these data (and the resulting model predictions) may represent an overestimate the survival of a fully pre-treated patient population.

- Taking all of these points into consideration, the available evidence suggests that the majority of patients with pre-treated *RET* fusion-positive TC receiving BSC are expected to have a life expectancy under two years.

Extension to life of at least three months

The ERG have emphasised that for the second EOL criterion (an extension to life of at least three months), the Company relies on evidence from the economic model that is based on results from highly uncertain MAIC analyses. The March 2020 data cut-off of the LIBRETTO-001 trial presented above addresses some of this uncertainty, indicating that, directionally, there is no difference in the efficacy of selpercatinib with a larger sample size and longer follow up. Therefore, with the substantial improvements predicted in mOS for patients treated with selpercatinib versus BSC ([redacted] versus [redacted] months for *RET*-mutant MTC patients, and [redacted] versus [redacted] for *RET* fusion-positive TC patients) the evidence suggests that selpercatinib offers significantly greater than three months extension to life compared with current NHS treatment.

2 Summary of remaining key issues

Issue 3: Reliability of the MAIC for RET-mutant MTC population

As per the Company response to ERG Clarification Question A21, the LIBRETTO-001 and EXAM trials included both treatment-naïve and pre-treated patients. In the LIBRETTO-001 trial, patients enrolled in the IAS (n=124) had received 1 or more lines of prior cabozantinib or vandetanib. Patients enrolled in the SAS1 (n=88) were cabozantinib and vandetanib naïve. Clinical effectiveness results are reported separately for these two analysis sets. In the *RET*-mutant subgroup of the EXAM trial (cabozantinib arm), 81/219 (37.0%) patients had received prior systemic therapy for MTC. However, clinical effectiveness results were not reported separately for treatment-naïve and pre-treated patients. It must be noted that comparing pre-treated patients from one trial (LIBRETTO-001 IAS) with a mix of naïve and pre-treated patients from another (EXAM) is likely to be biased.

Given the limitations in the available data from EXAM, an unanchored population-adjusted ITC was conducted using individual patient-level data from the any-line patients adjusted for prior TKI use in the LIBRETTO-001 trial (IAS+SAS1; n=212) and summary evidence for the *RET*-mutant subgroup of the EXAM trial, as reported in Schlumberger *et al.* (2017) and Sherman *et al.* (2016).[6, 11] The Company consider this analysis to provide the most unbiased estimate of the relative treatment effect for selpercatinib versus BSC based on the available evidence sources. However, the limitations raised by the ERG relating to the potential differences between trials included in the MAIC cannot be resolved. As such, the Company ask the Committee to consider this uncertainty in their decision-making.

The ERG promote an update to the MAIC to include the placebo arm of the ZETA trial for vandetanib instead of EXAM. It should be noted that during the course of the feasibility assessment ZETA was identified as a potential data source for BSC but was not considered in the ITC because the patient characteristics for the ZETA trial are available only for the ITT populations, and not for the *RET*-mutant subgroup. There are also no data available for the *RET*-mutant MTC subgroup for OS for placebo, therefore, it is not appropriate to indirectly compare to the placebo arms of the ZETA trial. Furthermore, OS in the ZETA trial is confounded by crossover after disease progression and vandetanib was not accepted by NICE, citing a lack of robustness in clinical data of the ZETA trial.[4]

Issue 4: Reliability of naïve ITC for RET-fusion positive TC population

Whilst the March 2020 data cut corroborates the results for selpercatinib in the *RET*-fusion TC population, the limitations raised by the ERG relating to the potential differences between trials included in the naïve comparison cannot be resolved.

Of the available evidence sources, the placebo arm of the intention-to-treat population of the SELECT trial was considered to represent the most appropriate proxy for the clinical effectiveness of BSC for patients with *RET* fusion-positive TC, and was therefore used to inform the efficacy of BSC in the economic model. However, given the intent-to-treat population includes patients who are naïve to TKI treatment and are of unknown RET-status, it is plausible that the efficacy of BSC in pre-treated patients may be lower than predicted in the model. As such, the Company ask the Committee to consider this uncertainty in their decision-making.

Issue 6: Health-state utility values

An attempt was made to map EORTC-QLQ-C30 data from the pre-treated RET-mutant and RET-fusion TC population in LIBRETTO-001 to the EQ-5D-3L which resulted in implausibly high health state utility value (HSUV) for progression free (PF) and progressed disease (PD) health states, as presented in Clarification Question B11. The ERG attempted its own validation of the PF health state with the baseline EORTC-QLQ-C30 data provided by the Company.[12] The ERG used a mapping algorithm from Kontodimopoulos *et al.* (2009) estimated in patients with gastric cancer and another by Marriott *et al.* (2017) in a colorectal cancer population resulting in baseline EQ-5D-3L utilities of [redacted] and [redacted] respectively, which supports the 0.8 value for the PF state used in the Company's base case.

A further attempt was made to map using an alternative mapping algorithm for NSCLC, Young *et al.* (2015), to the EQ-5D-3L.[13] This further supported the 0.8 value for the PF state used in the Company's base case. However, unrealistic values for the progressed disease (PD) health state were produced (exceeding the PF value), as presented in Table 5. This is likely due to very few observations for patients with PD. As such, the Company maintain that the utility value reported by Fordham *et al.* (2015) represents the most appropriate value to inform the PD state but acknowledge the remaining uncertainty in this assumption.

Table 5: LIBRETTO-001 HRQoL data mapped to EQ-5D-3L using the Young et al. mapping algorithm

	RET-mutant MTC		Previously treated RET fusion-positive TC (N=19)	Previously treated RET fusion-positive TC and RET-mutant MTC (IAS)
	IAS Prior cabozantinib /vandetanib (N=124)	SAS1 Prior cabozantinib /vandetanib (N=88)		
All pre-progression assessments				
N (n)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
CI	[redacted]	[redacted]	[redacted]	[redacted]
All post-progression assessments				
N (n)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

CI	[redacted]	[redacted]	[redacted]	[redacted]

N = number of patients with assessments; n = total number of assessments.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS1: Treatment-naïve; TC: thyroid cancer

Issue 8: Time on treatment:

Given clinical expert opinion and data from the LIBRETTO-001 trial indicates that treatment with selpercatinib may be continued beyond progression, the Company have aligned with the ERG's preference regarding the modelling of time on treatment (see Appendix B.2).

3 Additional updates to the economic model

A number of additional changes have been made to the economic model since submission. Full details of the updates to the base case economic analysis have been presented in Appendix A. In addition, an annotated version of the model detailing all of the updates since submission has been provided alongside this response. Additional changes include:

- Inclusion of the updated list price for selpercatinib (Appendix B.3)
- Inclusion of the approved PAS price for selpercatinib (Appendix B.3)
- Modelling of dose intensity in line with dose distribution observed in the LIBRETTO-001 trial to align with recommended dose reductions in the selpercatinib SmPC (Appendix B.3)[2]
- Electrocardiogram (ECG) costs applied for selpercatinib in alignment with the SmPC (Appendix B.3)[2]
- MTC BSC resource and costs corrected based on error identified during clarification (Appendix B.4)
- Other minor changes to align with ERG corrections (annotated model)

Appendix A: LIBRETTO-001 30th March 2020 data cut-off

A.1 RET-mutant MTC

Objective Rate By RECIST v1.1 (primary endpoint)

Table 6: Best overall response and objective response rate for *RET*-mutant MTC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut-off

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib/ vandetanib N=143	SAS1 Cabozantinib/ vandetanib-naïve N=[redacted]
Best overall response, n (%)[a]			
Complete response	6 (10.9)	6 (4.2)	[redacted]
Partial response	32 (58.2)	93 (65.0)	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
SD*	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
Objective response rate (CR + PR)[b,d]			
n (%)	[redacted] (69.1)	[redacted] (69.2)	[redacted]
95% CI	(55.2, 80.9)	(61.0, 76.7)	[redacted]
Clinical Benefit Rate (CR +PR + SD)[c,d]			
n (%)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days. [c] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of selpercatinib until the criteria for disease progression was first met. [d] 95% Confidence Interval was calculated using Clopper-Pearson method.
* Indicates SD lasting >16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MTC: medullary thyroid cancer; No.: number; PAS: Primary Analysis Set; PR: partial response; RET: rearranged during transfection; SAS1: Treatment-naïve; SD: stable disease.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Duration of response

Table 7: Duration of response for *RET*-mutant MTC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut-off

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib/ vandetanib N=143	SAS1 Cabozantinib/ vandetanib-naïve N=[redacted]
Patients with best response of confirmed CR or PR (n)[a]	[redacted]	[redacted]	[redacted]
Response status n (%)[b]			
Disease progression	[redacted]	[redacted]	[redacted]
Died (No disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]

Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)[c,d]			
Median	NE	NE	[redacted]
95% CI	19.1, NE	19.1, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of duration of response[c,e]			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)[c]			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)[b]			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥= 24 months	[redacted]	[redacted]	[redacted]
Response status (n, %)			
Disease progression	[redacted]	[redacted]	[redacted]
Died (no prior disease progression)	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b]Status as of the patients last disease assessment on or before cutoff date. [c] Estimate based on Kaplan-Meier method [d] 95% Confidence Interval was calculated using Brookmeyer and Crowley method. [e] 95% Confidence Interval was calculated using Greenwood's formula.
+ = censored observations
Abbreviations: CI: confidence interval; CR: complete response; IAS: prior platinum chemotherapy; NE: not estimable; PAS: Primary Analysis Set; PD: disease progression; PR: partial response; SAS1: treatment-naïve.
Source: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Progression-free survival

Table 8: Progression free survival for *RET*-mutant MTC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut-off

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=143	SAS1 Cabozantinib/ vandetanib-naïve N=[redacted]
Status (n, %)[a]			
Disease Progression	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)[b]			

Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival[b,c]			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
18 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
24 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b] Estimate based on Kaplan-Meier method. [c] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
+ = censored observations
Abbreviations: CI: confidence interval; IAS: prior cabozantinib/vandetanib; PD: disease progression; PAS: Primary Analysis Set; SAS1: cabozantinib/vandetanib naive.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Figure 1: Kaplan–Meier plot of progression free survival in *RET*-mutant MTC (IAS), 30th March 2020 data cut-off

Abbreviations: CI: confidence interval; IAS: Prior Platinum Chemotherapy; PD: disease progression; PAS: Primary Analysis Set; SAS1: Treatment-naïve.

Figure 2: Kaplan–Meier plot of progression free survival in *RET*-mutant MTC (IAS+SAS1), 30th March 2020 data cut-off

Abbreviations: IAS: prior cabozantinib/vandetanib; MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS1: cabozantinib/vandetanib naive.

Overall Survival

Table 9: Overall survival for *RET*-mutant MTC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut-off

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=143	SAS1 Cabozantinib/ vandetanib-naïve N=[redacted]
Status (n, %)[a]			
Disease Progression	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Duration of overall survival (months)			
Median[b]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of overall survival[b,c]			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
18 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
24 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			

Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]

[a] Status as of the last contact on or before 30th March 2020 [b] Estimate based on Kaplan-Meier method. [c] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
+ = censored observations
Abbreviations: CI: confidence interval; IAS: prior cabozantinib/vandetanib; PD: disease progression; PAS: Primary Analysis Set; SAS1: cabozantinib/vandetanib naive.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Figure 3: Kaplan–Meier plot of overall survival in *RET*-mutant MTC (IAS), 30th March 2020 data cut-off

Abbreviations: IAS: prior cabozantinib/vandetanib; MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS1: cabozantinib/vandetanib naive.

Figure 4: Kaplan–Meier plot of overall survival in *RET*-mutant MTC (IAS+SAS1), 30th March 2020 data cut-off

Abbreviations: IAS: prior cabozantinib/vandetanib; MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS1: cabozantinib/vandetanib naive.

A.2 RET fusion-positive TC

Objective Rate By RECIST v1.1 (primary endpoint)

Table 10: Best overall response and objective response rate for *RET* fusion-positive TC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut

	Previously treated N=22	Systemic therapy naïve N=[redacted]	Total N=[redacted]
Best overall response, n (%)[a]			
Complete response	2 (9.1)	[redacted]	[redacted]
Partial response	15 (68.2)	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
SD*	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
Objective response rate (CR + PR)[b,d]			
n (%)	[redacted] (77.3)	[redacted]	[redacted]
95% CI	(54.6, 92.2)	[redacted]	[redacted]
Clinical Benefit Rate (CR +PR + SD)[c,d]			
n (%)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b] Objective Response Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, or PR. Response was confirmed by a repeat assessment no less than 28 days. [c] Clinical Benefit Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of selpercatinib until the criteria for disease progression was first met. [d] 95% Confidence Interval was calculated using Clopper-Pearson method.
* Indicates SD lasting >16 weeks following initiation of selpercatinib until the criteria for disease progression was first met.
Abbreviations: CI: confidence interval; CR: complete response; IRC: Independent Review Committee; No.: number; PR: partial response; RET: rearranged during transfection; SD: stable disease; TC: thyroid cancer.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Duration of response

Table 11: Duration of response for *RET* fusion-positive TC in the LIBRETTO-001 trial by IRC assessment, 30th March 2020 data cut-off

	Previously treated N=22	Systemic therapy naïve N=[redacted]	Total N=[redacted]
Patients with Best Response of Confirmed CR or PR (n)[a]	[redacted]	[redacted]	[redacted]
Response status (n, %)[b]			
Disease progression	[redacted]	[redacted]	[redacted]
Died (No disease progression beforehand)	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Duration of response (months)[c,d]			
Median	18.43	[redacted]	[redacted]
95% CI	10.1, NE	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of duration of response[c,e]			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of response follow-up (months)[c]			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Observed duration of response (n, %)			
<6 months	[redacted]	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b] Status as of the patients last disease assessment on or before cut-off date. [c] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation. [d] 95% Confidence Interval was calculated using Brookmeyer and Crowley method. [e] 95% Confidence Interval was calculated using Greenwood's formula.
+ = censored observations
Abbreviations: CI: confidence interval; CR: complete response; NE: not estimable; PR: partial response; PD: disease progression; TC: thyroid cancer.
Source: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

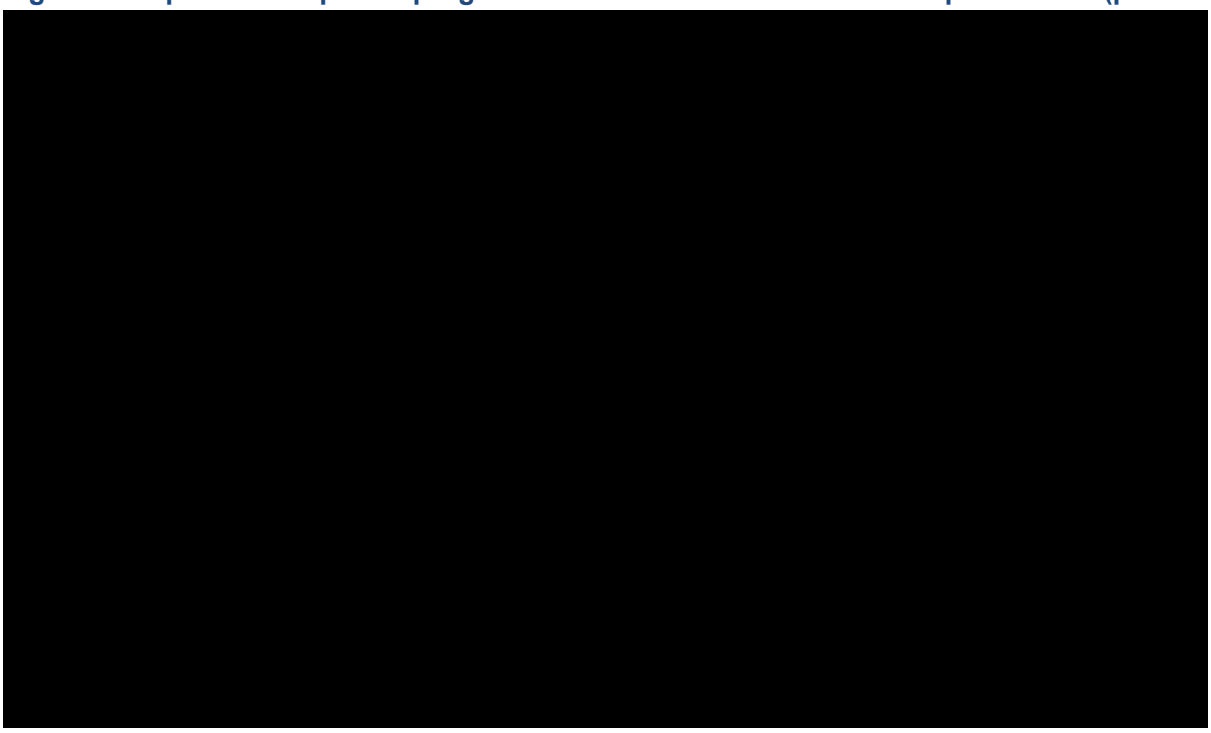
Progression-free survival

Table 12: Progression free survival for *RET* fusion-positive TC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020 30th March 2020 data cut-off

	Previously treated N=22	Systemic therapy naïve N=[redacted]	Total N=[redacted]
Status (n, %)[a]			
Disease Progression	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Duration of progression-free survival (months)[b]			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of progression-free survival[b,c]			
6 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
18 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
24 months or more	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]

[a] Based on IRC assessments using RECIST (version 1.1). [b] Estimate based on Kaplan-Meier method. [c] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
+ = censored observations
Abbreviations: CI: confidence interval; NE: not estimable; TC: thyroid cancer.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Figure 5: Kaplan–Meier plot of progression free survival in *RET* fusion-positive TC (pre-treated)



Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.

Overall Survival

Table 13: Overall survival for *RET* fusion-positive TC in the LIBRETTO-001 trial by IRC assessment, patients enrolled by 30th March 2020, 30th March 2020 data cut-off

	Previously treated N=22	Systemic therapy naïve N=	Total N=
Status (n, %)			
Disease Progression			
Censored			
Duration of overall survival (months)			
Median			
95% CI			
Minimum, maximum			
Rate (%) of overall survival			
6 months or more			
95% CI			
12 months or more			
95% CI			
18 months or more			
95% CI			
24 months or more			
95% CI			
Duration of follow-up (months)			
Median			
25th, 75th percentiles			

[a] Status as of the last contact on or before 30th March 2020 [b] Estimate based on Kaplan-Meier method. [c] 95% Confidence Interval was calculated using Brookmeyer and Crowley method.
+ = censored observations
Abbreviations: CI: confidence interval; NE: not estimable; TC: thyroid cancer.
Sources: Eli Lilly Data on File (30th March 2020 data cut-off)[5]

Figure 6: Kaplan–Meier plot of overall survival in *RET* fusion-positive TC (pre-treated)

Abbreviations: RET: rearranged during transfection; TC: thyroid cancer.

Appendix B: Revised company base case

Following feedback from the ERG, the Company has updated the economic model to produce a revised base case. This updated model is provided alongside this document. A summary of the updates made to the revised base case of the model, which are applied to all analyses, is presented in Table 14.

Table 14: Summary of changes in the revised base case

Model input /assumption	Company base case (following clarification)	Revised company base case	Section	New input data	ERG Report Issue
Comparators	Cabozantinib included	Cabozantinib excluded given changes to the licence for selpercatinib	NA	NA	Issue 1
OS extrapolation for *RET*-mutant MTC	Unstratified Weibull	Stratified Gamma	B.1	Figure 9	Issue 5
Time to treatment discontinuation	Assumed TTD was equivalent to PFS	TTD curves were based on PFS but shifted to account for the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial	B.2	Table 17	Issue 8
Selpercatinib acquisition costs	List price of a 60 capsule bottle of 80 mg or 40 mg: £[redacted]	Price (with proposed PAS discount applied) 60 capsule bottle of 80 mg: £[redacted] 60 capsule bottle and 40 mg: £[redacted]	B.3	Table 18	NA
Selpercatinib dose reductions	A proportion of patients assumed to receive 120 mg orally, twice daily, such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted]%)	Proportions of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the LIBRETTO-001 trial	B.3	Table 19, Table 20	NA
ECG costs	ECG costs applied to intervention and comparators in health state costs	One-off cost of 7 ECGs is included in the model for selpercatinib only	B.3, B.5	Selpercatinib SmPC[2]	NA
BSC costs and resource use	No additional costs included beyond health state costs for PF and PD	BSC resource use and costs updated and modelled to be the same in the PF and PD health states for *RET*-mutant MTC	B.4	Table 21, Table 22	NA
Diagnostic costs	The cost of *RET* testing not included	Cost specifically attributed to the *RET*-fusion or *RET*-mutant portion of a multi-gene testing NGS panel included in the model	B.6	NHS England, 2020	Issue 7

Abbreviations: BSC: best supportive care; ECG: electrocardiogram; ERG: evidence review group; MTC: medullary thyroid cancer; NA: not applicable; NGS: next generation sequencing; NHS: National Health Service; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PF: progression free; PFS: progression free survival; RET: rearranged during transfection; SmPC: Summary of Product Characteristics; TTD: time to discontinuation.

B.1 OS extrapolation for RET-mutant MTC

As noted in the ERG report, updated survival analyses for *RET*-mutant MTC were provided to the ERG as an addendum to the response to the clarification letter. These survival analyses were based on the updated MAIC analysis including the LIBRETTO-001 any-line population, adjusted for prior TKI use, which informs the revised Company base case (see response to Clarification Question A21). A range of parametric functions were fitted to the weighted OS curves for selpercatinib generated in the MAIC and the unweighted OS curve for the *RET* M918T-positive subgroup receiving placebo (n=45) in the EXAM trial. Table 16 summarises the AIC and BIC values for each survival model, and the long-term extrapolations of OS for selpercatinib and BSC are presented in Figure 7 and Figure 8, respectively. Extrapolations are not presented for cabozantinib since it is not a relevant comparator for this population (see Section 1.1).

The ERG considered that a predicted OS of 10% of patients still alive after 25 years was overly optimistic. The ERG also considered that too much emphasis was placed on the results of the statistical test for the PH assumption. As such, the Company have sought additional clinical validation of the presented survival curves, considering both PH and non-PH models.

Statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit and clinical plausibility. During the validation exercise with the clinical expert, the Stratified Weibull, Stratified Gamma and Stratified Log-logistic extrapolations were selected to potentially provide plausible projections based on their long-term survival estimates (Table 15).

Table 15: Long-term predicted survival estimates with the Stratified log-logistic, Stratified Gamm and Stratified Weibull

	Median PFS (months)	Median OS (months)	5-year	10-year	25-year
Stratified Log-logistic, mean LY = [redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma, mean LY = [redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull (ERG preferred), mean LY = [redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG: Evidence Review Group; LY: life year; OS: overall survival; PFS: progression-free survival.

The stratified Gamma was selected as it provided a good visual fit to the early Kaplan–Meier data as presented in Figure 9. Considering the population under assessment, the stratified Gamma was considered the most plausible extrapolation based on clinical expert feedback for the population informing the model, which included a mixed treatment population of pre-treated and patients naïve to systemic therapy, and a proportion of patients with non-progressive stable disease who are expected to have better survival outcomes. Therefore, a small proportion of patients with indolent disease are expected to live longer. With this model, only a very small proportion of patients remained alive in the long term ([redacted] and [redacted] at 25 years for patients treated with selpercatinib and BSC respectively). In the any-line population of the LIBRETTO-001 trial

(n=212), [redacted] had progressive disease at baseline and [redacted] had stable disease. Therefore, the stratified Weibull was not selected since it predicted a lower % survival in the long-term and [redacted] at 25-years. It should be noted that a log-logistic model was chosen and accepted as the base case curve for the placebo arm of the EXAM ITT population selected by the ERG in NICE TA516 based on the best fit statistics and clinical expert validation.[3] Other potentially plausible stratified curves were explored in scenario analyses as well as the best fitting curves determined by AIC/BIC scores.

Table 16: Summary of goodness-of-fit data for selpercatinib and BSC overall survival in *RET*-mutant MTC

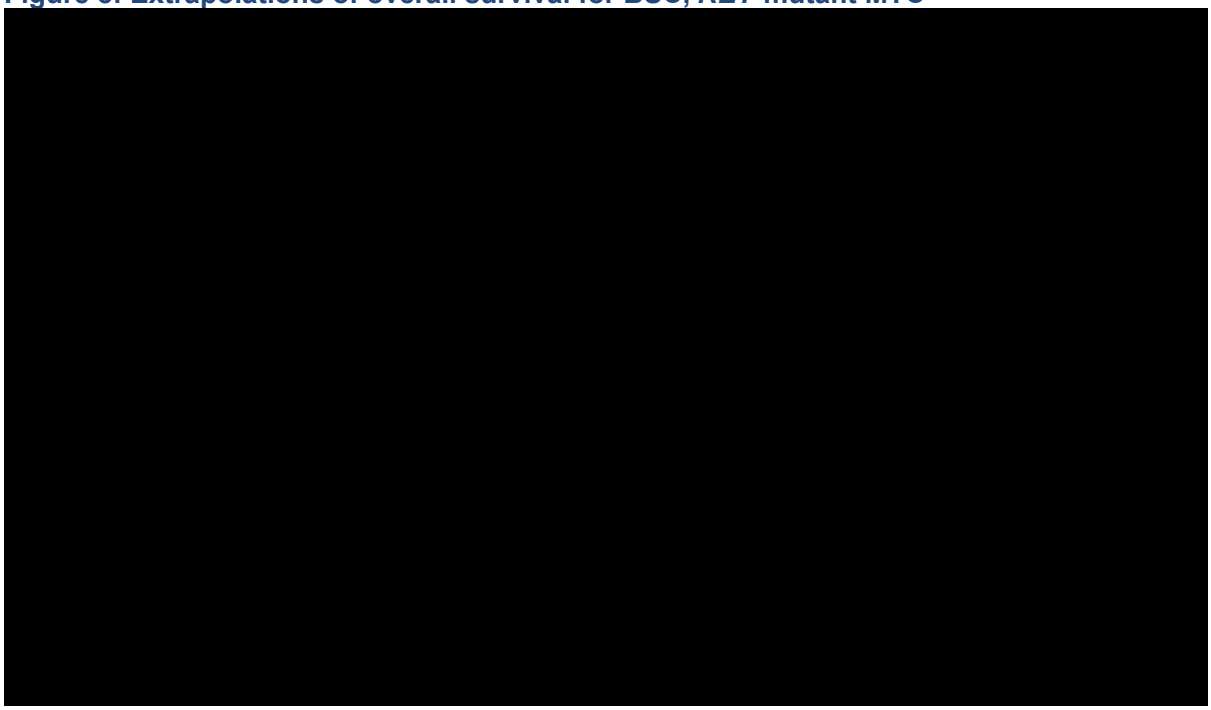
Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; MTC: medullary thyroid cancer.

Figure 7: Extrapolations of overall survival for selpercatinib, *RET*-mutant MTC

Abbreviations: KM: Kaplan–Meier; MTC: medullary thyroid cancer; RET: rearranged during transfection.

Figure 8: Extrapolations of overall survival for BSC, *RET*-mutant MTC



Abbreviations: BSC: best supportive care; KM: Kaplan–Meier, MTC: medullary thyroid cancer; RET: rearranged during transfection.

Figure 9: Stratified Gamma overall survival curves for *RET*-mutant MTC

Abbreviations: BSC: best supportive care; KM: Kaplan–Meier, MTC: medullary thyroid cancer; RET: rearranged during transfection.

B.2 Time to treatment discontinuation

As noted in Section 5.2.9.1 of the ERG report, patients with documented PD in the LIBRETTO-001 trial could continue selpercatinib beyond progression if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the Sponsor. Therefore, in line with the preferences of the ERG, in the revised Company base case, time on treatment curves were based on PFS, but were shifted by [redacted] for pre-treated *RET*-mutant MTC and by [redacted] for pre-treated *RET* fusion-positive TC, to account for the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial ([redacted] days for *RET*-mutant MTC patients and [redacted] days for *RET* fusion-positive TC patients; Table 17).

Table 17: Mean time (days) between meeting the PFS endpoint and treatment discontinuation for patients discontinuing treatment in LIBRETTO-001

	Pre-treated MTC (N=124)	Any-line MTC (N=[redacted])	Pre-treated TC (N=19)
Discontinued treatment during trial follow-up, n (%)	[redacted]	[redacted]	[redacted]
Time between PFS and treatment discontinuation			
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
95% CIs	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; PFS: progress-free survival; SD: standard deviation; TC: thyroid cancer; TKI: tyrosine kinase inhibitor.

B.3 Selpercatinib costs and resource use

Drug acquisition costs

As noted in Section 3, the list prices for selpercatinib formulations have been updated. In addition a PAS has been approved for selpercatinib, representing a simple discount of [redacted]% to the list price. Table 18 presents the drug acquisition costs for selpercatinib based on its current PAS price, licensed dose and modelled dose reductions.

To account for selpercatinib dose reductions (in line with dose reductions recommended in the selpercatinib SmPC),[2] a proportion of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the LIBRETTO-001 trial. Table 19 presents the weighted drug acquisition costs for selpercatinib for patients in the first cycle of treatment and Table 20 presents the weighted drug acquisition costs for selpercatinib for patients in the second cycle of treatment and beyond.

As described in Appendix B.2, time on treatment curves were based on PFS shifted to account for the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial. Time on BSC is continuous throughout the progression-free (PF) and PD health states until death.

For oral drugs, drug wastage is included and assumes 4-week prescriptions.

Drug administration and monitoring

Administration costs were based on National Health Service (NHS) National Cost Collection (2018/19).[14] For selpercatinib, 12 minutes of pharmacy time (£9.20) was assumed every 30 days. During treatment, patients were assumed to have one oncologist visit every 3 weeks.

In addition, due to QT prolongation reported in some patients receiving selpercatinib, the Summary of Product Characteristics recommends that the QT interval be monitored more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.[2] Accordingly, the cost of 7 ECGs (one at baseline and once a month thereafter for 6 months) is included in the model in the selpercatinib arm as a one-off cost. Consequently, ECGs are removed from the PF and PD resource use.

Table 18: Drug acquisition costs for selpercatinib at each dose level

Regimen description	Capsule strength (mg)	Capsules per pack	Pack cost (£)	Capsule cost (£)	Capsules per dose	Doses per week	Capsules per treatment cycle[a]	Costs per treatment cycle[a]
160 mg, orally, twice daily	80	60	[redacted]	[redacted]	2	14	112	[redacted]
120 mg, orally, twice daily	80	60	[redacted]	[redacted]	1	14	56	[redacted]
	40	60	[redacted]	[redacted]	1		56	
80mg, orally, twice daily	80	60	[redacted]	[redacted]	1	14	56	[redacted]
40mg, orally, twice daily	40	60	[redacted]	[redacted]	1	14	56	[redacted]

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.

Table 19: Weighted drug acquisition costs for selpercatinib in treatment cycle 1 (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, MTC	Proportion of patients on each dose, TC	Total cost per treatment cycle, MTC	Total cost per treatment cycle, TC
160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80 mg	[redacted]	[redacted]	[redacted]		

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.
Abbreviations: MTC: medullary thyroid cancer; TC: thyroid cancer.

Table 20: Weighted drug acquisition costs for selpercatinib in treatment cycles 2+ (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, MTC	Proportion of patients on each dose, TC	Total cost per treatment cycle, MTC	Total cost per treatment cycle, TC
160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 mg	[redacted]	[redacted]	[redacted]		
80 mg	[redacted]	[redacted]	[redacted]		
40 mg	[redacted]	[redacted]	[redacted]		

[a] A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.
Abbreviations: MTC: medullary thyroid cancer; TC: thyroid cancer.

B.4 BSC costs and resource use

In line with the preferences of the ERG (see Section 5.2.9.3 of the ERG report), BSC costs are modelled to be the same in the PF and PD health states, since the relevant population for this appraisal consists of patients who have progressed disease by definition.

RET-mutant MTC

For *RET*-mutant MTC, BSC was assumed to be consistent with the BSC resource use reported in the Assessment Group model in NICE TA516 (as shown in Table 21).[3] Clinical advice received by the Assessment Group suggested that the resource use associated with BSC is likely to be the same for both the PF and PD health states as these patients have, by definition, progressed disease. Clinical opinion suggested care has not changed since these rates were estimated for patients receiving BSC only. No additional health state costs were applied for BSC in the model.

Table 21: Annual MTC BSC resource use (across PF and PD health states)

Resource	Unit cost	Items per year
Consultant-led outpatient visits	£194.17	6 (2–12)
CT scan	£124.42	2 (0–4)
MRI scan	£145.75	1 (0–2)
Community palliative care support	£184.77	12 (0–20)
Palliative radiotherapy	£116.34	2 (fixed)
Bisphosphonates (for bone metastases)	£150.00	0.6 (fixed)[a]
Palliative surgery	£3,935.01	0.03 (fixed)

One clinical expert provided resource use estimates (central estimates, minimums and maximums); these were then verified and augmented with additional components by a second clinical expert. As the elicited information relates to ranges and some of the distributions are highly skewed, uncertainty surrounding these parameters was represented using triangular distributions. The experts' central estimates were taken to be the mode of the distribution; means were calculated as (lower limit+mode+upper limit)/3. The number of CT scans, and blood tests were not associated with uncertain ranges and were thus held as fixed values within the probabilistic analysis.
[a] Assumed to reflect monthly IV regimen for 5% of patients, also costed to include outpatient visit.
Abbreviations: CT: computerised tomography; ECG: electrocardiogram; MTC: medullary thyroid cancer.
Source: NHS National Cost Collection 2018/19,[14] NICE TA516 (Table 52)[3]

RET-fusion positive TC

In the *RET* fusion-positive TC patient population, BSC resource use was assumed to be consistent with the health state resource use for cabozantinib and vandetanib reported in the NICE TA516 Assessment Group model, which in turn were based on clinical expert opinion (as shown in Table 22Table 23).[3] The PD rates and costs were applied across the PF and PD heath states as by definition patients on BSC are in progressed disease. No additional health state costs were applied for BSC in the model.

Table 22: Annual TC BSC resource use (across PF and PD health states)

Resource	Unit cost	Items per year
Consultant-led outpatient visits (range)	£194.17	6 (4–12)
Nurse-led outpatient visits (range)	£147.38	6 (0–6)

Blood tests	£3.71	6
CT scan	£124.43	4

Abbreviations: BSC: best supportive care; CT: computerised tomography; MTC: medullary thyroid cancer; PF: progression-free; PD: progressed disease.
Source: NICE TA516 (Table 53)[3]

B.5 Health state costs

No additional health state costs were applied for BSC in the model beyond those described in Appendix B.4. For selpercatinib, the types of resource and frequency of use in the PF and PD health states in the MTC and TC analyses were based on the NICE TA516 Assessment Group model, which in turn were based on clinical expert opinion (as shown in Table 23). In contrast to the submitted model, no ECG costs were applied as part of the health state costs. ECG costs were applied as descripted in Appendix B.3.

Table 23: Unit costs and resource use per year in *RET*-mutation MTC and *RET*-fusion positive TC

Resource	Unit cost	PF	PD
Consultant-led outpatient visits (range)	£194.17	12 (4–16)	6 (4–12)
Nurse-led outpatient visits (range)	£147.38	4 (0–6)	6 (0–6)
Blood tests	£3.71	12	6
CT scan	£124.43	4	4

Abbreviations: CT: computerised tomography; MTC: medullary thyroid cancer; PF: progression-free; PD: progressed disease; RET: rearranged during transfection.
Source: NICE TA516[3]

B.6 Diagnostic costs

It is likely that NGS at genetic hubs will become the routine method for conducting molecular genetic testing in the NHS in England. The use of NGS to identify *RET* gene fusions is considered to be cost-effective, as it allows multiple genes to be tested for abnormalities in parallel. Since this approach will be routinely implemented across NHS England, the Company believes that the cost of screening a population of pre-treated TC patients for *RET* fusions, to identify which patients will receive selpercatinib, should theoretically not be included in the economic assessment.

However, as it is uncertain when NGS within these hubs will be fully operational an incremental cost specifically attributed to the *RET*-fusion or *RET*-mutant portion of a multi-gene testing NGS panel is applied in the model at a cost of [redacted] per test based on performing RET testing in a multi-gene NGS panel. This figure was provided by NHS England. The Company believes these costs represent a suitable proxy for testing for multiple genetic markers in England via the genetic hub structure. Diagnostic costs of [redacted] per advanced *RET*-mutant MTC patient, and [redacted] per advanced *RET* fusion-positive TC patient have been applied. These costs were calculated by dividing the unit cost per test of [redacted] (NHS England, 2020) by the positive test rate for each population: 61%[15, 16] and 14%[17] for *RET*-mutant MTC and *RET* fusion-positive TC patients, respectively.

Appendix C: Cost-effectiveness results

C.1 Revised company base case results

A summary of the results in the revised company base case analysis for *RET*-mutant MTC and *RET* fusion-positive TC is presented below.

RET-mutant MTC

The summary of the revised company base case cost-effectiveness results for the any-line *RET*-mutant MTC population adjusted for prior TKI use is presented in Table 24. The base-case pairwise cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental cost of [redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 24: Pairwise revised base case results for any-line *RET*-mutant MTC adjusted for prior TKI use, with PAS

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (QALYs) vs BSC
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTC: medullary thyroid cancer; OS: overall survival; PFS: progression free survival; QALYs: quality-adjusted life years; RET: rearranged during transfection.

RET fusion-positive TC

The summary of base-case cost-effectiveness results for the *RET* fusion-positive TC population can be found in Table 25. The base case incremental cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental cost of [redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained versus BSC.

Table 25: Base-case revised results for pre-treated *RET* fusion-positive TC, with PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; RET: rearranged during transfection; TC: thyroid cancer.

The deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) conducted to test the robustness of the model to the uncertainties within the model parameters are presented below.

C.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed in order to assess the uncertainty associated with model input parameters, as described in Section B.3.8.1 of the CS.

The probabilistic base case pairwise results versus BSC are presented in Table 26. Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves versus BSC are presented in Figure 10 and Figure 11, respectively.

Table 26: Probabilistic revised company base case pairwise results versus BSC – any-line *RET*-mutant MTC adjusted for prior TKI use

	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)[a]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; MTC: medullary thyroid cancer; QALYs: quality-adjusted life years; TKI: tyrosine kinase inhibitor.

Figure 10: Cost-effectiveness plane scatterplot versus BSC – any-line *RET*-mutant MTC adjusted for prior TKI use

Generated using 1,000 iterations of the PSA.
Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; RET: rearranged during transfection; TKI: tyrosine kinase inhibitor.

Figure 11: Cost-effectiveness acceptability curve versus BSC – any-line *RET*-mutant MTC adjusted for prior TKI use

Generated using 1,000 iterations of the PSA.
Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; RET: rearranged during transfection; TKI: tyrosine kinase inhibitor.

RET fusion-positive TC

The probabilistic base case results are presented in and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are presented in Figure 12 and Figure 13, respectively.

Table 27: Probabilistic base case results – *RET* fusion-positive TC

	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Figure 12: Cost-effectiveness plane scatterplot versus BSC – *RET* fusion-positive TC

Generated using 1,000 iterations of the PSA.
Abbreviations: BSC: best supportive care; RET: rearranged during transfection; TC: thyroid cancer.

Figure 13: Cost-effectiveness acceptability curve versus BSC – *RET* fusion-positive TC

Generated using 1,000 iterations of the PSA.
Abbreviations: BSC: best supportive care; RET: rearranged during transfection; TC: thyroid cancer.

C.3 Determinisitic sensitivity analyses

RET-mutant MTC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus BSC are presented in Figure 14.

Figure 14: Tornado plot (ICER) of selpercatinib versus BSC – any-line *RET*-mutant MTC adjusted for prior TKI use

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; MTC: medullary thyroid cancer; RET: rearranged during transfection, TKI: tyrosine kinase inhibitor.

RET fusion-positive TC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus BSC are presented as a tornado plot in Figure 15.

Figure 15: Tornado plot (ICER) of selpercatinib versus BSC – *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; RET: rearranged during transfection, TC: thyroid cancer.

C.4 Scenario analyses

A number of scenario analyses were explored in which model assumptions or parameters were altered. Recognising the complexity and inherent uncertainty in the survival analyses for *RET*-mutant MTC and the limitations of the data sources, a variety of extrapolation sets were explored. The results of the scenario analyses for *RET*-mutant MTC are presented in Table 28, and for *RET* fusion-positive TC in Table 29.

Table 28: Scenario analyses (pairwise) for the any-line *RET*-mutant MTC adjusted for prior TKI use (selpercatinib PAS price)

Scenario	Incremental costs (£)	Incremental QALYs	Pairwise ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
Discount rate 1.5% (benefits)	[redacted]	[redacted]	[redacted]
Discount rate 6%	[redacted]	[redacted]	[redacted]
Undiscounted health outcomes and costs	[redacted]	[redacted]	[redacted]
Utilities, progression-free values for sorafenib PF: 0.72 PD: 0.64	[redacted]	[redacted]	[redacted]
Utilities, SMC cabozantinib PF: 0.796 PD: 0.624	[redacted]	[redacted]	[redacted]
Disutility, SMC lenvatinib -0.042 (all treatments)	[redacted]	[redacted]	[redacted]
No diagnostic testing costs	[redacted]	[redacted]	[redacted]
TTD equal to PFS curve	[redacted]	[redacted]	[redacted]
Curve choice: OS – stratified Weibull	[redacted]	[redacted]	[redacted]
Curve choice: OS – stratified log-logistic	[redacted]	[redacted]	[redacted]
Curve choice: OS – Exponential	[redacted]	[redacted]	[redacted]
Curve choice: OS – log-logistic	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; PD: progressed disease; PF: progression free; SMC: Scottish Medicine Consortium.

Table 29: Scenario analyses for the *RET* fusion-positive TC pre-treated population (selpercatinib PAS price)

Scenario	Incremental costs (£)	Incremental QALYs	Pairwise ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
Discount rate 1.5% (benefits)	[redacted]	[redacted]	[redacted]
Discount rate 6%	[redacted]	[redacted]	[redacted]
Undiscounted health outcomes and costs	[redacted]	[redacted]	[redacted]
Utilities, progression-free values for sorafenib	[redacted]	[redacted]	[redacted]

PF: 0.72 PD: 0.64			
Utilities, SMC cabozantinib PF: 0.796 PD: 0.624	[redacted]	[redacted]	[redacted]
Disutility, SMC lenvatinib -0.042 (all treatments)	[redacted]	[redacted]	[redacted]
No diagnostic testing costs	[redacted]	[redacted]	[redacted]
TTD equal to PFS curve	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; PD: progressed disease; PF: progression free; SMC: Scottish Medicine Consortium.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 4 June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with advanced thyroid cancer with RET alterations and current treatment options	
About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	x a patient with advanced thyroid cancer with RET alterations ? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with advanced thyroid cancer with RET alterations ? ☐ a patient organisation employee or volunteer? x other (please specify): A patient with experience of an alternative RET inhibitor (Pralsetinib/ BLU-667).
3. Name of your nominating organisation.	AMEND
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) x Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement x I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	**x** I am drawing from personal experience. **x** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: also drawing on others experiences who are on Selpercatinib/Pralsetinib. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference x I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with advanced thyroid cancer with RET alterations ? If you are a carer (for someone with this condition) please share your experience of caring for them.	I was diagnosed with Metastatic MTC in 2015 at the age of 26. My only presenting symptom at the time was a slight swelling in the front of my neck which persisted for a number of months. My initial surgery (within 6 weeks of diagnosis) was a total thyroidectomy with radical neck dissection. A year later I had to have a further neck dissection and a left Thoracotomy due to increasing tumor burden. It is my understanding that the location of tumors in my chest/mediastinum was of particular concern due to their proximity to major arteries and the entryways to my lungs. After this second surgery it was 'watch and wait', all the while I was still asymptomatic and maintained an extremely good quality of life. We then began to see progression in my blood markers and then in tumors in my liver - An increase in size of an existing tumor, and some new areas of concern. It was at this point my oncologist first spoke with me about the available systemic treatments (TKI's Cabozantinib /Vandetinib) as the surgeon in my MDT meetings had deemed surgical removal/embolization not viable. Having learned of and researched the significant toxicity and resulting side effects of the TKI's , and the inevitable impact this would have on my (currently good) physical health/QOL, I made the decision to decline systemic therapy with either of these drugs at that time. My rationale for this was that owing to my (currently incurable) MTC, it is extremely likely that there is going to be a significant period of my life in which I am suffering, and my QOL is extremely poor. I will not be able to control this, and when it comes to this time it's unlikely that my consultants will be

	able to do much beyond try to make me more comfortable. Since diagnosis, I have tried my best to accept the card that fate has dealt me with strength and grace, however as a young and otherwise healthy person, I was in no rush to fast-track the (seemingly inevitable) decline in my overall health/quality of life. It was at this point a potential alternative treatment (PRRT with Lutathera) was mentioned to me. Side effects for this seemed more tolerable/ shorter lived, and there was a good chance it would have some efficacy for my MTC despite initially being developed for neuroendocrine tumors of the gut. Funding for this was not consistently/routinely available at the time, and so I had to travel quite far in order to receive this treatment. This meant multiple visits to a strange city on my own, which caused me a lot of anxiety at the time. Still this was a better option than the available TKI's. Its my understanding that I would/should have been able to receive the treatment closer to home, had it not been removed from the cancer drugs fund not long prior. I was very fortunate to be able to access this treatment, which kept me stable with no evidence of progressive disease in imaging for over 18months. – It was a very welcome break from having had something new pop up on every scan up to that point. Even when progression did start, it was at a much slower pace than it had been prior to the treatment. It was at this time we began to see progression in my symptoms (flushing, diarrhea) and my liver (growth of existing tumor, and new multi focal lesions). Again my oncologist discussed with me the likely inevitability of me needing a systemic therapy within the next 6-12 months. Again the TKI (now only Cabo) was discussed, and again I politely declined this option for the same reasons as before. It was at this point that the trial for Blu-667 RET Inhibitor was discussed with me. (The only Loxo trial available at the time was at the other end of the country at the Royal Marsden, so not a really viable option for me due to the frequency of visits required during the trial.) I already had some awareness of the phase 1 trials and the drugs apparent efficacy, and the study was now in expanded access and there was an available slot on the trial at the Christie Hospital. My options at this point, as I was so keen to avoid Cabozantinib, were to have another round of PRRT (which is often just as effective second time round) or to join the Arrow trial for the RET Inhibitor drug Blu-667/Pralsetinib at the Christie. My decision to join the clinical trial of Pralsetinib, as I was aware of how much more tolerable, and potentially efficous these drugs are than exsisting treatment with Cabo/PRRT, and it was now or never in terms of securing myself long term access to them. I was acutely aware that they may never be recommended by NICE for use on the NHS due to the costs involved, and wanted to ensure that I could still access them. This was probably the main driving force behind my decision to join a clinical trial at this time – most patients would not consider a trial unless it was a last resort due to the unknown risks involved.

	The risk/reward of securing access made the decision easier to make, but I still felt a little shoehorned into the decision timing wise, as I could (and would) likely have waited another 6-12 months before really needing any further systemic therapy, however there were only two slots available on the trial, and once they had been filled, its unlikely id have been able to get access to these drugs atall when the time came for me to need them. I decided to jump the gun a little and start long-term systemic therapy much sooner than I had wanted to, or sooner perhaps than was medically necessary, in order to secure myself access to drugs that were going to help maintain (if not improve) my QOL, rather than have to endure treatments that would impact it more negatively. I should not have felt I had to do this, and would like to have had more confidence that these treatments would be available to me on the NHS further down the line when I needed them. Instead, I had to take a 'now or never' approach and join a phase 1 clinical trial, which is less than ideal and caused me significant anxiety at the time. I have been taking pralsetinib now for around 25 months. For the first 18+ months of treatment I was being kept stable, but was sticking at aroung 6% reduction in tumor burden overall. Then suddenly, across my last 3 scans, I have seen that reduction % jump to a total of 50%, and still appears to be on a downward trend. This is amazing and I am sure it is going to significantly contribute to my overall survival in a very tangible way. Its confirmed for me that I made the right decision in deciding to take the risk and join the trial, as I am clearly now beginning to reap the benefits of this therapy. For now I can only hope that this trend continues. I cannot stress enough how poorly my mental health has suffered since my diagnosis. I have suffered with severe anxiety and depression, and have sought therapy for this. It helps a little, but there's very little that can be said or done to stop you having to face your own mortality, and the immense suffering that so often accompanies this. When I was diagnosed I was told there were very few treatments options available to me, that the only drugs that could help to slow progression were likely to significantly impact my quality of life and overall day-to day physical health, if I was even able to tolerate them atall. This was heartbreaking and terrifying, especially at the age of 26. I thought I had all the time in the world to live my life, but it was clear my time was now finite, although the extent to which remained to be seen. I was, and am to this day, keen to maintain as high QOL as I possibly can for as long as possible. This is due to the high probabability of me having to suffer greatly due to my cancer further down the line, with little that can be done about that when the time comes.

	My experience with RET altered MTC has both emotionally and physically draining. Being on a RET inhibitor has given me a new lease of life, and the efficacy I am seeing has given me a glimmer hope for the future, where previously there was none. This is absolutely invaluable in terms of the impact on my day to day QOL, particularly my mental helath/ anxieties over my future. I feel very fortunate to be receiving this treatment, and I worry greatly about what happens to all the other patients who would benefit, but are unable to access a trial. I also worry about what happens if for any reason the manufacturer decide not to continue to provide me with the drug through the trail, as there are no guarantees I will have access on the NHS in the future.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for advanced thyroid cancer with RET alterations on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There is only one currently available treatment for MTC on NHS– Cabozantinib. Deciding wether to take this drug theresfore feels like a Hobsons choice. Unfortunately for most patients with MTC, declining a TKI will mean disease progression and all that comes with it (inevitable death) Its not the BEST routinely available option, it is simply the ONLY one. Humanistically speaking, this is a horrendous situation to be in. You are sacrificing quality of life for a relatively low increase in length of life, and deciding when to do that is a tough and daunting decision. Its my understanding that the other treatment that was available (Vandetinib) is no longer funded, and that PRRT with Lutathera is not routinely funded for patients with MTC, despite its efficacy in many cases (mine included) and limited side effects. I was very lucky to get this treatment, and I think other people with MTC should have the same option made available to them. There appears to be a distinct lack of treatment options for MTC, with the only one that is routinely offered on the NHS being the most toxic. I don't think this is acceptable given that there are known alternatives (PRRT, RET inhibitors). Treatments for MTC are always going to be few as it is so rare, and so I feel any and all available options should be embraced, as they are unlikely to come around very often. I am aware that that many, many patients with MTC are just as reluctant and anxious as I was/am at the prospect of the existing TKIs,for the same reasons, and prefer to take them only as a last resort and only when absolutely medically necessary. Many people stop them due to adverse effects or disease progression.
8. If there are disadvantages for patients of **current NHS treatments** for advanced thyroid cancer with RET alterations (for example how the treatment is	Cabozantinib is significantly toxic, and has many high-grade side effects for many patients. It notably (and quite often negatively) impacts on peoples quality of life (debilitationg and life-limiting side effects), for seemingly little reward. (median PFS and OS figures leave a lot to be desired). Having spoken to many people on both the Arrow and Libretto trials respectively, in addition to my own experience, it is evident that many people would like to see Selpercatinib/ RET Inhibitors

given or taken, side effects of treatment etc) please describe these	offered as a first line therapy for MTC, so that they can avoid what now feels like an unnecessary decline in QOL caused by Cabozantinib.
Advantages of this treatment	
9a. If there are advantages of selpercatinib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does selpercatinib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	I have been able to continue to work, and to improve & maintain an extremely good QOL on Pralsetinib (alternative RET Inhibitor currently in clinical trials). I'd previously had extreme fatigue caused by poor sleep due to excessive night sweats/flushing & increasingly chronic diarrhoea. These symptoms both disappeared almost immediately upon starting the drug. I was not missing work often anymore, and was able to socialise more freely. High selectivity means the drug is much kinder than existing TKI's and side effects are significantly less debilitating for most patients. I also suffered greatly with anxiety and depression over my future,which I saw little positivity in. This is improving more and more as I see the drug working so effectively for me, and for others. . The significant decreases in tumor burden seen by many patients on RET Inhibtor drugs also gives patients with MTC hope, where previously none existed. – I personally have seen a 50% reduction in tumor burden up to now – For a drug that is Palliative and only aiming to slow progression/ provide stability, that is a fantastic and unexpected result. It is almost impossible to articulate how crucial having a glimmer of hope like this can be for patients in a situation as dire as mine. I now feel like I can (to some extent) plan for my future, as I believe I'll be around longer than anyone had anticipated due to this therapy. The improved QOL is by far the most important advantage RET inhibitors for many patients on RET inhibitors, myself included. This is inclusive of noticable improvements to both physical and mental health. Selpercatinib seems to overcome the issues relating to debilitating, life-limiting side effects caused by the toxicity of Cabozantinib.
Disadvantages of this treatment	
10. If there are disadvantages of selpercatinib over current treatments on the NHS please describe	There are of course side effects with Selpercatinib,as with all drugs. I did have some concerns over these as I was unsure how my body would react. I do not feel it has any disadvantages over Cabozantinib, if anything quite the opposite. I feel the potential benefits of RET Inhibitor drugs

these? For example, are there any risks with selpercatinib ? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	outweigh the risks/possible adverse effects. I do not feel this way about Cabozantinib.
Patient population	
11. Are there any groups of patients who might benefit more from selpercatinib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I believe those with mutation M918T, which is known to be more aggressive, could possibly benefit more from RET Inhibitors due to the speed at which these patients' disease burden often progress' in comparison to others with MTC who's tumors are often very slow growing. There are also many RET-positive patients who are unable to tolerate Cabozantinib, who would benefit from access to this drug as a second line treatment if not made available as first line treatment option.
Equality	
12. Are there any potential equality issues that should be taken into account when considering advanced thyroid cancer with RET alterations and treatment? Please explain if you think any groups of people with	I think individuals below a certain socio-economic bracket or those without private health insurance are at a disadvantage, as they are likely unable to obtain this treatment by any other means if it is not routinely offered on the NHS. More affluent patients may not have this same issue and may find the drug more accessible. I also feel that anyone with advanced MTC (as a shared characteristic) is automatically disadvantaged in terms of treatment, as it is such a rare disease. I think it's vital that we/ health organisations embrace innovative treatments for rare cancers, as they so often go overlooked and

this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	new treatments don't come around very often. If we do not embrace them – where is the incentive for pharmaceutical companies to keep developing them? And then what does the future look like for people like me?
Other issues	
13. Are there any other issues that you would like the committee to consider?	I think its important that rare cancers are categorised and decided on slightly differently to more common ones, especially in terms of deciding on what consititutes efficacy/ cost effectiveness. There is not, and likely will never be as many available treatment options for patients with MTC as there will be for example a breast or lung cancer patient, who would have more treatment options available to them due to the large amounts of money constantly being invested in trying to find

	newer,better treatments for these cancers. I understand that NICE recommendations work to a set amount of money per year of life gained, and that there has to be some limit on this. However I also think my life is just as important as anyone elses, and that I shouldn't suffer a detriment in terms of treatment availability due to the rarity of my disease. If NICE are able to recommend treatments costing upto £50,000 that may be used on tens of thousands of people per year, they can perhaps justify recommending spending more than that on the comparatively minute number of patients with MTC who require systemic therapy? There surely has to be an understanding that these drugs will inevitably cost more, as they will never make as much money due to small patient numbers. If NICEand the NHS lobby big pharma for innovative drugs then do not embrace them when they become available, there is little incentive for them to continue to be developed. That is a very bleak prospect for those such as myself with rare cancers. As a step-change treatment, this is the direction in which many cancer treatments now seem to be heading (highly selective). We must embrace these newer, kinder therapies and offer them where possible. We cannot continue to push for new, innovative treatments for rare diseases that we have no intention of ever providing to patients. As a patient it is horrendous and heartbreaking to hear there are treatments available that could help, but that they are just not available to you due to their cost. At this point many patients suffer the indignity of having to try and crowd-fund for treatments, as they are desperate to stay alive. This is something I know myself and other patients worry a lot about, and would rather never have to deal with.

PART 2 – Technical engagement questions for patient experts

Issues arising from technical engagement

We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of advanced thyroid cancer with RET alterations ? 14c. What are the main benefits of selpercatinib for patients? If there are several benefits please list them in order of importance. Are there any benefits of selpercatinib	14a: Yes – it is my understanding that both Cabozantinib and BSC are used. 14b: In my instance,I believe the assessment tool was appropriate as I was deemed eligible for the trial due to tumor burden above a certain level. MTC is complicated and manifests/reacts differently in all patients, so I would imagine any assessment tools would have to account for this. Some patients are very symptomatic with little evidence of disease on imaging, and others have huge disease burden but maintain a high QOL and few symptoms, so I believe it would need to be looked at on a case by case basis with regards to MTC. 14c: The main benefits to patients are as follows: - Less toxicity than exsisting treatment (Cabozantininb), meaning fewer/ less severe side effects and improved physical health. - Selpercatinib offers patients who previously had no options/hope, the potential for a partial or even a complete response. - The psychological burden of being diagnosed with an incurable cancer is monumental. The fact that this gives many patients hope for their future where previously they had none, and the impact of this on the mental health of patients should not go unrecognised and is far more significant than is accounted for by health professionals much of the time. - Gives patients a sense of control over their situation, and to feel like perhaps they actually have a fighting chance. It allows them to breath after years of feeling stifled by their prognosis, leading to an imporved QOL for many patients, myself included.

that have not been captured? d. What are the benefits of selpercatinib for carers?	
15. Are there any important issues that have been missed in ERG report?	I have not yet had chance to read the full report, due to time constrains in having to return this form.(Uncertain)

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- RET inhibitors offer significantly enhanced QOL in comparison to Cabozantinib, due to decreased toxicity and increased efficacy in many patients. (consistent reductions in tumor burden, significantly less/ lower grade adverse effects, longer median PFS.)
- The psychological burden of MTC diagnosis on the individual is not to be underestimated, & neither is the positive impact of seeing rapid & consistent reductions in tumor markers and tumor size following RET Inhibitors, where previously there was only progressive disease. This drug offers patients hope (in addition to clinical efficancy) and that is priceless.
- I Started RET Inhibitor therapy via a clinical trial earlier than was medically necessary, to secure my access to the drug. My decision was driven by me having little to no confidence that NICE will ever recommend the drugs for use on NHS if that decision was to be based soley on cost, rather than taking a more humanistic approach to the assessment.
- Innovative treatments for MTC are not commonplace, as it is so rare. They are therefore likely to cost more than drugs for more common cancers, but must still be embraced if pharma companies are to continue to be incentivised to develop them. Decision making should account for this & different cost effectiveness criteria used for treatments required by a only a small handful of patients with a rare disease, who have limtited treatments options currently available to them.
- We have one of the best social healthcare systems in the world, and we should not have patients having to suffer the indignity of crowdfunding for drugs that could be made available to them via the NHS. This seems to be happening more and more, and its important we don't fall behind the rest of the world in terms of treatment options. Geography should not be the deciding factor in whether people get to stay alive.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 4 June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with advanced thyroid cancer with RET alterations and current treatment options	
About you	
1.Your name	**Kirstie Purnell**
2. Are you (please tick all that apply):	☐ a patient with advanced thyroid cancer with RET alterations ? ☐ a patient with experience of the treatment being evaluated? ☑ a carer of a patient with advanced thyroid cancer with RET alterations ? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	AMEND
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☑ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☑ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: **My two children are taking selpercatinib, granted for compassionate use, for advanced RET mutation-positive MTC** ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☑ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with advanced thyroid cancer with RET alterations ? If you are a carer (for someone with this condition) please share your experience of caring for them.	Devastating. The problem with RET mutation-positive MTC is that it doesn't affect one person. I do not wish to sound dramatic but am trying to be honest. My daughter was diagnosed with advanced metastatic disease at the age of 6, a few days before her 7th birthday, in 2018. We were advised that surgical intervention was the only viable treatment at that time to remove as much of the cancer as possible. A few days prior to her surgery we were advised that surgery alone would not cure her and that there were no clear second line treatment options. She had multiple complications from her surgery due to the extent of her disease and other structures in her neck that were affected, some of which had to be removed resulting in loss of function in an attempt to preserve life. In summary, her speech and swallow were affected and she had a new Horner's Syndrome (which is ptosis of her eyelid with a persistently constricted pupil, absence of sweating on that side of the face, and sinking of the eyeball into the eye socket). Following a 10 day stay in hospital, she was discharged with a very weak voice, swallowing issues which necessitated her to have thickened fluids and specific diet,

	and a very different appearance. Being a child, over time she has miraculously managed to strengthen her voice and learn how to swallow again but her Horner's Syndrome will never resolve. She was what we could call the 'index case'. She inherited her mutation from me, it transpired, so we then had to start testing other family members, including our son (we only have the two children). Unfortunately, our son also inherited the mutation and so he was investigated and had a thyroidectomy performed a few months later (aged 5 at the time). This was meant to be prophylactic as his scans did not demonstrate disease, however at surgery it was noted that he had some abnormal looking lymph nodes and histology confirmed he also had metastatic MTC. His surgery was far less complicated but he was traumatised psychologically by the entire situation, as of course were we. My daughter showed signs of progressive disease and so we consulted with Oncologists who suggested that given that her quality of life was relatively good (she was attending school and doing activities as relatively normal) that they would not advise any alternative treatment at this stage, as it would essentially be palliative and there were no specific symptoms to palliate (other than mild fatigue, episodic diarrhoea and reduced exercise tolerance compared to her peers). We were briefed on external beam radiotherapy, but due to her young age advised against it due to the high risk of complications, such as tracheal scarring and stenosis (seen in another case) resulting in the need for a permanent tracheostomy. This particular thyroid cancer does not respond to radio-active iodine treatment, as you will be aware. The only NICE-recommended systemic agent available was cabozatinib but this was not licensed for children and, as it was not a specific TKI, the side effect profile was likely to be quite negative and would affect her quality of life, the duration of which may not be very long. Also the research suggested that her specific mutation was apparently not very responsive to cabozatinib anyway (Val804Met – gatekeeper mutation). We were aware that vandetanib had not been approved for use by NICE but knew little more about it.

	In the end, she had a second, difficult surgery at the end of 2019 (resulting in a 6-day hospital stay with a need for NG feeding), but very quickly it became evident that this had not been very successful and her disease continued to progress. At this time, her brother's disease also started to progress. As you will be aware, as both children are under 12, the only treatments at this point would have been palliative: external beam radiotherapy (and the negative consequences and variable results that could offer), repeated surgeries (risking further post-surgical complications), possibly cabozatinib/vandetanib on an individual funding basis (and with concerns about efficacy vs adverse effects), or supportive care. They were granted selpercatinib for use on compassionate grounds just at the beginning of the Covid pandemic, around March 2020 for my daughter and May 2020 for my son. At this point, we weren't even sure that my daughter would survive to see another Christmas and there was no indication as to what the future might hold for our son. I asked each of my children for a statement about selpercatinib. My daughter said "Selpercatinib has changed my life", my son said "The medicine is easy to take".
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for advanced thyroid cancer with RET alterations on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	From what I have learned from specialists and doing my own reading, it would appear that the majority of currently available options have quite a dramatic side effect profile, with clear consequences for quality of life. Radiotherapy obviously has to take place in a hospital, necessitating multiple visits and is considered palliative in the main. The currently available TKIs require regular monitoring and management of side effects (related to their lack of specificity) and tend not to be an efficient long term option.

	We do not have personal experience of these other treatments but I have spoken to other parents of children who have tried them, hence my above summary.
8. If there are disadvantages for patients of **current NHS treatments** for advanced thyroid cancer with RET alterations (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Please see above, but note we do not have personal experience of these. The clear disadvantage for children is that there are no NICE-approved treatments for advanced MTC.
Advantages of this treatment	
9a. If there are advantages of selpercatinib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does selpercatinib help to overcome/address any of the listed disadvantages of current treatment that	Selpercatinib is easy to take as it is an oral formulation (can be taken as liquid or capsules). It is taken twice a day and so does not interfere with daily routines. My children have continued life completely as usual and attend school, extra-curricular activities and are growing and developing as one would expect. To all intents and purposes, they are 'normal' children. Initial monitoring for them was understandably very cautious, but as time passes without side effects or complications occurring, we are managing to reduce the frequency of blood tests and other monitoring (which includes ECGs, chest x-rays, monitoring ultrasound scans – for disease stability). Selpercatinib is working well at suppressing their tumours and therefore any disease-related effects. As well as monitoring tumour burden via ultrasound scan, blood tests measuring CEA and calcitonin are done – these will detect microscopic changes that may not be seen on scans. To give you an idea of scale, my daughter's calcitonin started at around 36,000 (normal is <10) and dropped to around 3300 within a week; it is now around 70. Her CEA has gone from 250 to around 14. My son's calcitonin came down from approximately 180 to around 3 i.e.

you have described in question 8? If so, please describe these.	normal range. His CEA was never raised. For the children, the greatest advantage to them has been their ability to seem just like their peers. We often liken it to children who have other long term conditions which require them to take daily medication, such as epilepsy or diabetes. Selpercatinib is easy to take and has had no quality of life affecting side effects so far, which is a massive advantage (and probable cost efficiency benefit). Also of interest, my children still remain on a relatively low dose, so there is clearly room to titrate up if required, as they grow or if there are signs of any progression.
Disadvantages of this treatment	
10. If there are disadvantages of selpercatinib over current treatments on the NHS please describe these? For example, are there any risks with selpercatinib ? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Genuinely, I am not aware of any disadvantages over current treatments. I am aware that some people have had side effects but do not know a great deal about them and believe it has been in adults, rather than children.
Patient population	
11. Are there any groups of patients who might benefit more from selpercatinib or any who may benefit less? If so, please describe them and explain why.	Being an oral formulation makes it very accessible for almost all patient groups, even if PEG-fed or via NG tube. As it only needs to be taken twice a day, this will be easier for patients who need support taking their medication and also for working people who may be out of the house most of the day. Also, if people have to travel, the medication can still be administered.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I am not aware as to whether there is a parenteral (non-oral) formulation or not but the company should be able to clarify this. I am aware that this medication can affect the liver and am not sure therefore whether patients with liver disease can safely take selpercatinib or not.
Equality	
12. Are there any potential equality issues that should be taken into account when considering advanced thyroid cancer with RET alterations and treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	I cannot see any issues with equality here, even with age (considering that at the time she started it, my daughter was the youngest patient in the UK to be taking it).

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Yes – I used the term devastation above – a bit like a wild fire. There are 12 members of my family who have been found to have the gene mutation. 4 others had MTC on histology and 1 of those is still being monitored as surgery did not clear her disease. 1 of the 4 was also under 18 when diagnosed. 6 of us managed to have prophylactic surgery but 4 of those cases already had pre-cancerous changes (the youngest affected being just 1 year of age).

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of advanced thyroid cancer with RET alterations ? 14c. What are the main benefits of selpercatinib for patients? If there are several benefits please list them in order of importance. Are there	I believe cabozatinib is used in the NHS for treating MTC in adults. There is no currently NICE-recommended systemic treatment for people under the age of 18 with advanced RET-altered thyroid cancer. Palliative options include repeated surgery, external beam radiotherapy and supportive care. I am not fully familiar with the assessment tool used in the clinical trial for assessing severity. The main benefits of selpercatinib include: Disease control efficacy – suppressing the tumour has led to less GI effects (such as diarrhoea), increased energy levels and improved exercise tolerance; Lack of side effects (reportedly seen in other TKIs) and therefore maintained QOL; Ease of administration; Straight-forward monitoring and reduced hospital attendance as a result. On a personal note, I feel that selpercatinib could prevent the need for life-altering surgery in the future. If selpercatinib had been available at the time of diagnosis, my daughter could have had limited surgery to debulk the tumour rather than the extensive surgery which resulted in her post-operative complications, one of which has affected her appearance permanently, her self-confidence and is a daily reminder of

any benefits of selpercatinib that have not been captured? d. What are the benefits of selpercatinib for carers?	everything she has been through. Currently, we are managing to live a relatively normal family life on a day-to-day basis, which was unimaginable a couple of years ago. We still have two children.
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Selpercatinib is proving to be a safe and effective systemic treatment option for my children who have RET mutation positive advanced medullary thyroid cancer.
- Selpercatinib has radically improved our quality of life, both directly for the children and indirectly for us as parents.
- Selpercatinib is easy to administer as it is taken orally, as a capsule or liquid.
- Once stable, monitoring toxicity is straight-forward and tests could even be carried out in primary care (blood tests, ECGs) resulting in less frequent trips to hospital.
- Selpercatinib could reduce the need for life-altering and repeated surgeries.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Selpercatinib for treating advanced thyroid cancer with RET alterations [ID3744]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 3 June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with advanced thyroid cancer with RET alterations and current treatment options	
About you	
1. Your name	**Kate Garcez**
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	**Clinical Oncology Consultant**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with advanced thyroid cancer with RET alterations ? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	x☐ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have no disclosures**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in advanced thyroid cancer with RET alterations ?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or	

monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in	

the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when	

considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Appropriateness of cabozantinib as a comparator	In my opinion this is appropriate; as it is the only other established treatment for advanced RET mutant medullary thyroid cancer currently available in England.
Immaturity of effectiveness data	Ongoing follow up will clearly help to inform longer term outcomes, but the currently available data regarding response rates, disease and symptom control with selpercatinib are impressive and suggest that selpercatinib is an effective treatment.
Reliability of the matching-adjusted indirect comparison (MAIC) for the rearranged during transfection (RET)-mutant medullary thyroid	In my opinion, despite the inherent uncertainties, this seems a reasonable way to compare selpercatinib with cabozantinib and placebo, given there has not yet been a head to head comparison. The patient populations used for the MAIC (the RET mutant subgroup of the EXAM trial which included treatment naïve and pre-treated patients, and the any-line pooled population from the LIBRETT0-001 trial) should be similar. The currently recruiting LIBRETTO-531 trial should provide more data on this question.

cancer (MTC) population	
Reliability of the naïve indirect comparison for the RET fusion-positive thyroid cancer (TC) population	Again, in the absence of a head to head comparison it seems reasonable in my opinion to compare selpercatinib with the placebo groups of the SELECT and DECISION trials. Clearly the populations will not be homogenous as the RET status of patients was not reported in the SELECT and DECISION trials, but the PFS of around 3-4 months for patients on placebo is consistent with that seen in clinical practise in this group of patients.
Extrapolations of survival data	The aim of treatment for radioiodine refractory differentiated thyroid cancer (DTC) and advanced medullary thyroid cancer (MTC) is to delay progression, improve symptoms, reduce the risk of disease related morbidity as well as extending overall survival. An improvement in overall survival is an important measure and data on this should become available with longer term follow up, but it should be remembered that there are many other very meaningful benefits demonstrated in the available data that selpercatinib offers over existing treatments.
Source of health state utility values	
In- or exclusion of genetic testing costs	Facilities are available to perform molecular testing for RET fusions (DTC) and RET mutations (MTC) in England via the Genomics England Test Directory, and in Wales via the All Wales Medical Genetic Service. It is advised that these tests are undertaken at the point at which the patient is diagnosed with advanced disease, so this is increasingly part of routine clinical practise and would not be an additional cost.
Time on treatment	In clinical practise, patients receiving systemic therapy are carefully monitored for ongoing benefit, both in terms of control of symptoms, and radiological/biochemical disease control. In some instances, if the patient is tolerating the treatment and experiencing ongoing clinical benefit in terms of improved quality of

	life and symptom control, it may be appropriate to continue systemic therapy even if there is some radiological/biochemical evidence of disease progression.
Are there any important issues that have been missed in ERG report?	No additional comments

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Acknowledging that there have been no head to head trials comparing selpercatinib with currently available options for patients with radioiodine refractory differentiated thyroid cancer (DTC) or advanced medullary thyroid cancer (MTC) with RET alterations/mutations, the data presented on selpercatinib looks very promising in terms of producing clinically meaningful benefit with less toxicity than other less targeted treatment.
- As treatment with selpercatinib appears to be an effective treatment with reduced toxicity this may reduce the burden on other healthcare services in terms of the need to treat either symptoms of disease or management of toxicity.
- It is important that clinicians are aware of access to molecular testing for RET fusions and RET mutations, in order to identify patients who may be suitable for treatment with selpercatinib

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for advanced thyroid cancer with RET alterations

ADDENDUM: Critique of the company's additional evidence

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK Pim Wetzelaer, Health Economics Researcher, Erasmus School of Health Policy & Management (ESHPM), EUR, the Netherlands Hannah Penton, Health Economist, ESHPM, EUR Annette Chalker, Systematic Reviewer, KSR Ltd Edyta Ryczek, Systematic Reviewer, KSR Ltd Nigel Armstrong, Health Economist, KSR Ltd Steve Ryder, Health Economist, KSR Ltd Mohammed Islam, Health Economist, KSR Ltd Gill Worthy, Statistician, KSR Ltd Steven Duffy, Information Specialist, KSR Ltd Maiwenn Al, Health Economics Researcher, ESHPM, EUR Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University
Correspondence to	Rob Riemsma, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	03/06/2021

1. Company's additional evidence

The purpose of this addendum is to provide a critique of the new evidence submitted by the company prior to the first appraisal committee meeting.[1]

In their latest submission, dated 17th of May 2021, the company submitted responses to the key issues raised in the ERG Report, and some additional evidence relevant to these issues.[1] The company has also updated the list price and offered a new patient access scheme (PAS) price to NHS England which have been used to update the cost effectiveness model results.

1.1 Issue 1: Appropriateness of cabozantinib as a comparator

The company argues that cabozantinib cannot be a comparator because patients who have failed on it would not receive it again and vandetanib is not *"…recommended in England for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC."*

ERG comment: Although vandetanib was not recommended in TA550, it is not inconceivable that some patients were prescribed it and thus cabozantinib might have been given subsequently, which would therefore maintain its status as comparator. Evidence to show that cabozantinib is not currently being prescribed would be required to change this status.

1.2 Issue 2: Immaturity of effectiveness data

In Tables 2, 3 and 4 the company have updated the results from the original cut-off of 16th of December 2019 with those from a later cut-off of 30 March 2020 for objective response rate, progression-free survival, and overall survival. The company stated that *"…they have not been used to conduct additional match-adjusted indirect treatment comparisons (MAIC) and naïve indirect treatment comparisons (ITC) for the RET-mutant MTC and RET fusion-positive TC populations, respectively, nor to inform the revised base case, due to time constraints and as only a small number of additional events had occurred."*

ERG comment: On the whole the differences between the two cut-offs appears to be minimal. One potentially important exception is for OS, the point estimate for which had not been estimable, but now is for the RET-mutant MTC population and given that for the MAIC the results for the RET M918-positive population had to be used instead. However, given the fact that only a small number of additional events had occurred and the ERG's reservations regarding the reliability of the MAIC for the RET-mutant MTC population (Key Issue 3) and the reliability of the naïve indirect comparison for the RET fusion-positive TC population (Key Issues 4), the ERG does not believe that additional match-adjusted indirect treatment comparisons (MAIC) and naïve indirect treatment comparisons (ITC) for the RET-mutant MTC and RET fusion-positive TC populations, respectively, will be helpful in reducing uncertainty.

1.3 Issue 5: Extrapolation of survival data

For both the original company base-case as well as the company's post-clarification base-case model, using updated survival analyses that were based on a MAIC that was adjusted for 'prior TKI use' (which was not included in the MAIC that was used the inform the original company model), the company used a Weibull curve for the extrapolation of OS in RET-mutant MTC.[2] This was justified by noting that although it may overestimate OS for selpercatinib, the Weibull provided a plausible relative difference in OS compared to BSC. The ERG considered the Weibull curve to provide an overly optimistic estimate of OS for selpercatinib, with [redacted] of patients still alive after 25 years. The ERG explored alternative curves that included stratified functions and concluded that the stratified

Weibull function provided the best visual fit, best long-term plausibility for BSC, and the most reasonable estimate of the benefit of selpercatinib relative to BSC in light of the limited evidence and immature data that is available. Therefore, the ERG preferred to use the stratified Weibull curve for the extrapolation of OS in RET-mutant MTC.

The company has consulted additional clinical expert opinion for the validation of the OS extrapolation curves for RET-mutant MTC, which indicated that the stratified Weibull, stratified gamma and stratified log-logistic extrapolations potentially provide plausible estimates of long-term OS. Considering that the population used to inform the model consists of both pre-treated patients and patients naïve to systemic therapy, and contains a proportion of patients with non-progressive stable disease who are expected to have better survival outcomes, clinical expert opinion indicated the stratified gamma curves provide the most plausible estimates. Using the stratified gamma curves for OS resulted in a small proportion of [redacted]% patients remaining alive after 25 years and substantially higher survival rates overall for patients treated with selpercatinib than for those treated with BSC, for which it is estimated that no patients are alive after 25 years.

ERG comment: In the absence of empirical evidence to guide the choice of OS curves and in light of the ensuing uncertainty for this aspect, the ERG acknowledges that clinical expert opinion provides the most prominent basis to guide curve selection. No further details regarding the elicitation of clinical expert opinion, nor any documentation of this process were provided to the ERG other than what is summarized above. Thus, given that there is no difference in visual fit or statistical fit between stratified gamma and stratified Weibull, both extrapolations providing very similar results for BSC and there being no data to support the long-term validity of OS extrapolations for patients treated with selpercatinib, only clinical expert opinion remains to guide the choice of plausible OS extrapolations. As such, the ERG has no reason to disagree with the clinical expert opinion consulted by the company which indicated that the stratified gamma provided the most plausible estimates in light of the population used to inform the model.

To illustrate how the cost effectiveness results vary according to OS and PFS extrapolations, the ERG has reproduced Tables 7.6 and 7.7 of the ERG report using the updated company base-case model (i.e. including PAS discount) below in Table 1.1 (OS) and Table 1.2 (PFS).

Table 1.1: OS scenarios

OS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
RET-mutant MTC							
Stratified gamma (Updated company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull (ERG preferred base-case in ERG report)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Weibull (original company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive TC							
Piecewise exponential (Company and ERG preferred base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: the updated company model submitted alongside the company response to the ERG report.[3]
ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; OS = overall survival; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.

Table 1.2: PFS scenarios

PFS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
RET-mutant MTC							
Loglogistic (Company and ERG preferred base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline 3 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline 2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS	Selpercatinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline 2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive TC							
Stratified Weibull (Company and ERG preferred BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: the updated company model submitted alongside the company response to the ERG report.[3]
ICER = incremental cost-effectiveness ratio; Incr. = incremental; MTC = medullary thyroid cancer; PFS = progression free survival; QALYs = quality adjusted life years; RET = rearranged during transfection; TC = thyroid cancer.

1.4 Issue 7: Genetic testing cost

The company have updated the genetic testing cost using a figure provided by NHS England.

ERG comment: The ERG considers this an appropriate estimate to use as input for the model.

1.5 End-of-life criteria

The company presented no new evidence that either of the two criteria, short life expectancy, normally less than 24 months, or extension to life of at least three months were met.

ERG comment: Regarding the criterion of a life expectancy less than 24 months, the ERG stated in the ERG report: "Therefore, the company needs to show that life expectancy in the population for this appraisal is less than 24 months given that cabozantinib, lenvatinib and sorafenib have been recommended in previous appraisals and therefore constitute current best practice." However, these data were not provided.

For the criterion 'extension to life of at least three months' the company provided no additional data to support this. Therefore, as stated in the ERG report, "…there is no robust evidence that selpercatinib offers an extension to life of at least an additional 3 months compared with current NHS treatment."

2. Summary of remaining key issues

2.1 Issue 3: Reliability of the MAIC for RET-mutant MTC population

As described in the ERG report,[2] the reliability of the MAIC for the RET-mutant MTC population is questionable.

An unanchored MAIC was used to generate relative efficacy estimates vs. cabozantinib and placebo (used a proxy for BSC) for the RET-mutant MTC population. As pointed out in the CS both the MAIC for the RET-mutant MTC population and the indirect treatment comparison (ITC) for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators.

Specific problems are:

1. The EXAM study did not report separate results for treatment-naïve and pre-treated patients; therefore, the any-line pooled population from the LIBRETT0-001 trial was used in the MAIC to provide a larger patient-level data set and closer matching to the characteristics of the RET-mutant subgroup of the EXAM trial.
2. Results are also based on subgroups with small numbers of patients, which affects their reliability.
3. The baseline characteristics of the RET-mutant subgroups were not available for the placebo arm of the EXAM study, therefore the baseline characteristics of the cabozantinib group were assumed to be similar to those of the placebo arm and were use in the MAIC.
4. The MAIC only included those prognostic factors and effect modifiers which were reported by both studies; other important factors may be missing and MAIC results are likely to be biased due to unobserved confounding.
5. OS data were not available for the RET-mutant MTC population and had to be estimated using the results for the RET M918-positive population.
6. The CS did not contain any discussion on the likely amount of residual systematic error in the MAIC but did also present results from a naïve indirect treatment comparison (unweighted results) which were similar to the MAIC results. However, as both analyses used selpercatinib data from a single-arm study, the results may be unreliable.

2.2 Issue 4: Reliability of naïve ITC for RET-fusion positive TC population

As described in the ERG report,[2] the reliability of the naïve indirect comparison for the RET fusion-positive TC population is questionable.

A naïve (unanchored) indirect comparison was used to compare selpercatinib with BSC (using the placebo arms of two RCTs) for the RET fusion-positive TC population. As pointed out in the CS both the MAIC for the RET-mutant MTC population and the ITC for the RET fusion-positive TC population are affected by major limitations regarding the availability of and baseline similarity of data for the relevant comparators.

Specific problems:

1. The comparator arms only included patients with differentiated thyroid cancer (DTC). It was unknown to what extent these data are representative for patients with other types of TC. The company indicated that the prognosis for other types of TC is generally known to be worse.
2. A higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the SELECT and DECISION trials. Other important differences between the populations are: 100%

of patients are RET fusion-positive in LIBRETTO-001 but this was unknown in the SELECT trial; and differences in prior systemic therapy as selection was mostly first-line patients (100% of LIBRETTO-001 and 20.6% of SELECT had received at least one prior therapy).

3. Subgroup results by line of therapy were not reported for OS for the comparator arm. OS was also affected by patient crossover in the comparator trials as placebo patients could crossover to the intervention.
4. Given that this analysis was based on small patient numbers and a comparison of single arms without any attempts to balance the patient groups, the PFS results are also likely to be uncertain.

2.3 Issue 6: Health-state utility values

The ERG agrees that the utility values produced by the mapping in Table 5 of the company response to the ERG Report are indeed implausible and agrees that given the limited progressed disease observations available, it is unlikely that any algorithm will produce usable values.[1] Therefore the ERG agrees with the company that one of the sets of values identified from the literature in the company submission should be used in the base-case. The ERG outlined its opinion on the different literature sources presented in Section 5.2.8 of the ERG report.[2] The ERG's opinions have not changed and no change to the company's base-case choice of utility values has been made. The ERG notes that of the sets of utility values identified in the CS, the company's choice of the Fordham et al. values give the most conservative ICER.

2.4 Issue 8: Time on treatment:

In line with the ERG's preferences and clinical expert opinion, time on treatment was modelled to continue beyond progression based on data from LIBRETTO-001.

3. Additional updates to the economic model

Other updates to the company base-case model include an updated list price for selpercatinib and application of the [redacted]% PAS discount to the list price, modelling of selpercatinib dose reductions in line with data from LIBRETTO-001, inclusion of ECG costs in line with the selpercatinib SmPC, and assuming the same costs for BSC in PF and PD health states. For completeness, the results of the original company base-case, company's post-clarification base-case, ERG preferred base-case as presented in the ERG report, and updated company base-case based on the additional evidence (including updated list price and PAS discount) are presented in Table 3.1 below.

Table 3.1: Results of the different versions of the model

Model version	Selpercatinib		BSC		Inc. Costs (£)	Inc. QALYs	ICER (£ / QALY)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
***RET*-mutant MTC**							
Company original base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company post-clarification base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred base-case (ERG report)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**							
Company original base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company post-clarification base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred base-case (ERG report)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 7.11 in the ERG report,[2] Tables 24 and 25 in the company response to the ERG report,[1] and the updated company model submitted alongside the company response to the ERG report.[3]
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; MTC = medullary thyroid cancer; QALY(s) = quality-adjusted life year(s); RET = rearranged during transfection; TC = thyroid cancer.

Table 3.2 Comparison deterministic and probabilistic results

Model version	Selpercatinib		BSC		Inc. Costs (£)	Inc. QALYs	ICER (£ / QALY)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
***RET*-mutant MTC**							
Updated company base-case, deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base-case, probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**							
Updated company base-case, deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base-case, probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 24, 25, 26 and 27 in the company response to the ERG report,[1] and the updated company model submitted alongside the company response to the ERG report.[3]
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; MTC = medullary thyroid cancer; QALY(s) = quality-adjusted life year(s); RET = rearranged during transfection; TC = thyroid cancer.

ERG comment: The ERG considers the additional updates to the model appropriate. Regarding the use of the same BSC costs for PF and PD in line with the ERG's preferences, the company now indicates using a different set of estimates for BSC costs for RET-mutant MTC (Table 21 in the company response to the ERG report)[1] and RET-fusion positive TC (Table 22 in the company response to the ERG report).[1] It is not clear to the ERG for which reason this approach, which deviates from the explanation as provided in the original CS, was chosen. If the same estimates for BSC costs in RET-fusion positive TC are used as those in RET-mutant MTC, the ICER is decreased from £[redacted] to £[redacted] per QALY gained. If the same estimates for BSC costs in RET-mutant MTC are used as those in RET-fusion positive TC, the ICER is increased from £[redacted] to £[redacted] per QALY gained.

It is unfortunate that the company did not correct the errors in the PSA calculations that were pointed out by the ERG in section 6.2.1 of the ERG report.[2] As a result, the probabilistic ICER as reported by the company is higher than the deterministic ICER (see table 3.2). The ERG has corrected this error, leading to a probabilistic ICER that is almost the same as the deterministic ICER.

4. ERG conclusions

The ERG agrees with the updates that were made to the company base-case model,[1] which are mostly in line with the ERG preferences as formulated in the ERG report.[2]

One important deviation from the ERG's preferences as formulated in the ERG report is the choice for the stratified gamma OS curve for RET-mutant MTC, that was based on additional clinical expert feedback consulted by the company. As outlined in Section 1.3 above, the ERG has no reason to disagree with the clinical expert opinion consulted by the company which indicated that the stratified gamma OS curve provided the most plausible estimates in light of the population used to inform the model. Importantly, the company has provided the results of scenario analyses using the other two plausible extrapolations for OS in RET-mutant MTC that are based on the stratified Weibull and stratified log-logistic OS curves. When stratified Weibull curves are used the ICER is increased to £[redacted] per QALY gained, and when stratified log-logistic curves are used the ICER is decreased to £[redacted] per QALY gained, relative to an ICER of £[redacted] per QALY gained using the stratified gamma curve in the updated company base-case model.

For RET fusion-positive TC, the updated company base-case model resulted in an ICER of £[redacted] per QALY gained.

In addition to other updates in line with the ERG's preferences, the company has assumed the same health care resource use costs for BSC in PF and PD. However, a different set of BSC estimates was used for the two indications and it was not clear to the ERG why this approach was used. Exploratory analyses by the ERG indicated that the impact on the ICER of using either of the two sets of estimates for both indications was limited to a change of approximately [redacted]%.

In conclusion, the company's updated base-case model is mostly in line with the ERG's preferences as formulated in the ERG report. Additional clinical feedback consulted by the company, acknowledged by the ERG as the most prominent basis to guide curve selection in the current context, indicated that the stratified gamma provided the most plausible estimate of long-term OS in RET-mutant MTC instead of the stratified Weibull that was preferred by the ERG in their base-case model as described in the ERG report. Some uncertainty remains regarding the costs of BSC, but it's impact on the ICERs is limited.

REFERENCES

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[3] Eli Lilly and Company, RTI Health Solutions. *Economic Model for Selpercatinib (LOXO-292). Economic model to estimate the cost-effectiveness of selpercatinib for patients with RET mutation-positive medullary thyroid cancer [MTC], and previously treated RET fusion-positive thyroid cancer (TC) who may benefit from RET-targeted therapy. UK model. 16 February 2021 [Excel]*, 2021